Institute for Health and Consumer Protection

European Chemicals Bureau

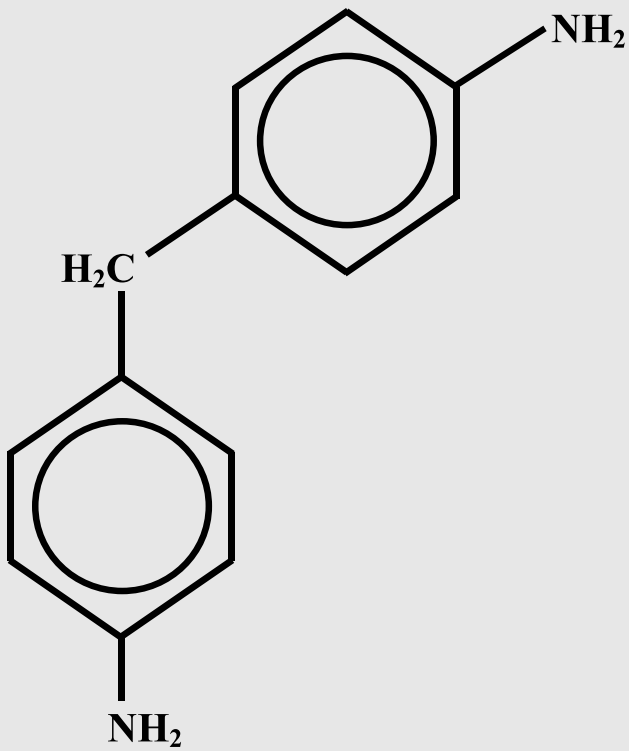
Existing Substances

European Union Risk Assessment Report

CAS No.: 101-77-9

EINECS No.: 202-974-4

4,4'-methylenedianiline



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RISK ASSESSMENT

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RISK ASSESSMENT

Final report, November 2001

Germany

Contact point:
Bundesanstalt für Arbeitsschutz und Arbeitsmedizin
Anmeldestelle Chemikaliengesetz (BAuA)
(Federal Institute for Occupational Safety and Health
Notification Unit)
Friedrich-Henkel-Weg 1-25
44149 Dortmund
Germany

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Foreword

We are pleased to present this Risk Assessment Report which is the result of in-depth work carried out by experts in one Member State, working in co-operation with their counterparts in the other Member States, the Commission Services, Industry and public interest groups.

The Risk Assessment was carried out in accordance with Council Regulation (EEC) 793/93[1] on the evaluation and control of the risks of "existing" substances. "Existing" substances are chemical substances in use within the European Community before September 1981 and listed in the European Inventory of Existing Commercial Chemical Substances. Regulation 793/93 provides a systematic framework for the evaluation of the risks to human health and the environment of these substances if they are produced or imported into the Community in volumes above 10 tonnes per year.

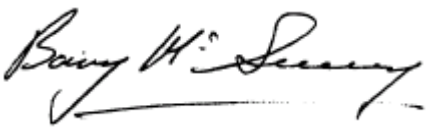
There are four overall stages in the Regulation for reducing the risks: data collection, priority setting, risk assessment and risk reduction. Data provided by Industry are used by Member States and the Commission services to determine the priority of the substances which need to be assessed. For each substance on a priority list, a Member State volunteers to act as "Rapporteur", undertaking the in-depth Risk Assessment and recommending a strategy to limit the risks of exposure to the substance, if necessary.

The methods for carrying out an in-depth Risk Assessment at Community level are laid down in Commission Regulation (EC) 1488/94[2], which is supported by a technical guidance document[3]. Normally, the "Rapporteur" and individual companies producing, importing and/or using the chemicals work closely together to develop a draft Risk Assessment Report, which is then presented at a Meeting of Member State technical experts for endorsement. The Risk Assessment Report is then peer-reviewed by the Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) which gives its opinion to the European Commission on the quality of the risk assessment.

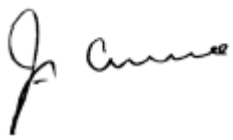
If a Risk Assessment Report concludes that measures to reduce the risks of exposure to the substances are needed, beyond any measures which may already be in place, the next step in the process is for the "Rapporteur" to develop a proposal for a strategy to limit those risks.

The Risk Assessment Report is also presented to the Organisation for Economic Co-operation and Development as a contribution to the Chapter 19, Agenda 21 goals for evaluating chemicals, agreed at the United Nations Conference on Environment and Development, held in Rio de Janeiro in 1992.

This Risk Assessment improves our knowledge about the risks to human health and the environment from exposure to chemicals. We hope you will agree that the results of this in-depth study and intensive co-operation will make a worthwhile contribution to the Community objective of reducing the overall risks from exposure to chemicals.



Barry Mc Sweeney
Director-General
Joint Research Centre



J. Currie
Director-General
Environment, Nuclear Safety and Civil Protection

[1] O.J. No L 084 , 05/04/199 p.0001 – 0075

[2] O.J. No L 161, 29/06/1994 p. 0003 – 0011

[3] Technical Guidance Document, Part I – V, ISBN 92-827-801 [1234]

0 OVERALL RESULTS OF THE RISK ASSESSMENT

CAS No. 101-77-9
EINECS No. 202-974-4
IUPAC Name 4,4'-Methylenedianiline

Overall results of the risk assessment:

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

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

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

Summary of conclusions

Environment

conclusion i)

As no information on the toxicity of sediment organisms is available, a long-term toxicity test on a sediment organism (Lumbriculus variegatus) should be performed.

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.

Workers

conclusion iii)

With regard to occupational risk assessment 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.

Further data on biological monitoring (industry, skilled trade, urinary MDA content, haemoglobin adducts) might be useful to assess different exposure situations.

Consumers

conclusion iiib)

Uremic patients or patients receiving blood transfusions frequently are identified to be at risk if polyurethanes used in medical devices as potty materials are sterilized by gamma irradiation. Other treatments for sterilization must be used.

Azodyes which can release MDA are recommended to be restricted for the use as dyes for paper, writing inks, leather and textiles.

Man exposed via the environment

conclusion iiia)

The risk assessment shows that the margin of safety can be assumed to be sufficient, but that risks cannot be excluded at any exposure, as the substance is identified as non-threshold carcinogen.

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TABLES

1 GENERAL SUBSTANCE INFORMATION

Identification of the substance

CAS No.: 101-77-9

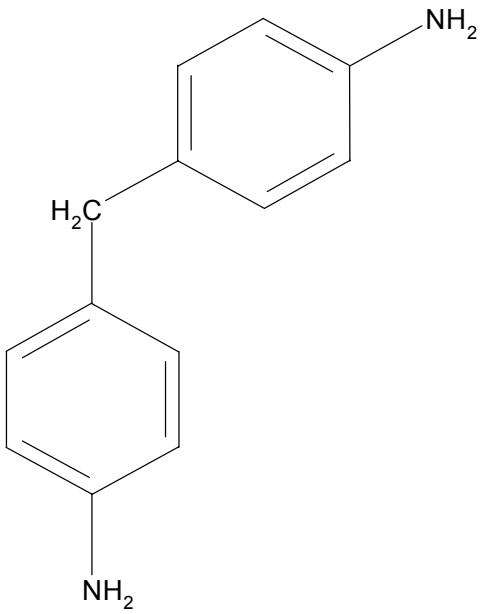
EINECS No.: 202-974-4

IUPAC Name: Bis (4-aminophenyl)methane

Synonyma: 4,4'-Methylenedianiline
4,4'-Diaminodiphenylmethane
4,4’-Diphenylmethane diamine
4,4’-Methylendibenzolamine
4,4’-Methylenebisbenzeneamine
4-(4-Aminobenzyl)aniline
MDA

Empirical formula: $C_{13}H_{14}N_2$

Structural formula:



Molecular weight: 198.3 g/mol

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 (BUA, 1994):

4,4'-MDA:	59 - 61% w/w [4)]
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:	<00 ppm

Pure 4,4'-MDA is also used as an intermediate and has the following composition (BUA, 1994):

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

Table 1.1 Physico-chemical properties of 4,4' -MDA*

Melting point	89°C	Moore, 1978
Boiling point	398 – 399°C at 1013 hPa	Windholz, 1976
Density	1.056 at 100°C	Moore, 1978
Vapour pressure	$2.87 * 10^{-8}$ hPa at 20°C[1)]	Bayer AG, 1988
Surface tension	69.5 mN/m[2)]	Bayer AG, 1995a
Water solubility	1.25 g/l at 20°C[3)]	Bayer AG, 1996a
Partition coefficient (log P_{ow})	1.59	Hansch & Leo, 1985
Flash point	not determined (solid)	Chemsafe, 1994
Auto flammability	not flammable[4)]	Chemsafe, 1994
Flammability	not flammable[5)]	Chemsafe, 1994
Explosive properties	not explosive	Chemsafe, 1994
Oxidizing properties	no oxidizing properties	Chemsafe, 1994

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

[1)]Experimental value (vapour pressure balance) measured in the range 63.5°C-117.2°C. The value at 20°C was received by extrapolation from the vapour pressure curve

[2)]Experimental value (ring method), concentration of the aqueous test solution c = 918.01 mg/l; T = 20.1°C

[3)]The water solubility of the technical product, that means the sum of all solved substances, is 1,55 g/l at 20°C (4,4'-MDA = 1372 mg/l, 2,4'-MDA = 127 mg/l, trinuclear MDA = 42.5 mg/l; measured with the flask method, Bayer AG, 1996a)
The value of 1372 mg/l is the result of the water solubility of the 4,4´-MDA in the technical grade substance
The value of 1.25 g/l was determined using the pure substance (purity >98%) and was used for the calculations

[4)]Test according A.16 not conducted, due to the melting point of 89°C an auto-flammability of the substance is not expected

[5)]Test according A.10, A.12 and A.13 not conducted because of structural reasons

4 Depending on the production process the content of 4,4'-MDA can vary, the minimum content produced has been 30-40%

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 for the Environment	R 51/53	Toxic to aquatic organisms, may cause 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 for the Environment	R 51/53	Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.

2 GENERAL INFORMATION ON EXPOSURE

More than 98% of the total production volume of MDA, i.e. the technical-grade MDA, are used as an intermediate (UC = 33, IC = 3) for the production of Methylenediphenyldiiso-cyanate (MDI), exclusively at the same site (BUA, 1994). MDI is further processed to polyurethanes by almost 1000 users in Western Europe (Frey, 1990).

In Western Europe, 540,000 t MDI, the subsequent product of MDA, were manufactured in 1993. For this, in proportion about 432,000 t MDA were needed. The production and processing volumes have an increasing tendency. In 1980, 267,000 t MDI were produced and 215,000 t processed (Frey, 1990; CEH, 1994).

There are no informations about the total EU export and import volumes.

Further uses of MDA are:

- hardener for epoxy resins (UC = 55, IC = 11)
- hardener in adhesives (UC = 2, IC = 11)
- intermediate in the manufacture of high-performance polymers (UC = 33, IC = 11) (Ciba UK, IUCLID)
- processing to 4,4'-Methylenebis(cyclohexaneamine) (UC = 33, IC = 3) (BASF, 1992 a).

The amount for these non-MDI uses is estimated to be maximum 4000 t/a (APME 1995).

Actually there are no direct uses without chemical transformation (BUA, 1994).

In Denmark, 175 t/a are used in hardeners, adhesives, paint, lacquers and varnishes (Danish Product Register; 1995). 21 t/a are used in Norway (Norwegian Product Register; 1995) and 7 t/a in Sweden (Swedish Product Registry; 1992) in the same use categories.

There are information available, that 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.

For workers in general the uptake of azodyes (based on MDA) has to be considered because the amine component could be unintentionally released by reductive conditions in the body.

Concerning the environmental risk assessment the possibly released amounts of MDA are estimated to be negligible.

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

3.1.1 General discussion

Releases into the environment

MDA is synthesized by reaction of formaldehyde and aniline in the presence of hydrochloric acid. The condensation reaction may be carried out in a batch reactor or, alternatively, as a continuous process. The reaction product is a mixture of diamino and polyamino compounds. It is neutralised with an excess of caustic soda and allowed to settle into a two layer mixture. The organic layer is separated, washed with hot water and distilled. The water recovered is recycled to provide the wash water for the washing stage. Unreacted aniline is recycled to the condensation reaction stage. The aqueous layer produced after neutralisation is combined with the aqueous washings from the crude MDA washing stage. This mixture is then washed with aniline to remove dissolved MDA. The remaining aqueous layer is distilled to remove aniline and then discharged into the sewer (HMSO, 1995). As the volume of the wash water and the partitioning of MDA in aniline/water is not known, the emissions can not be estimated on this basis.

After the neutralisation step, the water phase is saturated with MDA. As the polyamines are substantially less soluble than the diamine (4,4'-MDA: 1.25 g/l; 3-core-MDA: 42.5 mg/l; cf. 1.3), and this phase is finally discharged after aniline treatment, it can be concluded that polyamines are emitted in much lower amounts than diamines. If the waste water is monitored, always the 4,4'-MDA is detected only. It is unlikely that the polyamines will significantly raise the total emissions. Therefore, the emissions of polyamines are of less importance in the exposure assessment.

More than 98% of the MDA are processed to methylenediphenyldiisocyanate (MDI) by reaction with phosgene. Releases to water are expected to be not significant, since any application of cleaning water is scrupulously avoided to prevent deleterious effects on product quality (HMSO, 1995; Gilbert International Isocyanates, 1996).

Maximum 4000 t/a of the produced MDA are sold and used for other applications than MDI synthesis (APME 1995).

The releases into the atmosphere during production of MDA and processing to MDI are expected to be not significant for the environmental risk assessment.

MDA can be formed by hydrolysis of MDI under certain conditions. However, this reaction is depending on the ratio of MDI/water mixing: If the pure isocyanate is spilled into water, polyurea is formed as the main product, while with small MDI amounts mixed with a great excess of water MDA will be formed (Hirzy, 1985). These results are confirmed by Gilbert International Isocyanates (1996): In any case the course of reaction of MDI with water depends on the reaction conditions. Generally if the diisocyanate is spilled into water polyurea is formed as the main product with no detectable or only trace amounts of MDA. Only when small amounts of MDI are vigorously mixed with a great excess of water is MDA formed in significant yield, and then of necessity at very low concentrations (Gilbert International Isocyanates, 1996). As polyurea would

cause deleterious effects on the equipment, any application of cleaning water is avoided at the technical processes.

Releases of MDA into the atmosphere during the further (non-MDI) uses do not occur in significant amounts.

Diffuse releases can occur from MDA or MDI (after hydrolysis) chemically reacted in polyurethane or epoxy matrices during use and disposal of polymer products. Trace amounts of residual monomeres may be released via migration and leaching.

Degradation

Water

All available biodegradation tests were performed with the pure 4,4`-MDA.

As the biodegradation tests clearly show, MDA is not readily biodegradable. The three available tests on ready biodegradation (OECD 301 B and 301 C) indicate 0 to 19% degradation after 28 days. The used substance concentration of 10, 20 and 100 mg/l could not have inhibiting activity on the microbial population, since the EC_{50} for activated sludge was determined to >100 mg/l (Ciba Geigy, 1985; MITI, 1993; Yakabe, 1993, Bayer AG, 1986).

Different tests on inherent biodegradation are available. A modified MITI-II-Test (OECD 302 C) with activated sludge from predominantly municipal source indicates 43% degradation after 28 days (99.7% purity, Bayer AG, 1986). The used substance concentration of 30 mg/l was too low to have inhibiting activity on the microbial population.

A degradation test with activated sludge from an industrial waste water treatment plant (OECD 302 B, "Inherent biodegradability: Modified Zahn-Wellens-Test") indicates 95% degradation after 14 days and 97% after 21 days (BASF, 1988). The substance concentration in this test was 389 mg/l. This study is confirmed by another Zahn-Wellens-Test (OECD 302 B) performed also under the use of activated sludge from industrial wwtp. The results of this test indicates >70% degradation after 3 days (BASF, 1994).

A Coupled Units Test (OECD 303 A, Ciba Geigy, 1986) with activated sludge produced from a mixed inoculum (secondary effluent, Rhine-water, suspension of garden soil) with an adaptation phase of 25 days indicate only 6.5% biodegradation after 34 days.

These results show very clearly that 4,4`-MDA is not readily biodegradable and fulfils the criteria stated for inherent biodegradation only if an adapted industrial inoculum is used. From the Coupled Units Test can be deduced that an adaptation time of 25 days is not sufficient. Therefore 4,4`-MDA has to be considered as inherently biodegradable in industrial wwtps only. Degradation in municipal wwtps cannot be deduced from these results, as shown in the test with activated sludge from predominantly municipal or mixed source.

On the basis of the available biodegradation tests it is not possible to conclude that the substance is biodegraded under environmental conditions.

The UV-spectrum (lmax at 289 nm) indicates that direct photolysis in water may occur. In a test on photolytic degradation in aqueous solution, a quantum yield of 0.006 for direct photodegradation in polychromatic light was determined and half-lifes were calculated (Bayer, 1996b). According to the GC-SOLAR program, the half-lives are 3.0 d in summer and 52 d in winter (marginal conditions: pure water from close to the surface, 10th degree of longitude, 50th degree of latitude, clear sky, typical ozone concentrations in the atmosphere). According to the Frank & Klöpffer program, the mean values of the half-lives range from 4.0 d in June to 190 d in December (marginal conditions: pure water from close to the surface, stagnant water, geographic and climatic conditions of 50^{th} degree of latitude, no contribution of another mono- or bimolecular elimination process). As the model of Frank & Klöpffer is closer to real environmental conditions, the respective values seem to be more valid. However, dullness and adsorption of surface waters are not considered. Because of these effects, the photolytical active zone is only close to the surface of real surface waters. Considering the total water body, the real environmental half-lives should be at least one order of range higher than the calculated. Therefore a degradation rate constant of $3.6 \cdot 10^{-4}$ d^{-1} (DT_{50} = 1900 d) is used in the exposure assessment.

Based on the molecular structure, hydrolysis is not to be expected under environmental conditions.

Soil

The microbial degradation of MDA in soil was investigated under aerobic and anaerobic conditions using carbon-^{14}C labeled MDA (International Isocyanate Institute, 1996). The results show, that biodegradation started immediatly after mixing with the aerobic soil. With the binding of the amine to soil the degradation rate decreased later. The test indicates biodegradation of 2.9% after 3 days, 9.1% after 7 days and 11.6% after 56 days. During the latter period of the incubation some of the $^{14}CO_2$ was lost, so the results for 210 and 365 days must be rejected. The degradation rates after 7 and 56 days indicate that biodegradation is disrupted after MDA had formed covalent bounds with humic substances (cf 3.1.1.c). From the remaining results it is not possible to calculate a half-life, but it can be assumed that MDA covalently bound to organic matter is degraded almost similar to the humic acids themselves. Analogously to the investigations for 3,4-dichloroaniline, a mean half-life of 1000 d can be assumed (cf. 3.1.1.c).

Under anaerobic methanogen conditions no $^{14}CH_4$ or $^{14}CO_2$ was recovered after 73 days of incubation (Gilbert International Isocyanates, 1996).

Sediments

There are no data available on biodegradation of 4,4'-MDA in sediments. For the oxic sediment layer, the same reaction constant (1000 d) as for soils is used. Thus, in the following exposure calculations a half-life of 10,000 d is assumed for the sediment compartment.

Atmosphere

In a test on photochemical-oxidative degradation in the atmosphere the reaction constant with OH-radicals was determined (Becker, 1987), from this a half-life of 12.8 h can be calculated ($C_{OH} = 5 \cdot 10^5$ molec/cm^3).

Summary

The following degradation rates are used in the further exposure assessment:

Table 3.1 Degradation rates

kbio$_{stp}$	0.1 h^{-1}
kbio$_{water}$	0
kphoto$_{water}$	$3.6 \cdot 10^{-4}$ d^{-1}
kdeg$_{water}$	$3.6 \cdot 10^{-4}$ d^{-1}
kbio$_{sed}$	$6.9 \cdot 10^{-5}$ d^{-1}
kbio$_{soil}$	$6.9 \cdot 10^{-4}$ d^{-1}
kdeg$_{air}$	1.3 d^{-1}

Distribution

The major releases of MDA occur into the hydrosphere. With a Henry's law-constant of $4.4 . 10^{-7}$ $Pa \cdot m^3 \cdot mol^{-1}$ no significant volatilisation from water is expected.

Experiments with radiolabelled 4,4'-MDA revealed that the substance forms covalent bonds with the organic fraction in soils. Intitial sorption of MDA in silt loam was nearly completed by 4 hours under aerobic conditions. Under anaerobic conditions, sorption appeared to still be proceeding at 7 days. The K_{oc} values were determined to 4,848 $l . kg^{-1}$ after 8 hours and 7,041 $l.kg^{-1}$ after 7 days for aerobic conditions. The values for anaerobic conditions are 3,828 $l . kg^{-1}$ and 10,729 $l.kg^{-1}$ for 8 h and 7 d, respectively. Furthermore, surface adsorption or ion exchange processes were found with minerals without organic content (III, 1996). It should be kept in mind that the term "K_{oc}" generally describes the distribution of a substance between the pore water and the organic matter when the substance is physically bound; if chemisorption occurs the use of this term is not quite correct. The chemical binding effects are already well-known as a property of aniline and 3,4-dichloroaniline and are described in detail in the respective environmental risk assessment reports in the scope of the first EU priority list.

Investigations were carried out on the binding of different aniline derivatives (toluidines, chloroanilines, not MDA) with various humus extracts and model substances. Reaction partners of the amino moiety were found to be aldehyde or keto groups as well as double bonds of quinoid systems which are typically for humic substances (Parris, 1980). Because of the specifity of the reaction partners, chemisorption onto sewage sludge is not expected. The adsorption of MDA onto sludge should only be physisorption, which is described by the TGD models based on the log P_{ow} of 1.59.

There are no empirically determined values for $K_{susp\text{-}water}$ and $K_{sed\text{-}water}$ available.

With a K_{oc} of 7,041 $l \cdot kg^{-1}$, the following distribution constants are calculated in accordance to the TGD models:

Table 3.2 Distribution constants

Kp_{soil}	141 $l \cdot kg^{-1}$	$K_{soil\text{-}water}$	211 $m^3 \cdot m^{-3}$
Kp_{susp}	704 $l \cdot kg^{-1}$	$K_{susp\text{-}water}$	177 $m^3 \cdot m^{-3}$
Kp_{sed}	352 $l \cdot kg^{-1}$	$K_{sed\text{-}water}$	177 $m^3 \cdot m^{-3}$

With a concentration of 15 mg suspended matter per liter river water, 1% of the MDA are particle-bound.

The fate of 4,4'-MDA in treatment plants according to the SIMPLETREAT model is:

Table 3.3 Fate of 4,4'-MDA in treatment plants

elimination by biodegradation	41%
emission via effluent	59%

Accumulation

In a bioaccumulation test on carp BCFs of 3 - 14 resp. <3.1 - 15 were determined after 6 weeks at concentrations of 200 and 20 µg/l (MITI, 1993). These values indicate a low bioaccumulation in fish.

The bioavailability of the reaction product of MDA with humic acids was not examined. In experiments with 3,4-dichloroaniline an extraordinarily high bioaccumulation was found in organisms with sediment ingestion. While BCFs between 4 and 45 l/kg were determined for fish, values up to 800 l/kg for sediment dwelling organisms indicate that the reaction product of 3,4-dichloroaniline with humic acids is bioavailable.

We expect that MDA has similar properties.

Biodegradation in the environment is extremely low and MDA may combine with humic substances in soils and sediments. Thus, through fixation on humic substances, persistence in the environment and bio-accumulation may occur.

3.1.2 Aquatic compartment

There are no monitoring data for the hydrosphere available.

3.1.2.1 Estimation of Clocal / Generic approach: production and processing

In the *Technical Guidance Documents for New and Existing Substances*, a generic exposure scenario for the release of intermediates into surface water during production is proposed. A release factor of 0.3% into the sewage and subsequent purification in a wwtp (41% elimination according to SIMPLETREAT) is assumed. At the largest sites the total production volume or the major part is processed to MDI. For this reaction no releases are expected (cf. 3.1.1).

Using the highest single production quantity of yearly 110,000 t 55% MDA, the C_{local} is estimated according to the TGD model:

production volume of technical grade MDA:	110,000 t/a
content 55% 4,4'-MDA ⇒	60,500 t/a
release into waste water (0.3%):	182 t/a
elimination in stp (41%): release into hydrosphere =	107 t/a
production during 300 d/a: release into hydrosphere =	357 kg/d
river flow 60 m^3/s: C_{local} =	69 µg/l

3.1.3 Estimation of C_{local} / Site-specific approach: production and processing

The MDA emissions during production and processing to MDI have to be assessed as point source emissions as the single production/processing sites are identifiable.

Valid data about the discharges via waste water are available for all production sites. The emission amounts are calculated from the effluent concentrations and the sewage flows.

For calculating of the C_{local}, the dilution of the waste water in the river is considered according to

$$C_{local} = C_{eff} / D \text{ with } D = Q_{river} / Q_{ww}$$

C_{eff}: concentration in wwtp effluent. If measurements are available, they are always related to 4,4'-MDA.

D: dilution factor
Q_{ww}: sewage flow
Q_{river}: river flow

In the following table, the estimated emissions, C_{locals} and underlying specific data of these sites which are localized at rivers or river mouths are summarized:

Table 3.4 Estimated emissions, C_{locals} and site specific data

Company	Specific Data	Clocal [µg/l]	Emission [kg/a]
A	effluent concentration, sewage and river flow	$8.0 \cdot 10^{-3}$	60
B	effluent concentration, sewage and river flow	$2.7 \cdot 10^{-3}$	75
C	effluent concentration, sewage and river flow	0.40	14
D	processing stopped		
E	effluent concentration (mean and 90%ile), sewage and river flow	0.11	360
F	effluent concentration, sewage and river flow	0.088	76
H	effluent concentration, sewage and river flow	0.23	110
I	effluent concentration, sewage and river flow	0.02	38
N	production stopped		

There are two rivers which receive the effluents from 2 resp. 3 sites. This can lead to environmental concentrations which are higher than the C_{local} figures calculated from single site

emissions. At the first river, sites F and H are in close vicinity, so the C_{local} figures are added as a worst case approach. At the second river, sites A and E are vicinal, and site C is located at a small tributary. As the emission volume of site C (14 kg/a) is relatively small compared with 60 (A) and 360 kg/a (E), only the C_{locals} of the sites A and E are added in order to prevent an overestimation of the exposure:

Table 3.5 C_{locals} of the sites

Sites	Σ Clocal [µg/l]
F, H	0.32
A, E	0.12

5 MDA producers are located at the sea, the waste waters are emitted into the estuary. In the following table, these data are summarized:

Table 3.6 Summarized data

Company	Specific data	Clocal [µg/l]	Emission [kg/a]
G	effluent concentration, sewage flow, no wwtp	1.0	51
J	effluent concentration, sewage flow	0.047	144
K	effluent concentration, sewage flow	1.0	1,870
L	production stopped		
M	effluent concentration, sewage flow	1.0	29

Remarks

Company G

The end of the sewage pipe is in a distance of 2,000 m from the coast in a depth of 20 m. The local authority accepted a dilution factor of 1:1,400, however it is unknown how this value was derived. Considering the available information a dilution factor of 100 seems to be appropriate for an initial step.

Company J

The wwtp effluent is added to a cooling water stream where it is diluted 1:105 before entering the sea. For the Clocal calculation a further dilution with seawater of 1:10 is considered.

Company K

The waste water is emitted into an industrial harbour which contains seawater and which has an open connection to the sea. In 8 measurements, the MDA concentration in the harbour and the connected canal was below the detection limit of 1 µg/l which is chosen as Clocal. A model calculation (which considers the tides) results in dilution factors of 1:10 after 7 m canal length, 1:100 after 500 m and 1:5,000 after 8,000 m.

Company M

The end of the sewage pipe is in a depth of 18 m. Considering the available information a dilution factor of 100 seems to be appropriate for an initial step.

The total 4,4'-MDA emission volume during production is calculated to 2,830 kg/a.

Releases from use of MDI in polyurethane manufacturing

As MDA can be formed by hydrolysis of MDI under certain conditions (cf. 3.1.1.a), there is the question if there are MDA releases during MDI processing, e.g. during polyurethane production. Production of polyurethanes on a MDI-basis is essentially an anhydrous process not leading to waste waters that could be contaminated with traces of MDA. Also, PUR-products are not "washed". Generally, equipment cleaning is done predominantly using mechanical procedures, e.g. sand blasting or organic solvents in order to exclude any water from the machinery. Occasionally, sometimes may be cleaned with hot water, possibly containing tensides. This water will not be in contact with MDI, but with polymeric polyurethanes and polyureas, instead. These polymeric materials are not sources of MDA from hydrolysis.

Work area washdowns are always done with water (and tensides) to remove dirt, oil, spots and stains. Again, these spots and stains may be polyurethanes or polyureas, but normally not MDI. In case there was unreacted MDI in the work area, the washdowns may contain detectable amounts of MDA in the lower ppm range (up to approximately 10 ppm, locally). Hirzy (1985) estimated the amount of MDA emitted via wash water to be 5 g/t PUR produced. In the light of explanations above this figure appears not to be applicable to today's production units. Instead, emissions of MDA from polyurethane manufacturing sites into the aquatic compartment may occur in a small number of cases. However, both their concentrations and their absolute masses can reasonably be considered as being negligible (i.e. occasionally occurring traces, certainly lower than 1 µg/l, due to the dilution in the wash water).

In order to assess the possible hazard due to MDA formed when MDI enters the water compartment, in the Risk Assessment Report for MDI, PECs of MDA due to the reaction of MDI with water are calculated. Using a yield for MDI hydrolysis of 2 %, local PECs of MDA associated with MDI hydrolysis are as follows:

Table 3.7 Local PECs of MDA associated with MDI hydrolysis are as follows

Environmental compartment	Production	Procesing to PU	Processing to prepolymers	Processing of prepolymers speciality MDI`s	Processing of prepolymers other than speciality MDI´s
Surface water µg/l	$2.8 \cdot 10^{-5}$	$2.8 \cdot 10^{-5}$	$2.8 \cdot 10^{-5}$	$2.8 \cdot 10^{-5}$	$2.8 \cdot 10^{-5}$

If these concentrations are compared to those calculated in the present MDA report (C_{local} in surface water of 69 µg/l for the generic approach and of 0.4 µg/l for a site specific approach of company C), it appears that they are negligible and adding them to the C_{local} calculated without considering MDA releases due to MDI production and processing will not change the results significant.

Releases from further uses (epoxy hardener, hardener in adhesives, intermediate for polymers)

In this use categories, pure 4,4'-MDA is used in preference. The use amount was estimated to be 4000 t/a. Generally, dry processes are used. The presence of even trace amounts of water in systems used for any of the applications would inevitably impair performance. In the majority of the applications, totally "100% solids" systems are used, i.e. resin, hardener, viscosity modifier, fillers etc. In some cases (e.g. laminating and surface coating systems), organic solvents may be added in order to reduce viscosity. Water is totally unsuitable as a solvent in this cases. Similarly, equipment used in the processing of such systems (e.g. moulds, mandrels) can not be cleaned after use with water, because water is an ineffective solvent for the systems being processed. Cleaning is always performed with organic solvents, which are then collected and either recycled to recover used solvent, or burned in a "state of the art" incinerator. Thus in summary, all uses of MDA as a hardener for epoxy resins must for technical reasons be totally non-aqueous. The above conditions/reasoning also applies to the use of MDA as a coreactant for polyurethanes, and use in polyimides/bismaleimide (APME, 1995).

As significant MDA releases into the hydrosphere from these uses are not expected, the calculation of a PEC is not necessary.

Releases from polyurethanes and epoxy resins

Several tests on migration of unreacted MDA from polyurethanes and epoxy resins are available. In water extracts from polyurethanes at 47-48°C, no MDA was detected after 2 weeks resp. 6 months. After autoclaving of PU-films, up to 24 µg MDA/l were found in the elution water. The extracted MDA was just formed during the thermic treatment (Ernes & Hanshumaker, 1983). In a migration test with MDA-cured epoxy resins amounts up to 0.11 µg MDA/dm^2 were determined (Baumann & Marek, 1980). In different wine simulants which were in contact with expoxy resin barrels, up to 7.6 mg MDA/kg epoxyd migrated (Larroque, 1988). Because of the small amounts there will be no significant pollution of the environment.

Sediments

Because of the binding properties of MDA onto humic substances, an accumulation of the substance in sediments is expected. With a $K_{susp\text{-}water}$ of 177 $m^3 \cdot m^{-3}$ and the $C_{local\text{-}water}$ values calculated above, the following $C_{local\text{-}sed}$ are calculated:

Table 3.8 Calculated $C_{local\text{-}sed}$

Company	$C_{local\text{-}water}$ [µg/l]	$C_{local\text{-}sed}$ [µg/kg ww]
A	$8.0 \cdot 10^{-3}$	1.2
B	$2.7 \cdot 10^{-3}$	0.42
C	0.40	62
E	0.11	17
F	0.088	14
H	0.23	35
I	0.02	3.1
J	0.047	7.2
G	1.0	150
K	1.0	150
M	1.0	150
Σ A, E	0.12	18
Σ F, H	0.32	49

It has to be kept in mind that in sediments MDA is always covalently bound onto the organic fraction, although the calculated concentrations are related to 4,4'-MDA.

3.1.4 Atmosphere

Production and processing

The production of MDA and processing to MDI is generally carried out in continuous processes, and no significant MDA releases into the atmosphere are expected.

However, one company which produces MDA for sale to the polymer industry reports emissions from the pastillation unit. The exhaust air is filtered prior to discharge to atmosphere. From monitoring results, the MDA emissions were estimated to 80-140 (∅ 100) mg/hour (Ciba-Geigy, 1997). Assuming production during 24h/d and 300 d/a, the emissions would be 720 g/a.

Use in polymer industry

During processing to epoxy resins, a MDA contamination of the air at working places is reported (Boeniger, 1984; Boeniger & Phillips, 1984). There were no emission data submitted for European plants. For an American plant which processes 1000 t MDA per year, an exposure estimation is available. The room concentration of MDA was measured (17 values) to 0.4-46.1 (∅ 9.5) µg/m^3. With a total air volume (60,000 m3) removed during one day, the emission amount is calculated to 0.57 g/a. This calculation does not take into account that the exhausted air is filtered, which may reduce the MDA release, therefore it has to be regarded as a worst case estimation (Ciba-Geigy, 1997).

The Technical Guidance Documents propose a release factor of 0.075. For a plant with a consumption of 1000 t/a and a production period of 300 d/a, the emission would amount to 75 t/a or 250 kg/d. Compared with the 0.57 g/a calculated above, this value seems to be unrealistic high and is not used.

Although the representativity of the American plant is not quite clear (other plants may apply other techniques and produce other resins), the emissions of the polymer industry seem to be negligible.

3.1.5 Terrestrial compartment

During production and processing of MDA, no significant releases into the soil are expected. Only trace amounts may be discharged during deposition of polyurethane and epoxy resin wastes on controlled landfills.

As no significant releases into the atmosphere are to be expected, also a relevant deposition into soils will not occur.

Adsorption onto sewage sludge is negligible, thus significant releases into agricultural soils due to the use of sludge as fertilizer will not occur.

3.1.6 Regional exposure

According to the *Technical Guidance Document*, generally the regional and the local PECs have to be added to calculate the total PEC which is relevant for the environmental risk assessment.

This method is not appropriate for MDA, because of the following reasons:

- Point sources which are scattered over a large region cause the major releases into the hydrosphere. The substance is only emitted into surface waters, and it is unlikely that the emission of one site will reach a second source. Thus, it cannot be assumed that the producers are emitting into a pre-polluted environment. Therefore, only local PECs are taken for the aquatic risk assessment.

- The MDA releases from non-MDI uses are relatively small related to the producers emissions. It will give no significant contribution to the total environmental concentrations.

Therefore, for the environmental risk assessment the aqueous PEC_{local} are equated with the C_{local}.

However, regional PECs should be calculated as input parameters for the indirect exposure of human via the environment. The total emissions were estimated to 2,830 kg/a (cf. 3.1.2.2). The input is 2,550 kg/a for the continental and 283 kg/a for the EU standard regional model. The EUSES output is given in Appendix I. The results are:

Table 3.9 Results of the EUSES output

Compartment	Continental concentration	Regional concentration
Surface water	$2.^{9} \cdot 10^{-3}$ µg/l	0.01 µg/l
Sediment	1.9 µg/kg dw	6.4 µg/kg dw
Atmosphere	$1.3 \cdot 10^{-15}$ µg/m³	$4.6 \cdot 10^{-15}$ µg/m³
Agric. soil	$9.5 \cdot 10^{-9}$ µg/kg dw	$3.2 \cdot 10^{-8}$ µg/kg dw
Agr. soil, porewater	$6.7 \cdot 10^{-11}$ µg/l	$2.3 \cdot 10^{-10}$ µg/l
Industr. soil	$3.5 \cdot 10^{-8}$ µg/kg dw	$1.2 \cdot 10^{-7}$ µg/kg dw
Nat. Soil	$3.5 \cdot 10^{-8}$ µg/kg dw	$1.2 \cdot 10^{-7}$ µg/kg dw

3.1.7 Non compartment specific exposure relevant to the food chain

Because of the low accumulation of MDA in fish via water, the exposure route fish - fish eating bird is likely to be not relevant. However, the reaction product of MDA with sediment organics accumulates in sediments and is probably bioavailable. A biomagnification via the route sediment - sediment dwelling organisms - fish or bird cannot be excluded.

3.2 EFFECTS ASSESSMENT: HAZARD IDENTIFICATION AND DOSE (CONCENTRATION) - RESPONSE (EFFECT) ASSESSMENT

Most of the available tests were performed with the pure 4,4'-MDA. Limit data are available for the technical grade MDA. The most relevant results from toxicity tests with aquatic organisms are presented below, differentiating the two products.

3.2.1 Aquatic compartment

By validating the ecotoxicological tests, the photolytical degradation of MDA in water (cf. 3.1.1.b) has to be considered. According to experience with other anilines, the test solution is not stable over a few days. Therefore it has to be assumed that tests without analytical control would be not valid. That means, that all tests using nominal concentrations as bases for the derivation of the effects data cannot be taken as valid.

In some tests of Ciba-Geigy an analysis was provided, but after 2 or 3 days the substance concentrations were found to be higher than at the beginning of the test; the analytical part of these tests have to be taken as not valid. However, the prepared concentrations are accepted as nominal effect concentrations, and the test results were calculated on this basis.

Effects data for 4,4'- MDA Available

Vertebrates

Only results from short-term tests are available. The acute effect concentrations (LC_{50}) range from 32 mg/l to 65 mg/l.

Brachydanio rerio 96 h-LC_{50} = 42.0 mg/l

(static, nominal concentration, DMF, 95.5-98% purity, Ciba-Geigy 1985a)

Brachydanio rerio 96 h-LC_{50} = 65.0 mg/l

(static, nominal concentration, 99.7% purity, Bayer 1986)

Leuciscus idus 96 h-LC_{50} = 53.0 mg/l
96 h-NOEC = 10.0 mg/l

(static, nominal concentration, 96% purity, BASF 1988a)

Oryzias latipes 48 h-LC_{50} = 32.0 mg/l

(static/semi-static, MITI 1993)

Oncorhynchus mykiss 96 h-LC_{50} = 39.0 mg/l

(static, nominal concentration, DMF, 95.5-98 % purity, Ciba-Geigy 1985b)

Invertebrates (daphnia)

Results from short-term tests

Moina macrocopa 24 h-EC_{50} = 2.3 mg/l

(effect: immobilisation, static, nominal concentration, extra pure, Fujiwara 1982)

Results from long-term toxicity tests

Moina macrocopa 14 d-NOEC = 0.15 mg/l

(effect: reproduction, semi-static, test solution renewed every 48 h, nominal concentration, extra pure, Fujiwara 1982)

Moina macrocopa STRAUS belongs to the daphnids. The difference is that *Moina macrocopa* has a shorter generation time than *Daphnia magna*. So, it is possible by using of *M. macrocopa* to examine the effects of MDA on the reproduction of daphnids in three generations within two weeks. The reproduction test was performed according OECD guidlines 202, part II using at the beginning of the test less than 24 hours old daphnids. The daphnids were fed once daily with unicellular green algae. Under this semi-static condition the test solutions were renewed every 48 hours. The newborn young of the F1 generation are counted every two days.

Plants:

Scenedesmus subspicatus 72 h-EC_{50} = 21 mg/l

(effect: growth inhibition, nominal concentration, DMF, 95.5-98% purity, Ciba-Geigy 1985c)

As shown in a laboratory test, an aqueous solution of 4,4'-MDA can be photolytically degraded (cf. 3.1.1.b). In fact, calculation of the half-life according to Frank & Klöpffer shows a lowest half-life of 3 days. In the long-term invertebrate test (*Moina macrocopa*), solutions were replaced every 48 h, which means 37% loss of concentrations between renewal (worst-case assumption: the degradation rate is similar as estimated by Frank & Klöpffer). That also means for all available short-term test with duration times of 96 h a loss of concentration of 60%. The loss of concentration more than 20% is not valid anymore in the understanding of all available test guidelines.

We don't know the degradation rate under the real test conditions, as the test protocols give no sufficient information about the light conditions. Therefore, we feel that the worst-case-reflection is appropriate at this stage.

Having in mind the facts, that none of the available tests for MDA were done under analytical control, the tests can only be accepted as range-finding tests, but not as a precise determination of the ecotoxicity. The two tests presented by Ciba-Geigy for *Brachydanio rerio* (1985a) and

Scenedesmus subspicatus (1985c) were indeed performed with analytical control, but from our point of view the analytical part of these tests is not valid as the substance concentration was sometimes higher at the end of the test than at the beginning.

Microorganisms

Photobacterium phosphoreum 30min-EC_{50} = 6.6 mg/l

(effect: inhibition, nominal concentration, 99% purity, Kaiser 1991)

Pseudomonas fluorescens 16 h-TGK ≥15.0 mg/l

(effect: inhibition of glucose degradation; Bringmann & Meinck 1964)

Escherichia coli 10 d-EC_0 ≥100.0 mg/l

(effect: growth, nominal concentration, purity not specified, Fujiwara 1981)

Activated sludge 3 h EC_{50} >100 mg/l

(effect: inhibition of respiration, nominal concentration, OECD 209, Bayer AG,1987)

Determination of $PNEC_{wwtp}$

For the determination of $PNEC_{wwtp}$, the test result with activated sludge (3 h-EC_{50} >100 mg/l) is used. The results with *Pseudomonas fluorescens* (TGK = NOEC = 15 mg/l) and with *Photobacterium phosphoreum* (EC_{50} = 6.6 mg/l) can not be used according to TGD and the test with *Escherichia coli* (10 d-EC_{50} ≥ 100.0 mg/l) is considered as less relevant.

With an assessment factor F = 100, the PNEC is calculated as

$PNEC_{wwtp}$ >/= 1 mg/l

Determination of $PNEC_{aqua}$ for the 4,4' MDA

For the 4,4'-MDA, results from acute tests with species from 3 trophic levels without valid analytical control are available. The lowest acute toxicity was recorded for the daphnid *Moina macrocopa* (24 h-EC_{50} = 2.3 mg/l). For the most sensitive species also a long-term study is available (*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 will be additionally used.

Therefore: $PNEC_{aqua}$ = 150 µg/l / 50 = 3 µg/l

The long term tests with *Moina macrocopa* is a semi-static one done with a renewing of the test solution every 48 hour, but without analytical control. Because of the photodegradation of MDA during the test time, the PNEC based on effective concentrations should be lower. However, it is ensured that daphnids are the most sensitive species, and the application of an assessment factor of 50 will cover this uncertainty. The determination of the PNEC based on the acute test on *Moina* and an assessment factor of 1000 would lead to a similar result (2.3 µg/l).

Determination of $PNEC_{sed}$

A determination of a PNEC sediment is not possible, because there are no data with sediment dwelling organisms available. The equilibrium partitioning method is not applicable due to the binding of MDA to the humic substances of the sediment (cf. 3.1.1.c). Sediment organisms will be exposed both to MDA dissolved in the porewater and to the reaction product of MDA with humic acids.

An investigation with other aniline derivatives indicates that the reaction product of anilines with humic acids could be bioavailable. Similar as MDA, 4-chloroaniline and 3,4-dichloroaniline form covalent bounds to the humic fraction of soils and sediments. In a plant-uptake test, radiolabelled chloroanilines were preincubated into soils until the covalent bounds had been formed. Then different plants were sowed and the radioacticity was measured. It was shown that radioactivity was taken up by the plants indicating that the complexes of the humic substances with aniline derivatives are bioavailable (Fuchsbichler, 1978 a,b). This point is elaborated more precisely in the RAR „3,4-dichloroaniline".

In single species tests and a microcosm experiment, an extraordinary high bioaccumulation of radiolabelled 3,4-dichloroaniline was found. The tests give strong indication that the reaction product of 3,4-dichloroaniline with humic acids is bioavailable. We expect that MDA has similar properties.

A reproduction test with sediment organisms with pre-incubated MDA is necessary to determine the toxicity to sediment organisms.

Available effects data for technical-grade MDA

For the technical product (technical-grade MDA 70 - phenylbase MDA 70), only test results based on nominal concentrations for algae are available.

Plants

Scenedesmus subspicatus	72 h-EC_{10}	= 2.4 mg/l
	72 h-EC_{50}	= 9.8 mg/l

(Effect: biomass, nominal concentration, Bayer AG, 1992b)

Scenedesmus subspicatus	72 h-EC_{10}	= 0.3 mg/l
	72 h-EC_{50}	= 11.0 mg/l

(Effect: growth rate, nominal concentration, Bayer AG, 1992b)

Determination of PNECaqua for the technical-grade MDA

For the technical-grade MDA only tests on algae are available. So, it is not possible to derive a special PNEC on the basis of this few data. Because there is no significant exposure of the polyamine compounds (cf. 3.1.1) the derivation of a PNEC for the technical grade MDA is not necessary.

3.2.2 Atmosphere

There are no data available.

3.2.3 Terrestrial compartment

For the 4,4'-MDA, valide results from the following tests are available:

Invertebrates

Eisenia fetida	14 d-LC_{50}	= 444.0 mg/kg dw soil
	14 d-NOEC	= 32.0 mg/kg dw soil

(effect: weight increase)

	14 d-NOEC	= 56 mg/kg dw soil

(effect: behavior and appearance, 99,5% purity, nominal concentrations, TNO 1992a).

Plants

Avena sativa

(>99.5% purity, nominal concentrations, TNO 1992 b)

(Effect: emergence)	17 d-NOEC	= 320.0 mg/kg dw soil
(Effect: growth)	14 d-EC_{50}	= 353.0 mg/kg dw soil
(Effect: growth)	14 d-NOEC	= 100.0 mg/kg dw soil
(Effect: survival, 14 d after germination)	14 d-NOEC	≥1000.0 mg/kg dw soil

Lactuca sativa

(>99.5% purity, nominal concentrations, TNO 1992 b)

(Effect: emergence)	17 d-NOEC	= 100.0 mg/kg dw soil
(Effect: growth)	14 d-EC_{50}	= 128.0 mg/kg dw soil
(Effect: growth)	14 d-NOEC	= 10.0 mg/kg dw soil
(Effect: survival, 14 d after germination)	14 d-NOEC	≥1 000.0 mg/kg dw soil

Determination of the $PNEC_{soil}$

For the 4,4'-MDA 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). As results from long-term tests are not available, the assessment factor is set at F = 1000.

$$PNEC_{soil} = 128 \text{ mg/kg} / 1000 = 128 \text{ µg/kg}$$

Applying the equilibrium partitioning approach (TGD, eq. 56), a $PNEC_{soil}$ of 370 µg/kg is calculated from a $PNEC_{aqua}$ of 3 µg/l. However, this approach is not appropriate for the MDA

assessment as the plants are exposed both to "free,, MDA in the porewater and the reaction product of MDA with humic acids (which is a different compound!). The last is assumed to be taken up by the plant (see above), but not considered by the model.

3.2.4 Non compartment specific effects relevant to the food chain

Vertebrates: (bird)

Agelaius phoeniceus LC_{50} = 148 mg/kg body weight
(Schafer et al. 1983)

As there are no indications of a bioaccumulation potential for MDA, an effect assessment for secondary poisoning is not required.

3.3 RISK CHARACTERISATION

3.3.1 Aquatic compartment

Surface water

The PEC/PNEC ratios for the MDA emissions during production for the sites emitting into rivers or river mouths are given in the following table (PNEC = 3 µg/l):

Table 3.10 PEC/PNEC ratios emitting into river or river mouths

Company	PEC_{local} [µg/l]	PEC / PNEC
Generic	69	23
A	$8.0 . 10^{-3}$	0.0027
B	$2.7 . 10^{-3}$	0.0009
C	0.40	0.13
E	0.11	0.04
F	0.088	0.029
H	0.23	0.077
I	0.02	0.0067

The PEC/PNEC ratios for the sites emitting into the sea are:

Table 3.11 PEC/PNEC ratios for the sites emitting into the sea

Company	PEC_{local} [µg/l]	PEC / PNEC
G	1.0	0.028
J	0.047	0.016
K	1.0	0.33
M	1.0	0.022

The PEC/PNEC ratios for the rivers polluted from several sites are:

Table 3.12 PEC/PNEC ratios for the rivers polluted from several sites

Sites	Σ Clocal [µg/l]	PEC/PNEC
A, E	0.12	0.04
F, H	0.32	0.11

The result is that the PEC/PNEC ratios for all sites are clearly below 1. Thus, no risk to aquatic organisms is expected.

Releases from use of MDI in polyurethane manufacturing are negligible and will not change the risk characterisation ratios (RCR) as shown in the Risk Assessment Report for MDI (Draft of 12-11-1999). It can be concluded that MDA amounts yielded by the hydrolysis of MDI will not lead to environmental hazard for aquatic organisms and will not influence the hazard due to production and use of MDA, if a hydrolysis rate of 2% is assumed.

Table 3.13 Risk characterisation ratios (RCR)

	RCR
Generic approach	23
Site specific approach, company C	0.13

During polyurethane manufacturing and the use of MDA as epoxy hardener, no significant releases are expected. The PEC/PNEC ratios are considered to be negligible.

Sewage treatment plants

The highest submitted wwtp effluent concentration is below 500 µg/l. Compared with the $PNEC_{wwtp}$ of 1 mg/l (cf. 3.2.1), a PEC/PNEC ratio of maximum 0.5 is derived. This value indicates that no hazard onto sewage sludge has to be expected.

Sediment

As no PNECsed could be estimated, a risk assessment for this sub-compartment is not possible. A test on sediment organisms (Lumbriculus variegatus) with pre-incubated MDA should be performed.

3.3.2 Atmosphere

As no significant releases into the atmosphere are expected, an assessment for this compartment is not necessary.

3.3.3 Terrestrial compartment

As no significant releases into soils are expected, an assessment for this compartment is not necessary.

3.3.4 Non compartment specific effects relevant to the food chain

Because of the low accumulation of MDA in fish via water, the exposure route fish - fish eating bird is likely to be not relevant. However, the reaction product of MDA with sediment organics accumulates in sediments and is probably bioavailable. A biomagnification via the route sediment - sediment dwelling organisms - fish or bird cannot be excluded.

Because of missing experimental data, this issue cannot be assessed.

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

4.1.1.1 General discussion

Approximately 98 - 99% of all 4,4'-methylene dianiline (MDA) produced is used in the chemical industry as an intermediate which is further processed to methylene diphenyl di-isocyanate (MDI).

Approximately 2% of MDA is employed as a chemical intermediate and as a cross-linking agent

- in plastics processing for high-performance polymers
- as a co-reactant for polyurethane elastomers, foams (used as insulating material for walls and roofs, for containers and tubing, or for filling of cavaties and as upholstering material for furniture, cars and mattresses) and special-purpose coatings, and for epoxy resins and two-component adhesives.

The use of MDA as a hardener is declining, since the development of substitutes is strengthened.

Further it is possible to use the raw material for processing azodyes; at present it does not correspond to the state of the art in Germany and in UK.

Azodyes in general could release the amine component unintentionally under special conditions (reductive cleavage). The import of azodyes to the EU-market from a Non-EU country cannot be excluded, as the notification of the new substance Cartasol Yellow shows (import of more than 10 tones/year). Azodyes could be used as dyes for paper, leather, writing inks and textiles. Quantitative information on the use of the substances are normally not available. The extent of decomposition under use conditions (e.g. dying) is assumed to be not significant. But 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.

On account of the physicochemical properties of the pure substance (solid, vapour pressure << 1 Pa), inhalative exposure to dust at the workplace during the handling of the substance in solid form (flakes, granules and crystalls) must be taken into consideration.

The occupational exposure limits (OELs) are in the Netherlands, Denmark, Belgium, Italy, Switzerland, Australia and USA (ACGIH) 0.8 mg/m^3, in Germany 0.1 mg/m^3 (TRK, technical based occupational exposure limit) and in the United Kingdom 0.08 mg/m^3 (ILO, 1994; BAuA, 1997; HSE, 1997).

In the Swedish Product Register (1995) two out of 36 products containing MDA are noted to be consumer products. No further information is given.

The Swedish "National Chemicals Inspectorate,, stated that in 1996 hardeners for paint containing 35-49% of MDA were not imported to Sweden. MDA could be used also in paints, but there is no information available indicating that such paints are offered in Europe.

4.1.1.2 Occupational exposure

4.1.1.2.1 Occupational exposure during production and further processing in the chemical industry

Production and further processing as a chemical intermediate

MDA is produced continuously at about 90 - 100°C in closed systems. The reaction product is a liquid mixture (technical grade) rich in methylene dianiline isomers which typically contains about 60% 4,4'-methylene dianiline (4,4'-MDA). The main by-products are other polynuclear amines together with smaller quantities of 2,4'-MDA and 2,2'-MDA. Pure 4,4'-MDA (approx. 99%) is recovered from this mixture in flake form by distillation. The liquid isomer mixture and also pure MDA are placed on the market; pure MDA is sold in flake or granulate form or as a prill (Hirzy, 1985; Layer, 1991; Fairhurst, 1993).

For the production of methylene di-isocyanate, mainly the liquid isomer mixture is employed, though pure MDA is used for particular applications.

MDA is further used in the production of dicyclohexyl methane-4-4'-di-isocyanate, which is of importance as a special component of polyurethane lacquers, (2K-lacquers, automobile and buildings, Baumann et al, 1997 a) and it is used as a cross-linking agent in the manufacture of high-performance polymers such as polyester imides, polyamide imides and polybismaleinimides. The latter are sold as resins (e.g. polyamide imides, bismaleinimides) with a free MDA content of 0.1 - 10% (APME 1995).

Inhalative and dermal exposure is possible during handling of the flakes e. g. sampling and analysis, filling and drumming, repair, maintenance and cleaning activities. In dependence on these activities, differing levels of exposure are to be expected. Dermal exposure is also possible during handling of the technical grade MDA and other mixtures.

In the state of knowledge of one german producer samples are taken in closed sample equipments with exhaustion. Pumps for MDA are leak-proof, as shut-off devices special values are used. As a rule MDA is transported through pipes directly to further processing. In very few cases tank trucks are loaded using gas displacement device.

All employees are supplied with work dress, safety shoes, protecting glasses. At some occupations e. g. coupling or decoupling of tanks, taking samples, repairing, chloroprene-gloves are worn. Chloroprene and other materials like rubber, PVC and other plastics are recommended by the producers, but there are no information about the suitability of these materials.

Measuring results

Several approved methods for measuring 4,4'-MDA in air in working areas are known. Here four methodes are described.

Determination limit for method 1 (sampling is carried out by adsorption on acid-treated silicagel, elution and diazotation followed by photometric determination) is 0.1 mg MDA/m^3 at 80 l air sampled, and 0.025 mg MDA/m^3 at 320 l air (in 8 hours).

Method 2 (sampling by adsorption on acid-treated filter and processing as described above) has a determination limit of 0.008 mg MDA/m^3 at 500 l air sampled.

In method 3 determination is carried out without derivatisation by liquid chromatography. The determination limit is also 0.008 mg/m^3 at 500 l air sampled.

For Method 4 absorption in 0.05 M sulphuric acid and gas chromatography with a nitrogen selective detector is used. Determination limit is 0.001 mg/m^3 for two hours (BG Chemie, 1997).

For the methods described, sampling was in accordance with the total dust definition. The methods 1 and 2 are not specific for 4,4'-MDA; aryl amines and aromatic isocyanates are determined also, phenol disturbes. If a selective method is needed the third and fourth one are recommended. The results of workplace measurements in the field of production and further processing in the chemical industry submitted by several companies are presented in the following table:

Table 4.1 Results of workplace measurements in the field of production and further processing in the chemical industry

Job category / activities	Company	Year of measurement	Number of samples	Range of measurement data [mg/m^3]	Geometric mean [mg/m^3]	95% Value [mg/m^3]	Duration and frequency
8h TWA							
Manufacture	M	'91-'94 '90 - '94	4 (p.s.*) 5 (f.p.m.*)	< 0.02[1)2)] < 0.01[1)2)]		no information available	no information available
Production /processing plant	N	1992			0.08	no information available	no information available
Production/non isolated to MDI	O	1993 - 1994	15	< 0.01		no information available	no information available
Production[3)]	P	1995	3	< 0.02[3)]		no information available	no information available
Production[3)]	Q(1)	1993- 1997	47	≤ 0.03[3)]		no information available	no information available
Plant operator and technicians[6)]	R(1)	?	58	0.002 - 0.083		no information available	no information available
Plant operator [6)] Senior operator[6)] Work-up operator[6)] Maintenance worker[6)] Process technicians[6)]	R(2)	?	65 52 20 5 5	<0.001-0.314 <0.001-0.118 <0.001-0.084 <0.001-0.024 <0.001- 0.003	0.021 0.012 0.011 0.011 0.0024	no information available	no information available
Manufacture MDA[6)]	R(3)	'89 - '90 '91 - '94	21 39	0 - 4.95 0 - < 0.04[4)]	0.43 0.002[4)]	no information available	no information available
Plant worker	R(4)	?	46	<0.0002 (det.limit)		no information available	no information available

Table 4.1 continued overleaf

Table 4.1 continued

Job category / activities	Company	Year of measurement	Number of samples	Range of measurement data [mg/m³]	Geometric mean [mg/m³]	95 % Value [mg/m³]	Duration and frequency
Production[3)]	S	1992 1995	8 9	analytical result[3)]; not used		no information available	no information available
Production[3)]	Q(2)			biolog. Monitoring[3)]; not used		no information available	no information available
Manufacture of MDA[6)]	U	1993 1994	10 3	<0.09 <0.025		no information available	no information available
	V	-	-	-	-	-	-
Reactor floor[6)]	W	'93 – '95	50 (f.p.m.)	< 0.001 – 0.179[1)2)]	0.029[1)2)]	no information available	no information available
	Z	-	-	-	-	-	-
MDA manufacture[5)] reactor operation, drumming liquid	X	'89 – '90	10 (p.s.)	nd – 0.003		no information available	no information available
Manufacture	Y	'81 – '93	19	< 0.005 - < 0.05[2)]	0.007[2)] (50%)	0.01[2)] (90%)	no information available
Pastillator floor[6)]	W	'93 – '95	36 (f.p.m.)	< 0.001 – 0.085[1)2)]	0.027[1)2)]	no information available	no information available
MDA packaging floor[6)]	W	'93 – '95	26 (f.p.m.)	< 0.001 – 0.08[1)2)]	0.016[1)2)]	no information available	no information available
Laboratory work	M	'90 – '94 '91 '94	9 (p.s.) 1 (p.s.) 3 (f.p.m.)	< 0.01 - 0.04[1)2)] 0.13[1)2)] < 0.01[1)2)]		no information available	no information available
QC laboratory[6)]	W	'93 – '95	4 (p.s.)	< 0.001[1)2)]		no information available	no information available
Residue drumming area[6)]	W	'93 – '95	4 (f.p.m.)	< 0.001[1)2)]		no information available	no information available
Filling/tank truck	M	'94	1 (p.s.)	< 0.01[1)2)]		no information available	no information available
Warehouse area[6)]	W	'93 – '95	3 (p.s.)	< 0.001[1)2)]		no information available	no information available
Bagging flake MDA[5)6)]	X	'89 – '90	3 (p.s.)	0.004 – 0.012	0.007	no information available	no information available

Table 4.1 continued overleaf

Table 4.1 continued

Job category / activities	Company	Year of measurement	Number of samples	Range of measurement data [mg/m³]	Geometric mean [mg/m³]	95 % Value [mg/m³]	Duration and frequency
Further processing[3)]	T	1990 - 1998	7	0.008 - 0.01[3)]		no information available	very short; not daily
Conversion to MDI	M	'90 - '94 '91 - '93	7 (p.s.) 3 (f.p.m.)	< 0.02[1)2)]< 0.01[1)2)]		no information available	no information available
MDI operator[6)]	R(2)		46	<0.001 - 0.52	0.027	no information available	no information available

nd= Not detected
p.s. = Personal sampling
f.p.m. = Fixed point measurement
[1)]Sampling was in accordance with the total dust definition; no information has been provided concerning the other measurements
[2)]Measurement of total aromatic amines
[3)]New measurements
[4)]The reduction in exposure (from a mean value of 0.434 mg/m³ to 0.002 mg/m³) can probably be attributed to modifications made to the technical ventilation systems
[5)]Data from literature (Fairhurst,1993)
[6)]Particulate MDA; for R(1), R(2) and R(3) unknown, but assumed

The measurement results which were submitted for inhalative exposure during the continuous manufacture and further processing of MDA as a chemical intermediate are to be regarded as valid. But only for a few results details regarding activity-related data on the duration and frequency of exposure, the 90th - or 95th -percentile of the measurement results as well as information on the activities of cleaning and maintenance and on the collective of exposed persons are submitted.

Up to now two companies had not submitted data or detailed information. Furthermore it is not clear, which company has submitted their data anonymous (see company R in the table above).

In the majority of cases, the measurement results are located below the technical occupational exposure limit (TRK) of 0.1 mg/m³ which at present is valid in the Federal Republic of Germany. But for most of the measurements detailed information are missing, especially the 90th - or 95th percentile, which is necessary to describe the reasonable worst case for a collective of measurement results. It is not possible to calculate it on the basis of the submitted data (see above).

As far as it is known 6 of 14 companies/sites produce the liquid isomer mixture containing app. 60% 4,4'-MDA, 5 companies/sites produce pure 4,4'-MDA (but only in one case it is mentioned by the company), for one company it is unknown, one company processed the pure substance in a molten form and two companies stopped their production in 1997. The measurement data are assigned to dust exposure if no information is available or if they are submitted anonymous and the exposure results exceed the detection limit (see R(1), R(2) and R(3)in the table above), because it is unlikely that the exposure to MDA-vapour was measured (vapour pressure <<1Pa).

At present four companies of six had submitted data for exposure to dust, two submitted measurement results (see above U,W) the other (see above Q, S) more general information. Additionally the measurement data of three companies (or sites) which had submitted their data anonymous are assigned to dust exposure. The corresponding results show large differences from <0.001 to 0.52 mg/m^3. Some of them show that efforts are made to reduce the exposure (e.g. from mean 0.434 in '89 - '90 to 0.002 mg/m^3 in '91 - '94) by technical means which may be a

result of the implementation of (lower) OELs. According to the information of one company the duration and frequency of further processing is very short and not daily which is regarded as a particular case. The high production volume gives rise to the assumption that a daily exposure over the full shift is prevailed during production and further processing.

Because the implementation of OELs could lead to the decreasing of exposure levels by improving the technical means, it has to be taken into account, that in the member states the OELs differ about a factor of ten (0.08 mg/m^3, 0.1 mg/m^3 to 0.8 mg/m^3) and that not every member state, where MDA is produced, has established one (see chap. 4.1.1.1).

Because of the circumstances mentioned above and the lack of information it is very difficult to fix one value as a reasonable worst case on the basis of the submitted data.

Production of preparations within the chemicals industry

For the manufacture of high-performance polymers such as speciality epoxies, polyester imides, polyamide imides and polybismaleinimides and for polyurethane foams and elastomers 4,4'-MDA is used as a curing agent. The imid formulations are sold as resins (e.g. polyamide imides, bismaleinimides) with a free MDA content of 0.1 - 10% (APME 1995). Furthermore curing formulations containing MDA together with other ingredients like solvents or accelarators etc. are placed on the market. They are produced in form of liquids, pastes and granules. Imid formulations with a content of free MDA between 4 - 9 % (APME 1995) are also produced in form of powders. With regard to this further processing in the area of the large-scale chemical industry it is assumed that, as a rule, closed systems are used and that partially open systems are covered and equipped with suitable exhaust ventilation systems.

Activities relevant to exposure are transfer, weighing, filling and drumming and cleaning and maintenance work. The drumming of powdery imid preparations has to be taken into account as an additional exposure scenario compared to the production of the substance (liquid, flakes). Because of the lack of workplace measurements and information for assessing the risks for inhalative exposure the estimation according to the EASE-model is used (see chap. 4.1.1.2.5).

Workplace measurements

Workplace measurements and information on the duration and frequency of exposure as well as on the collective of exposed persons are missing.

Dermal exposure within the chemical industry

As a protection against dermal exposure materials like rubber, PVC, other plastics and chloroprene are recommended by the producers without testing. The dermal exposure of the hands during manufacturing and further processing of 4,4'-MDA has been investigated by HSE in 1989 -'90 as a function of glove material (Fairhurst 1993). Besides of chloroprene, the study shows that materials like PVC gauntlets, PVC coated fabric, natural rubber heavy- and lightwise and polyethylene mitts do not provide complete protection. In the area of manufacturing after drumming off crude liquid MDA with PVC gauntlets during 91 min the MDA contamination on the cotton gloves underneath was 1.1 mg; the highest exposure after packing flakes with gloves of natural rubber was 0.54 mg (max. 216 min). It is not known, whether the contamination is a result of penetration or permeation through the outer gloves or a low standard of hygiene. Information about the suitability of materials like chloroprene and other plastics are not available. Other investigations show that without gloves higher levels (app 4.2 - 42 mg) were

reached (Cocker et al 1988 in BUA 1994; EPA 1985 in EPA 1992). Because occlusion of the substance underneath the gloves cannot be excluded, when unsuitable gloves are worn, the estimation according to the EASE-model is used for assessing the risks for dermal exposure (see chap. 4.1.1.2.3).

4.1.1.2.2 Occupational exposure in fields of application outside the chemical industry (industrial and skilled trade sectors)

4,4'-MDA is used as a curing agent in one-component preparations with resins such as speciality epoxies or polyester imides, polyamide imides and polybismaleinimides for high performance composites. These preparations are combined with a reinforcing fiber as for example for prepregs, molding compounds or reinforced film adhesives.

Furthermore epoxies and polyurethanes can be sold as one- or two-component systems. Two-component systems are generally mixed immediately before use with the liquid, pasty or granulated curing formulation containing MDA or with MDA in pure form, which is assumed to be more seldom (Hirzy, 1985).

Production of preparations in the industrial sector

The processing of formulations with 4,4'-MDA as a curing agent (e.g. imid resins formulations containing 0.1-10% MDA, formulations for curing epoxid resins 9 - 60% MDA and formulations for polyurethane curing 4 - 5% MDA) is principal possible in the large-scale chemical industry (see chap. 4.1.1.2.1) and also in formulating companies. For formulating companies in the industrial area the high standard of occupational hygiene cannot be assumed generally. It cannot be excluded that workplaces exist which are not adequate to the state of the art (e.g. inadequate local exhaust ventilation). Activities relevant to exposure are transfer, weighing, filling and drumming and cleaning and maintenance work. The drumming of powdery imid preparations has to be taken into account as an additional exposure scenario compared to the production of the other preparations (liquid, flakes).

Handling of preparations in the industrial sector

The differentiation between the scenarios is because of the use as ready-to use system or as one- respectively two-component systems and the form of the MDA-containing component .

One-component systems

One-component systems can be distinguished in ready-to-use systems (liquid or pasty) and systems which has to be prepared by mixing with water or solvents before use.

1. If it is a ready-to-use one-component system which is liquid or more or less pasty then only handling will be the right scenario (dermal exposure);

2. If the one-component system is in flake or granulated form then before handling mixing with water or solvents is necessary to prepare a ready-to-use formulation. Mixing may include the activities weighing and filling. During mixing inhalation exposure (low dust technique) and dermal exposure is considered; during handling only dermal exposure.

3. If the one-component system is in powdery form then before handling mixing with water or solvents is necessary to prepare a ready-to-use formulation. Mixing may include the activities

weighing and filling. During mixing inhalation exposure (dry manipulation) and dermal exposure is considered; during handling only dermal exposure.

Two-component systems

Two-component systems always have to be prepared by mixing the two-components together before use.

4. If it is a two-component system and both components are liquid or pasty then only dermal exposure is to be expected.

5. If it is a two-component system and the MDA-containing component is in flake or granulated form then during mixing which includes the activities weighing and filling inhalative (low dust technique) and dermal exposure has to be considered; during handling only dermal exposure.

6. If it is a two-component system and the MDA-containing component is in powdery form then during mixing which includes the activities weighing and filling inhalation (dry manipulation) and dermal exposure has to be considered; during handling only dermal exposure.

For epoxy systems the scenarios 1, 2 and 4, 5 are taken into account; for polyurethane systems the scenarios 4, 5; for imid polymers scenario 3. There is no information which gives rise to consider scenario 6.

Epoxy resins

Epoxy resins which are used with 4,4'-MDA as the hardener component have applications in many fields. These extend from the production of structured laminates for heat- or chemical-resistent pipes and containers to corresponding coatings (e.g. for concrete floors). These epoxy resins are sold as one- and two-component systems. Two-component systems are generally mixed immediately before use, and the curing formulations may be liquids, pastes or granules (containing MDA between 9 - 60 %, APME, 1995), or MDA in pure form, which is assumed to be more seldom (Hirzy, 1985).

Polyurethane foams and elastomer

4,4'-MDA is employed as a curing additive (preparation containing 4-5%; APME, 1995) for two-component high-performance polyurethane foams and elastomer systems based on aliphatic isocyanates (Hirzy, 1985). For one-component solvent free PU-lacquer systems masked polyamines are used together with masked NCO-prepolymeres. By the occurence of humidity the amine is released and react with the isocyanate to a high-molecular polyurethane-polyurea (Baumann und Muth, 1997, Goldschmidt et al., 1984, Biethan et al., 1979). With regard to a comprehensive publication about 1800 chemicals which are used in paints and lacquers, where MDA is not mentioned (Baumann und Muth, 1997), the use of 4,4'-MDA as a masked polyamine for lacquers seems to be not relevant.

High-performance imid polymers

Resins for high-performance polymers are used for example in the electrical industry, e.g. as high-temperature cable insulation (polyester imides, polyamide imides), and also in aircraft construction (polybismaleinimides) (Hirzy, 1985). The free MDA content is between 0.1 - 10 % (APME, 1995).

The application methods include both closed, fully automatic processes and also partially open manual processes depending on the purpose of application e. g. prepregging, hand lay up of prepreg, wet filament winding, resin transfer molding (for detailed descriptions see: Hirzy, 1985; SACMA, 1991). Inhalative exposure is possible particularly during mixing when the substance/formulation is handled openly in granulated, flake or powder form (filling activities). Specialised coating procedures (e.g. spray painting) are assumed to be more seldom. Dermal exposure is possible during mixing and also filling activities and when non-automated coating procedures (e.g. painting concrete floors) are in use. Because of the lack of workplace measurements and information for assessing the risks for inhalative exposure the estimation according to the EASE-model is used (see chap. 4.1.1.2.5).

According to one manufacturer one-way protective clothing and breathing mask are worn if open handling is necessary. To avoid skin contact gloves made of rubber, PVC and other plastics are recommended by the producers. There are no information about the test of suitability of the materials available.

Workplace measurements

Table 4.2 Workplace measurements

Job category / activities	Year of measurement	Number of samples	Range of measurement data [mg/m³]	Geometric mean [mg/m³]	95 % Value [mg/m³]	Duration and frequency
8h TWA						
Using flake MDA	1989 - 19990	3 (p.s.)	0.002 - 0.185[1)]	0.112[1)]		
Further processing of synthetic resin (in total)[2)]	1992-1997	68		<0.02 (to 1993)[6)] < 0.001 (50th-%)	0.02	
With LEV		34			0.02	
Without LEV		32			0.01	
Further processing[3)]		12	< 0.025			
PU-components spraying [4)]	1990	1	0.045			
Background	1990	3	0.0005 - 0.132			
Exposure shorter than shift length						
Sack emptying flake MDA (41 min)	1989 - 1990 1989 - 1990	2 (p.s.) 1 (p.s.)	1.76 / 2.07[1)] 0.01			41 min 65 min
Batchwise filling with powdery 4,4'-MDA	-	1	2.5[5)]	-		120 min
PU-components laminating (hand) [4)]	1990	-	< 0.01			

[1)]The author states that the technical ventilation systems were inadequate during two of these measurements (Fairhurst 1993)
[2)]Measurement data of the workers compensation funds (BG Chemie, 1997)
[3)]Measurement data in the further processing industry (TRK-Wert Begründung Nr.24, 1989)
[4)]Measurement data HSE (HSE 1995)
[5)]The workplace was not in accordance with the state of the art (TRK-Wert Begründung Nr.24, 1989)
[6)]Up to 1993 0.02 mg/m³ was the determination limit of the method; later it was improved to 0.001 mg/m³

For the non-chemical industries, especially for the further processing of synthetic resins (see the table above), the workers compensation funds have submitted actual 8h TWA values (BG Chemie, 1997). During further processing of epoxy and polyurethane resins and coatings for solder-masks the values were determined for the activities preparing and mixing of the components, glueing, spraying, pouring, pressing and painting of the mixtures. Two of the results were determined when powders are used; the corresponding exposure levels were below the limit of determination (<0.001 mg/m³).

In the scope of the implementation of TRK-values for 4,4'-MDA, results of workplace measurements are published also. In the area of further processing 12 shift average values are measured below the detection limit (0.025 mg/m^3). During batchwise filling of a reaction vessel with powdery 4,4'-MDA the value of 2.5 mg/m^3 (duration of exposure: 2h) was measured**.** At this time the workplace was not in accordance with the state of the art (TRK-Wert Begründung Nr.24, 1989). Comparable measurement results (n = 2) are published by Fairhurst during sack emptying flake MDA with inadequate LEV (Fairhurst, 1993).

Again detailed information are missing, especially for the handling of solids. In total 6 measurements are made of dust exposure. Some of the descriptions indicate, that also powders are used. Probably the flakes are pulverised before use (Hirzy, 1985) or imid preparations are used. It cannot be excluded, that the LEV may work insufficient as 3 of these measurements show (Fairhurst, 1993; TRK-Wert Begründung Nr.24, 1989). Because of the small number of measuring results, the highest measurement result of 2.5 mg/m^3 (duration of exposure: 2h), respectively 0.63 mg/m^3 (8h-TWA) is used for assessing the risks for inhalative exposure (see chap. 4.1.1.2.3 and 4.1.1.2.5).

In one case of using specialised coating procedures (spray painting, without LEV), the exposure to aerosols was found to be 0.045 mg/m³ with background concentrations between 0.0005 - 0.132 mg/m³ (HSE, 1995). It is not known, which analytical method is used. Two methods are not specific for 4,4'-MDA aryl amines and aromatic isocyanates are determined also and phenol disturbes (see chap.4.1.1.2.1). Because of the high background concentrations the measured exposure is not regarded as significant.

Dermal exposure in the industrial area

In various working areas (MDA manufacturing and further processing of liquid/putty-like formulation) HSE has investigated in 1989 - '90 the dermal exposure of the hands as a function of glove material for a defined time of exposure [Fairhurst, 1993]. The result is that the materials investigated do not provide complete protection. The absolute quantity of MDA which reaches the skin decreases if the gloves are regularly changed. The highest values within the gloves - approx. 8 and 5 mg MDA - were determined during handling liquid crude MDA to formulate putties [exposure duration: 90 and 42 min; 2 hands). During extrusion of the product without gloves, exposure was 2 000 mg (exposure duration: 110 min; 2 hands)]. It is not known, whether the contamination is a result of penetration or permeation through the outer gloves or a low standard of hygiene. Other investigations [Cocker et al 1988 in BUA, 1994] in the field of manufacture and processing without gloves amount measurement results of the dermal exposure levels in the range 5 -50 µg/cm² (no information on exposure duration or the form in which the substance was handled). If the total surface area of both hands is assumed to be 840 cm², (EPA 1985 in EPA 1992), the dermal exposure is thus calculated to be 4.2 - 42 mg. During the production of reinforced plastic pipes the dermal exposure was investigated by measuring 4,4'-MDA in hand

washing and on cotton gloves underneath protective gloves made of natural rubber on a cotton matrix (Hoogendoorn et al in 1995, The Netherlands, comments 1997). In dependence of the tasks different material strength was used. The measuring results for actual exposure on the cotton gloves underneath ranges from not detected to 3.3 mg and agree with the study of Fairhurst.

Handling of epoxy resins in the skilled trade sector

In the skilled trade sector, too, the substance is handled in open systems. In the buildingtrade, MDA is used as a hardener for two-component epoxy resins in special cases (e.g. coating concrete floors). It may be assumed that the material is mixed on site lasting app. 0.5 hours. Hardener formulations are sold in liquid, pasty and granulated forms (with an MDA content up to 60 %), and possibly also as pure MDA but this is assumed more seldom; the available documents do not indicate in what form the hardener is used in the buildingtrade. About the_fregrency of exposure no information is available. Not daily is assumed, more detailed assumptions whether it is every second or third day is not possible.

Inhalative exposure is possible particularly during mixing when the substance/formulation is handled openly in granulated and flake form (filling activities). Dermal exposure is also possible during mixing and filling activities and when non-automated coating procedures (e.g. painting concrete floors) are in use.

4.1.1.2.3 Estimation of the exposure according to the EASE model

Estimation of the inhalative exposure level performed in accordance with the EASE model produces the following results:

Inhalative exposure

Inhalative exposure to dust during manufacture and processing of flakes or granulates in the chemical industry and in the industrial area with local exhaust ventilation (LEV).

Input parameters: T = 20°C
low dust technique
LEV present

estimated exposure level: 0 - 1 [mg/m³].

Inhalative exposure to dust during drumming of powdery imid preparations in the chemical industry and in the industrial area with local exhaust ventilation (LEV).

Input parameters: T = 20°C
dry manipulation
LEV present

estimated exposure level: 2 - 5 mg/m³.

Considering the content of MDA in imid resins is max. 10%, the exposure level is estimated to

0.2 - 0.5 mg/m^3

Inhalative exposure to dust during processing of preparations in the industrial area and skilled trades without local exhaust ventilation (LEV)

Input parameters: T = 20°C
low dust technique
LEV absent

estimated exposure level: 0 - 5 [mg/m³].

Considering the content of MDA in curing formulations for epoxy resins is max. 60%, the exposure level is estimated to 0 - 3 mg/m^3 .

Considering the content of MDA in curing formulations for polyurethane resins is max. 5%, the exposure level is estimated to 0 - 0.3 mg/m^3.

Inhalative exposure to dust during drumming of powdery imid preparations in the industrial area without local exhaust ventilation (LEV).

Input parameters: T = 20°C
dry manipulation
LEV absent

estimated exposure level: 5 - 50 mg/m³.

Considering the content of MDA in imid resins is max. 10%, the exposure level is estimated to 0.5 - 5 mg/m^3

Dermal exposure

Dermal exposure during manufacture, formulation and handling in the chemical industry and the industrial sector without using gloves.

Input parameters: T = 20°C
closed system, which is breached
direct handling
intermittent

estimated exposure level: 0.1 - 1 [mg/cm^2/day].

Considering the content of MDA in crude liquid MDA is app. 60%, the exposure level is estimated to 0.06 - 0.6 mg/cm^2/day.

Considering the content of MDA in curing formulations for epoxy resins is max. 60%, the exposure level is estimated to 0.06 - 0.6 mg/cm^2/day.

considering the content of MDA in curing formulations for polyurethane resins is max. 5%, the exposure level is estimated to 0.005- 0.05 mg/cm^2/day

considering the content of MDA in imid resins is max. 10%, the exposure level is estimated to 0.01 - 0.1 mg/cm^2/day

Dermal exposure to dust during mixing and handling of formulations without using gloves.

Input parameters: T = 20°C
wide dispersive use
direct handling
intermittent

estimated exposure level: 1 - 5 [mg/cm^2/day].

Considering the content of MDA in formulations is max. 60%, the exposure level is estimated to 0.6 - 3 mg/cm^2/day.

Further exposure data are provided by the federal monitoring authorities. Data from literature (USA, Canada and Sweden) published between 1978 - 1986 are collected in the BUA report No. 132. They correspond to the available data for inhalative exposure (see Chap. 4.1.1.2.1 and 4.1.1.2.2).

4.1.1.2.4 Other exposure data

Further exposure data are provided by the federal monitoring authorities. Data from literature (USA, Canada and Sweden) published between 1978 - 1986 are collected in the BUA report No. 132. They correspond to the available data for inhalative exposure (see Chap. 4.1.1.2.1 and 4.1.1.2.2).

4.1.1.2.5 Integrated Assessment Summary

General

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. The use of MDA as a curing agent is declining, since the development of substitutes is strengthened. Further it is possible to use the raw material for processing azo dyes; at present it does not correspond to the state of the art in Germany and in the UK.

MDA is produced continuously as a liquid isomer mixture (technical grade) which typically contains about 60% 4,4'- MDA or as pure 4,4'-MDA placed on the market in flake or granulate form or as a prill (Hirzy, 1985; Layer, 1991; Fairhurst, 1993).

On account of the low vapour pressure of the pure substance (<<1 Pa) inhalative exposure at the workplace to MDA vapour is not relevant. Exposure to MDA in dust form is of primary concern here.

Production and further processing as a chemical intermediate in the chemicals industry

The measurement results which were submitted for inhalative exposure during the continuous manufacture and further processing of MDA as a chemical intermediate are to be regarded as valid. In the majority of cases, they are located below the technical occupational exposure limit (TRK) of 0.1 mg/m³ which at present is valid in the Federal Republic of Germany.

As far as it is known 6 of 14 companies/sites produce the liquid isomer mixture containing app. 60% 4,4'-MDA, 5 companies/sites produce pure 4,4'-MDA (but only in one case it is mentioned by the company), for one company it is unknown, one company processed the pure substance in a molted form and two companies stopped their production in 1997.

The measurement data are assigned to dust exposure if no further specific information about the form is available or if they are submitted anonymous and the exposure results exceed the detection limit (see R(1), R(2) and R(3) in the table in chap. 4.1.1.2.1), because it is unlikely that the exposure to MDA-vapour was measured (vapour pressure <<1Pa). The 90th - or 95th percentile of the collective of the measurement results is missing and cannot be calculated on the basis of the submitted data (see chap.4.1.1.2.1).

Therefore the highest measuring result of 0.52 mg/m^3 is used for assessing the risks for inhalative exposure to dust on the basis of the presented measuring data. It is in good agreement with the estimated value of 0 - 1 mg/m³ according to the EASE-model.

The high production volume gives rise to the assumption that a daily exposure over the full shift is prevailed during production and further processing.

Production of preparations within the chemical industry

For the manufacture of high-performance polymers such as speciality epoxies, imides and polyurethane foams and elastomers 4,4'-MDA is used as a curing agent. The imid formulations (free MDA content of 0.1 - 10% (APME 1995)) and curing formulations for epoxies and polyurethanes containing MDA (free MDA content of max. 60% (APME 1995)) together with other ingredients like solvents or accelarators etc. are placed on the market. They are produced in form of liquids, pastes and granules; imid formulations also in form of powders (APME 1995). With regard to this further processing in the area of the large-scale chemical industry it is assumed that, as a rule, closed systems are prevailed and that partially open systems are covered and equipped with suitable exhaust ventilation systems (see chap. 4.1.1.2.1).

For drumming of curing formulations (flakes, pastes or granules) the assessment of the risks for inhalative exposure to dust the exposure level is assumed to be lower than for the drumming of the pure substance during production.

The drumming of powdery imid preparations has to be taken into account as an additional exposure scenario compared to the production of the substance. Because of the lack of workplace measurements and information for assessing the risks for inhalative exposure the estimation according to the EASE-model is used (see chap. 4.1.1.2.4).

For drumming of powdery imid preparations the assessment of the risks for inhalative exposure to dust is estimated to 2-5 mg/m³ (EASE-model) respectively 0.2 - 0.5 mg/m³ (8h -TWA for MDA content of max. 10% for imid formulations). Assuming batch processing over 2 hours the daily exposure of 0.05 - 0.125 mg/m³ has to be taken for assessing the risk.

Dermal exposure in the chemical industry

In assessing the risks of dermal exposure, it is to be assumed that, in the chemical industry, MDA is manufactured and further processed primarily in closed systems.

For Personal Protective Equipment (PPE) several materials like chloroprene, rubber, PVC and other plastics are recommended by the producers without testing. The study by Fairhurst shows that materials like PVC, PVC coated fabric, natural rubber heavy- and lightwise and polyethylene mitts do not provide complete protection (Fairhurst 1993). About the suitability of the other materials (chloroprene and other plastics) no information are available.

The dermal exposure level for the handling of crude liquid MDA with PVC gauntlets was 1.1 mg (91 min); the highest exposure after packing flakes with gloves of natural rubber was 0.54 mg (max. 216 min; see chap. 4.1.1.2.1). It is not known, whether the contamination is a result of penetration or permeation through the outer gloves or a low standard of hygiene. Other investigations show that without gloves higher levels (app. 4.2 - 42 mg) were reached (Cocker et al 1988 in BUA 1994; EPA 1985 in EPA 1992).

The estimation of daily dermal exposure according to the EASE-model (without PPE) results in a dermal exposure range of 0.1-1 mg/cm^2/day. For the handling of the crude MDA the exposure is reduced to 0.06-0.6 mg/cm^2/day with respect to the percentage of 4,4'-MDA in the liquid (app. 60%). It is further assumed, that the use of gloves has a high acceptance within the chemical industry. Because occlusion of the substance underneath the gloves cannot be excluded, when unsuitable gloves are worn, the estimation according to the EASE-model is used (see chap. 4.1.1.2.3). For assessing the risks for daily dermal exposure (EASE: 0.1-1 mg/cm^2/day with regard to an exposed area of 420 cm^2 (palms of two hands) an exposure level of 42 - 420 mg/p/day respectively 25 - 252 mg/p/day is used.

For the drumming of the imid and curing formulations the daily dermal exposure estimated with the EASE-model (EASE: 0.1-1 mg/cm^2/day) with regard to an exposed area of 420 cm^2 (palms of two hands) and the percentage of 4,4'-MDA in the preparations is used. For the curing formulations for epoxies with max. 60% free MDA the resulting dermal exposure level is about 25 - 252 mg/p/day, for imid formulations with max. 10% free MDA it is about 4 - 42 mg/p/day and for the curing formulations for polyurethanes with max. 5% free MDA it is about 2 - 21 mg/p/day.

Use of 4,4'-MDA in other sectors (industrial and skilled trade)

pasty MDA (typical content: 60 % or less) as a curing agent for various plastics systems. Furthermore curing formulations with MDA as ingredient for epoxies and polyurethanes and imid formulations containing MDA are placed on the market. Depending on the purpose of application e.g. manufacturing of formulations, prepregging, hand lay up of prepreg, wet filament winding, resin transfer molding both fully automatic processes and also partially open manual processes are used (for detailed descriptions see: Hirzy, 1985; SACMA, 1991).

The dermal exposure of the hands has been investigated during further processing of 4,4'-MDA (Fairhurst, 1993; Hoogendoorn et al, 1995 in: The Netherlands, comments 1997). The measurement results are in the range from 0.01 to 8 mg MDA when protective gloves are worn, and from 6 - 2 000 mg MDA (n = 2) when the hands are unprotected. With regard to the studies, the use of gloves is common, but for some tasks the gloves seems not to be suitable. Additionally several materials are recommended by the producers without testing. As far as it is known, occlusion of the substance underneath the gloves cannot be excluded, when they are taken off for a special task or when unsuitable gloves are worn (see chap. 4.1.1.2.3). The estimation of daily dermal exposure according to the EASE-model (without PPE) is used (see below).

Production of formulations in the industrial area

Curing formulations for epoxies and polyurethanes and imid formulations are assumed to be produced also in companies in the industrial area. For epoxies and polyurethanes low dust techniques prevailed, imid formulations are also produced as powders.

Again detailed information is missing, especially for the handling of solids. In total 6 measurements are made of dust exposure. Some of the descriptions indicate, that powders are also used for the production of preparations. Probably the flakes are pulverised before the process (Hirzy, 1985).

For formulating companies in this area the high standard of occupational hygiene cannot be assumed generally. It cannot be excluded that workplaces exist which are not adequate to the state of the art (e.g. inadequate local exhaust ventilation) or that the LEV works insufficient as 3 of these measurements show (Fairhurst, 1993; TRK-Wert Begründung Nr.24, 1989).

Assuming batch processing with an exposure duration shorter than shift length (approx. 2 h) daily exposures to MDA dust are to be expected when storage bins or reaction vessels are filled or when formulations are drummed.

For assessing the risks for inhalative exposure on the basis of the presented measuring data the highest measuring result (for batchwise filling of a reactor with powdery MDA) of 2.5 mg/m^3 for 2h is used to calculate an 8 h - TWA of 0.6 mg/m^3.

For the drumming of formulations no measurement data are available. Therefore the estimation according to the EASE-model is used. For the drumming of curing formulations for epoxies (containing 60% MDA) and polyurethanes (containing 5% MDA) the correponding estimated exposure levels are 0 - 3 mg/m^3 and 0 - 0.08 mg/m^3 and 0.5 -5 mg/m^3 for the drumming of powdery imid formulations (containing max. 10% MDA). With respect to the shortened exposure time of 2 h (batch processing) the following exposure levels of 0 - 0.75 mg/m^3 (for epoxies), 0 - 0.08 mg/m^3(for polyurethanes) and 0.1 - 1.25 mg/m^3 for imid formulations are used for the assessment of the risks.

For the dermal exposure of 0.1- 1 mg/cm^2/day (EASE, dust) and 0.06 -0.6 mg/cm^2/day (EASE, liquid containing app.60% MDA) with regard to an exposed area of 420 cm^2 (palms of two hands) an exposure level of 42 - 420 mg/p/day respectively of 25 - 250 mg/p/day is used.

With regard to an exposed area of 420 cm^2 (palms of two hands) for the drumming of curing formulations for epoxies (containing 60 % MDA) and polyurethanes (containing 5% MDA) and imid formulations (containing max. 10 % MDA) an exposure level of 25 - 252 mg/p/day, 2 - 21 mg/p/day, respectively 4 - 42 mg/p/day is used.

Handling in the industrial area

Epoxy resins

Epoxy resins which are used with 4,4'-MDA as the hardener component (preparations containing 9-60% 4,4'-MDA; APME, 1995) have applications in many fields. These extend from the production of structured laminates for heat- or chemical-resistent pipes and containers to corresponding coatings (e.g. for concrete floors). These epoxy resins are sold as one- and two-

component systems. Two-component systems (curing preparations, resin) are generally mixed immediately before use (ratio 1:1), and the hardener formulations may be liquid, pastes or granules, or MDA in pure form, which is assumed to be more seldom (Hirzy, 1985). For assessing the risks for inhalative exposure during mixing of the (dusty) formulation containing MDA (9-60%) with the epoxy resin the estimation according to the EASE-model of 0 - 0.2 mg/m^3 (EASE 0 - 3 mg/m^3; exposure duration 0.5h) is used and for dermal exposure 0.06 - 0.6 mg/cm^2/day (EASE) with regard to an exposed area of 840 cm^2 (two hands) an exposure level of 50 - 504 mg/p/day. The exposure during handling only is assessed to be lower (proportion of mixture 1:1): inhalative exposure is assumed to be very low; the dermal exposure of 0.03 - 0.3 mg/cm^2/day (EASE) results with regard to an exposed area of 840 cm^2 (two hands) in an exposure level of 25 - 252 mg/p/day.

Polyurethane foams and elastomer systems

4,4'-MDA is employed as a curing agent (formulation containing 4-5%; APME, 1995) for high-performance polyurethane (PU) foams and elastomer systems based on aliphatic icocyanates (Hirzy, 1985). For use of the two-component systems (curing formulation, polyurethane) the components are mixed in a ratio of 1:1 in general immediately before use. The curing formulations may be liquid, pastes or granules, or MDA in pure form, which is assumed to be more seldom.

For assessing the risks for inhalative exposure during mixing of the (dusty) formulation containing MDA (4-5%) the estimation according to the EASE-model of 0 - 0.02 mg/m^3 (EASE 0 - 0.3 mg/m^3, exposure duration of 0.5h) is used and for dermal exposure 0.005 - 0.05 mg/cm^2/day (EASE) with regard to an exposed area of 840 cm^2 (two hands) an exposure level of 4.2 - 42 mg/p/day. The exposure during handling only is assessed to be lower: inhalative exposure is assumed to be very low; the dermal exposure of 0.003 - 0.03 mg/cm^2/day (EASE) results with regard to an exposed area of 840 cm^2 (two hands) in an exposure level of 2.5 - 25 mg/p/day.

For one-component solvent free PU-lacquer systems masked polyamines are used together with masked NCO-prepolymeres. By the occurence of humidity the amine is released and react with the isocyanate to a high-molecular polyurethane-polyurea (Baumann und Muth, 1997, Goldschmidt et al., 1984, Biethan et al., 1979). With regard to a comprehensive publication about 1800 chemicals which are used in paints and lacquers, where MDA is not mentioned (Baumann und Muth, 1997), specialised coating procedures (e.g. spray painting) which use 4,4'-MDA are assumed to be more seldom.

In one case of using spray painting (without LEV), the exposure to aerosols was found to be 0.045 mg/m³ with background concentrations between 0.0005 - 0.132 mg/m³ (HSE, 1995). It is not known, which analytical method is used. Three methods are not specific for 4,4'-MDA aryl amines and aromatic isocyanates are determined also and phenol disturbes (see chap.4.1.1.2.1). Because of the high background concentrations the measured exposure is not regarded as significant.

High-performance imid polymers

Resins for high-performance polymers are used for example in the electrical industry, e.g. as high-temperature cable insulation (polyester imides, polyamide imides), and also in aircraft construction (polybismaleinimides) (Hirzy, 1985). The free MDA content is between 0.1 - 10% (APME, 1995).

The application methods include both closed, fully automatic processes and also partially open manual processes depending on the purpose of application e.g. prepregging, hand lay up of prepreg, wet filament winding, resin transfer molding (for detailed descriptions see: Hirzy, 1985; SACMA, 1991).

The handling of powdery imid preparations has to be taken into account as an additional exposure scenario.

For assessing the risks for inhalative exposure during handling of the powdery imid preparation the estimation according to the EASE-model is used: Considering a content of max. 10% MDA an exposure level of 0.2 - 0.5 mg/m³ (EASE) results.

With regard to a shortened exposure duration of 0.5 h an exposure level of 0.03 - 0.3 mg/m³ and for dermal exposure (0.01 - 0.1 mg/cm^2/day (EASE)) with regard to an exposed area of 840 cm^2 (two hands) an exposure level of 8.4 - 84 mg/p/day is used.

Handling of epoxy resins in the skilled trade

In the skilled trade sector, too, the substance is handled in open systems. In the buildingtrade, MDA is used as a hardener for epoxy resins in special cases (e.g. coating concrete floors). It may be assumed that the material is mixed on site lasting app. 0.5 hours. Hardener formulations are sold in liquid, pasty and solid forms (with an MDA content up to 60%), and possibly also as pure MDA but this is assumed more seldom; the available documents do not indicate in what form the hardener is used in the buildingtrade. About the frequency of exposure no information is available. Not daily is assumed, more detailed assumptions whether it is every second or third day is not possible.

For assessing the risks during mixing of the components using pure 4,4'-MDA the estimation according to the EASE-model of max. 0.2 mg/m^3 (8h-TWA;0.5h) is used and for dermal exposure 0.6 - 3 mg/cm^2/day (EASE) with regard to an exposed area of 840 cm^2 (palms of two hands) an exposure level of 504 - 2520 mg/p/day is used.

The exposure levels during handling only is assessed to be lower (proportion of mixture 1:1): inhalative exposure is assumed to be low; the dermal exposure of 0.3 - 1.5 mg/cm^2/day (EASE) results with regard to an exposed area of 840 cm^2 (two hands) in an exposure level of 252 - 1260 mg/p/day.

Summary of exposure data relevant for workplace risk assessment

The following table shows the exposure data of MDA which are relevant for occupational risk assessment.

Table 4.3 Relevant exposure data of MDA for occupational risk assessment

Exposure scenario	Form of exposure	Activity	Duration and frequency	Inhalative exposure shift average		Dermal exposure			
				Level of exposure [mg/m^3]	Method	Level of exposure [mg/cm^2/day]	exposed area [cm^2]	shift average [mg/p/day]	Method
Chemical industry									
Manufacturing and further processing as a chemical intermediate (methylene diphenyl di-isocyanate, MDI)	flakes, granules (dust)	drumming transfer cleaning main-tenance	shift length, daily	0.52	workplace measurements	0.1 - 1	420 (palms of two hands)	42 - 420	EASE
	liquid (vapour) (approx. 60 %)		shift length, daily	very low	exp. judg.	0.06 - 0.6		25 - 252	EASE
Production of preparations									
Imid preparations max. 10 % MDA	powder (dust)	drumming transfer cleaning main-tenance	batch processing 2 hours/daily	0.05 - 0.125	EASE	0.01 - 0.1	420 (palms of two hands)	4 - 42	EASE
Curing formulations max. 60 % MDA	flakes; granules (dust)		batch processing 2 hours/daily	lower than above	exp. judg.	0.06 - 0.6		25 - 252	EASE
Max. 5 % MDA			batch processing 2 hours/daily	lower than above	exp. judge.	0.005 - 0.05		2 - 21	EASE

Table 4.3 continued overleaf

Table 4.3 continued

Exposure scenario	Form of exposure	Activity	Duration and frequency	Inhalative exposure shift average		Dermal exposure			
				Level of exposure [mg/m^3]	Method	Level of exposure [mg/cm^2/day]	exposed area [cm^2]	shift average [mg/p/day]	Method
Industrial area									
Manufacturing of formulations using powdery MDA	powder (dust)	transfer weighing filling drumming	batch processing 2 hours/daily	0.6 (workplace was not at the state of the art)	workplace measurements	0.1 - 1	420 (palms of two hands)	42 - 420	EASE
Formulating putties using liquid MDA (approx. 60 %)	liquid MDA			very low	exp. judg.	0.06 - 0.6		25 - 252	EASE
Production of preparations									
Imid preparations max. 10 % MDA	powder (dust)	drumming transfer cleaning main-tenance	batch processing 2 hours/daily	0.1 - 1.25	EASE	0.01 - 0.1	420 (palms of two hands)	4 - 42	EASE
Curing formulations max. 60 % MDA	flakes; granules (dust)		batch processing 2 hours/daily	0 - 0.75	EASE.	0.06 - 0.6		25 - 252	EASE
max. 5 % MDA				0 - 0.08		0.005 - 0.05		2 - 21	EASE
Mixing curing formulations (max. 60% MDA) with resin for epoxies	flakes, granules (dust)	transfer weighing filling	short-term (0.5h), daily	0 - 0.2 (without LEV)	EASE	0.06 - 0.6	840 (two hands	50 - 504	EASE

Table 4.3 continued overleaf

Table 4.3 continued

Exposure scenario	Form of exposure	Activity	Duration and frequency	Inhalative exposure shift average		Dermal exposure			
				Level of exposure [mg/m^3]	Method	Level of exposure [mg/cm^2/day]	exposed area [cm^2]	shift average [mg/p/day]	Method
	liquids	handling	short-term (0.5 h), daily	very low	exp. judg.	0.06 - 0.6		50 - 504	EASE
Handling of formulations containing MDA and epoxid resins (4.5 - 30 %)			shift length,daily	very low	exp. judg.	0.03 - 0.3		25 - 252	EASE
Mixing curing formulations (max. 5 % MDA) with resin for polyurethanes	flakes, granules (dust)	transfer weighing filling	short-term (0.5h), daily	0 - 0.02 (without LEV)	EASE	0.005 - 0.05	840 (two hands)	4.2 - 42	EASE
Handling of formulations containing MDA and polyurethane (2 - 3 %)	liquid, pastes	handling	shift length,daily	very low	exp. judg.	0.003 - 0.03		2.5 - 25	EASE
Handling formulations containing MDA (0.1 - 10 %) and imid resins	powder	weighing filling	short-term (0.5h), daily	0.03 - 0.3	EASE	0.01 - 0.1	840 (two hands)	8.4 - 84	EASE
	paste	handling	shift length,daily	very low	exp. judg	0.01 - 0.1		8.4 - 84	EASE
Skilled trade									
Mixing of formulations containing MDA (9 - 60 %) with epoxid resins	flakes, granules(dust)	transfer weighing filling drumming	short-term (0.5h), not daily*	0 - 0.2 (without LEV	EASE	0.6 - 3	840 (two hands)	504 - 2 520	EASE
Handling of formulations containing MDA and epoxid resins (4 - 30 %)			duration and frequency not known assumed : not daily*	very low	exp. judg.	0.3 - 1.5	840 (two hands	252 - 1 260	EASE

*Information about frequency of exposure not available

4.1.1.3 Consumer exposure

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.

There is no information about MDA in consumer products, hence consumer exposure seems not to exist.

However, ATSDR (1996) reports an exposure to trace amounts of MDA through medical devices like polyurethane cushioning or epoxy-containing products.

Polyurethane is widely used in such medical devices as potting materials used in plasma separators and artificial dialyzers. Polyurethane in these materials contains methylene diphenyldiisocyanate, from which a release of 4,4'-methylenedianiline has been reported due to sterilization by gamma irradiation. Autoclave sterilization did not promote MDA formation (Shintani and Nakamura, 1991). However, no quantitative conclusion can be derived from this paper because of limited information regarding experimental conditions (e.g. amount of samples on a weight basis, extraction temperature, kind of extraction device). Furthermore, the interpretation of experimental data is unclear. Some findings reported in the paper may indicate an effect caused by the solvent methanol, used in this experiments. A correlation is observed between radiation dose and measured MDA by a second-order equation when using the methanol extraction. Thus a methanolic reesterification resulting in the liberation of MDA cannot be excluded. Although unresolved questions remain when weighting the findings; nevertheless for uremic patients or patients who receive frequent blood transfusions using devices being sterilized by gamma-irradiation a potential exposure cannot be excluded at present.

The Food and Drug Administration (FDA) reports that the level of exposure to MDA through food, food additives, and food packaging is virtually zero (ATSDR, 1996). It is also noted that consumers may be exposed to very minor amounts/traces of MDA via drinking water (cf. 4.1.1.4).

There are information available, that 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.

4.1.1.4 Indirect exposure via the environment

Based on the environmental concentrations in the different compartments, the indirect exposure to humans via the environment through food, drinking water and air is estimated.

On the local scale, the human intake is calculated on the basis of the exposure in the vicinity of the greatest point source which is emitting into a river (site C, cf. 3.1.2.2). The sites emitting into the sea are not considered here.

On the regional scale, the average intake due to exposure via the regional background concentration (cf. 3.1.5) is estimated.

The calculation according to the TGD model (Appendix I and II) is:

Table 4.4 Calculation according to the TGD model

	local	regional
PEC_{water} [µg/l]	0.4	0.01
PEC_{air} [g/m3]	0	$4.6 \cdot 0^{-21}$
PEC_{soil} [g/kg]	0	$3.3 \cdot 10^{-14}$
$PEC_{groundwater}$ [g/l]	0	$2.3 \cdot 10^{-16}$
$DOSE_{tot}$ [$mg_{chem}.kg_{bw}$-1.d-1]	**$2.1 \cdot 10^{-5}$**	**$5.4 \cdot 10^{-7}$**
$DOSE_{drw}$	$1.1 \cdot 10^{-5}$	$2.9 \cdot 10^{-7}$
$DOSE_{fish}$	$9.2 \cdot 10^{-6}$	$2.5 \cdot 10^{-7}$
$DOSE_{stem}$	0	$6.2 \cdot 10^{-14}$
$DOSE_{root}$	0	$1.8 \cdot 10^{-15}$
$DOSE_{meat}$	$9.2 \cdot 10^{-11}$	$2.3 \cdot 10^{-12}$
$DOSE_{milk}$	$1.4 \cdot 10^{-9}$	$3.5 \cdot 10^{-11}$
$DOSE_{air}$	0	$9.8 \cdot 10^{-19}$

The main contribution to the intake at both local and regional exposure are the $DOSE_{drw}$ and the $DOSE_{fish}$ with fractions of about 55% and 45%, respectively, to the total daily dose.

4.1.1.5 (Combined exposure)

4.1.2 Effects assessment: Hazard identification and Dose (concentration) - response (effect) assessment

4.1.2.1 Toxico-kinetics, metabolism and distribution

The solid substance MDA has no practically measurable vapour pressure. Therefore, inhalative exposure can be anticipated only as dust particles. Water solubility (1.0-1.25 g/l) at 20°C and partition coefficient (log P_{ow}) of 1.59 indicate good bioavailability of the substance.

Animal data

MDA is absorbed via skin as well as from the gastrointestinal tract.

To investigate the percutaneous absorption of MDA Hotchkiss et al. (1993) used full-thickness rat and human skin in vitro. In this study MDA was topically applied (17.7 - 40.6 µg/cm² in ethanol) to unoccluded skin, using a flow-through diffusion cell. After 72 hours the absorption into the receptor fluid reached 6.1 ± 2.0% for rat skin and 13.0 ± 4.3% for human skin related to applied dose. When the skin was occluded, the absorption of MDA was significantly enhanced reaching approx. 13.3% and 33% for rat and human skin, respectively. At the end of each experiment, considerable residual material remained with the skin (about 23-58%).

El-Hawari et al. (1986) performed studies in male rats, guinea pigs and monkeys treated topically with a low (2 mg/kg bw) or high (20 mg/kg bw) dose of 14C-MDA. In rats, 43% and 10% of the low dose was recovered in urine and feces during a 96 hours period; 2% remained in tissues and skin washing removed 25% of dose. The remainder (26%) was recovered by skin extraction and solubilisation. The percentage of dose absorbed decreased by increasing the dose, but the total amount absorbed (approx. 0.225 mg/rat) was similar after both doses. In guinea pigs, 10% and 18% of the low dose was excreted in urine and feces; 1% was recovered in tissue, 41% in the skin wash and 29% from the application area. The percent of dose absorbed decreased following the high dose, but the amounts absorbed (in mg/animal) doubled (El-Hawari et al. 1986).

The disposition of MDA was also examined following i.v. administration by the same authors (El-Hawari et al., 1986). In rats, 67% and 31% of the low dose (2 mg/kg bw) was recovered in urine and feces by 96 h after dosing. In monkeys, the radioactivity occurred primarily in the urine (85%) by 168 h after dosing (2 mg/kg bw). In guinea pigs, however, 35% and 57% of the dose were eliminated in urine and feces, respectively, during 96 hours.

Morgott (1984) studied the in vivo mass balance of 14C-MDA in rats and rabbits given a single i.p. dose of the compound. Four male rats, and a male rabbit of each acetylator phenotype were administered 30 mg/kg and 50 mg/kg of 14C-MDA, respectively. The excretion of radioactivity into the urine and feces was followed daily for 4 days. Since the compound was administered by the intraperitoneal route, the amount of fecal radioactivity provided an indication of biliary excretion. The results show that both species excrete a majority of the radioactivity within two days. In the rat, the main route of excretion is the feces (55.8%) compared to urine (35.0%); whereas the rabbit, regardless of phenotype, excretes about 80% of the radiolabel in the urine.

The total recovery of radioactivity from the rat and slow acetylator rabbit is about 10% less than the recovery from the fast acetylator rabbit. This difference in recovery between fast and slow acetylating rabbits is associated with the greater fecal excretion by the fast acetylator rabbit. The residual radioactivity in the organs tends to localize in the liver, kidney, spleen and thyroid at both 24 and 96 hours.

The relationship between "free" and conjugated 14C-MDA metabolites excreted in the urine after the administration of a single i.p. dose to the rat (30 mg/kg) and rabbit (50 mg/kg) is shown in **Table 4.5** (Morgott, 1984).

Table 4.5 Fractionation of the radioactive metabolites excreted in the urine after i.p. administration of 14C-MDA to rats and rabbits

	Relative Percentage of Radioactivity in the Urine (%)		
Fraction	**Rat (n=4)**	**Slow Acetylator**	**Fast Acetylator**
		Rabbit (n=1)	**Rabbit (n=1)**
Free	60.4 ± 7.2	69.8	50.1
N-Glucuronides	3.8 ± 0.8	13.9	25.8
O-Glucuronides	1.7 ± 0.5	0.2	2.4
O-Sulfates	1.2 ± 0.4	0.1	0.3
Acid Labile	2.5 ± 0.9	0.9	2.5
Total	69.7 ± 6.4	84.9	81.1

Renal excretion of MDA and its metabolites dominates in rats (after i.v. administration) and monkeys (El Hawari et al., 1986) and rabbits (Morgott, 1984). However, after i.p. administration of MDA Morgott (1984) reported for rats the excretion via the feces as main way.

In a further in vivo study with oral application of MDA to Sprague-Dawley rats (50 mg/kg bw) N-acetyl-MDA has been shown being the major metabolite (Tanaka et al., 1985). Minor amounts of N,N-diacetyl-MDA and free MDA were also detected in the urine.

Upon a single i.p. administration of MDA to Sprague-Dawley rats (30 mg/kg bw) at least 17 urinary metabolites were found (Morgott, 1984). Mainly, the following acetylated metabolites have been identified: N-acetyl-MDA, N,N-diacetyl-MDA, N,N-diacetyl-3-hydroxy-MDA, N-acetyl-4,4'-diaminobenzophenone, and N,N-diacetyl-4,4'-diamino-benzhydrol.

In vitro metabolism of MDA was investigated using rabbit liver microsomes (Kajbaf et al., 1992). The following three metabolites were detected: azo-MDA, azoxy-MDA, and nitroso-MDA (4-nitroso-4'-aminodiphenylmethane). The azo and azoxy compounds were produced enzymatically, whereas the nitroso compound may have been formed via a non-enzymatic process. The hydroxylamine of MDA could not been detected in this study. However, its initial formation has to be supposed as prerequisite for the formation of the dimeric MDA metabolites azo- and azoxy-MDA.

Although differences in the quantitative aspects of metabolism remains unelucidated, the in vivo biotransformation pathways of MDA involve N-acetylation reactions as well as an oxidation of the central C-atom and conjugation to glucuronides and sulfates.

Binding to macromolecules

24 hours after a single oral or i.p. administration of MDA a dose dependent increase of hemoglobin-adducts could be detected in the rat (Farmer & Bailey, 1989; Bailey et al., 1990). Predominately the monoacetylated MDA seems to react with hemoglobin. In contrast to these results, Neumann et al. (1993) who investigated the binding of MDA to hemoglobin after a single oral administration found more hemoglobin-adducts derived from the parent compound

than from the monoacetylated metabolite. In an insufficiently reported study DNA-adducts in the rat liver after a single i.p. injection of 40 mg MDA/kg b.w. were described (Endo & Hara, 1991).

More recently Schütze et al. (1996) reported the formation of DNA adducts after i.p. application of 5.6 and 116.5 µmol radiolabelled MDA/kg bw to male Wistar rats (corresponding to 1.1 and 23 mg/kg bw, respectively). The covalent binding index (CBI = µmol of adduct per mol of DNA/mmol of chemical applied per kg bw) of 1.05 and 2.3 was determined.

The ability of MDA to bind to hemoglobin and liver-DNA was confirmed in a further study (Ciba-Geigy, 1996). After a single i.p. injection of 0.2, 2 and 20 mg MDA/kg bw a dose-dependent increase of Hb- and DNA-adducts was observed. The amount of adducts ranged from 1 ng adduct/g DNA at a dose of 0.2 mg/kg bw to 56 ng adducts/g DNA at 20 mg/kg bw. Expressed in ng adduct/g macromolecule the amount of Hb adducts was ca. 10 times higher than the binding to the liver DNA. The DNA and Hb-adduct levels were persistent up to at least for 6 days.

Human data

From experience in the workplace and reports concerning consequences of an oral intake, for example consumption of MDA-contaminated bread, the absorption of MDA after inhalation, skin contact, and swallowing in humans have been observed, too. In the urine of exposed workers a renal excretion was demonstrated by determination of MDA and N-Acetyl-MDA, while the metabolized MDA dominates. About 13% of 33 mg MDA (0.5% in petrolatum) applied for 48 hours onto the back skin during patch testing were recovered in the urine within 57 hours. With the work-up procedure of the urine samples MDA and acetylated MDA could be detected (Brunmark et al., 1992). The biological half-time of excretion of these metabolites in urine can be estimated from levels in end-of-shift and next morning pre-shift urine samples to be between 9 and 14 hours.

Excretion of these metabolites occurs fastest when exposure is via inhalation, dermal absorption will result in slower excretion (Cokker et al., 1994). This results from a cross sectional study in which exposure to MDA was assessed in 45 UK factories. Urine samples were collected from 411 workers engaged in various activities. 91% of postshift urine samples and 88% of preshift samples had less than 50 nmol total MDA/mmol creatinine. Some evidence was obtained which showed that when exposure to MDA was through inhalation (as solid material or contaminated dust), postshift urine samples had higher MDA concentrations than samples taken preshift the next day. When exposure was most likely to be through the dermal route, urine samples taken preshift next day tended to have higher MDA concentrations than urine samples collected immediately postshift on the day of exposure. Much slower excretion has been observed in workers with relative high exposures to MDA via the skin, where half lives of approximately 48 hours were seen (Smith et al. 1990). Dermal absorption might here have been the rate limiting step in this instance.

Robert et al. (1995) have investigated the formation of stable urinary metabolites in post-shift urine from 63 workers exposed to MDA. MDA, N-acetyl-MDA (MAMDA) and N,N'-diacetyl-MDA (DAMDA) were determined in non-hydrolyzed urine samples, and that of total MDA on urine samples after alkaline hydrolysis. Their relative concentrations (arithmetic means) were found to be in the following order: total MDA >MAMDA >MDA >DAMDA. While MAMDA represented more than 50% of total MDA, MDA and DAMDA were lower than 15% and 3% respectively. Acetylation of MDA, described as a possible way of detoxication, is confirmed to be an important metabolization route in humans, essentially through the monoacetylated

metabolite. However, the individual ratio MAMDA/total MDA was found to vary widely (roughly from 0% to 100%). The half-life was found to be between 9 and 14 hours.

In a further study by the same authors (Robert et al., 1996) the exposure to MDA was assessed in workers in 10 French firms by measuring urinary MDA excretion levels. Analysis of 368 postshift urine samples collected from 133 workers reveals that urinary excretion of MDA is much higher in workers handling flaked MDA than in those handling MDA in solution (44% and 8% of values, respectively, in excess of 50 µg/l). The mean rates were 140 µg/l for the four factories using flaked MDA and 13 µg/l for the six factories using liquid formulations, with values ranging from 58 to 197 µg/l and from <2 to 33 µg/l respectively.

Brunmark et al. (1995) exposed five healthy volunteers dermally for 1 h to 0.75-2.25 µmol MDA dissolved in isopropanol, by use of a patch-test technique. Determination of MDA remaining in the patch units after exposure showed that a median of 28% (range 25-29%) was absorbed. After hydrolyzing MDA has been determined in plasma with an initial peak and a decline after removing the patch. MDA was also detected in hydrolyzed urine. The maximum rate of MDA excretion in urine was found 6-11 hours after the onset of exposure. Within two subjects studied at three doses, the urinary excretion was proportional to the exposure. The elimination half-lives in plasma and urine had medians at 13 and 7 hours, respectively. In eight out of nine exposures, the elimination half-life was longer in plasma than in urine. Slow acetylation seemed to be associated with short elimination half-life in urine. The median of total MDA amount excreted in urine during 48 hours, was 33 nmol for the five subjects exposed to 0.75 µmol, which corresponds to roughly 16% (range 2%-26%) of the absorbed dose.

Biological monitoring

In addition to the analysis of urine samples for MDA and acetylated metabolites, the ability of MDA to bind to hemoglobin is used for biological monitoring (Bailey et al., 1990; Greim & Lehnert, 1994). Both methods give a useful estimate of the internal dose of MDA absorbed via all routes of exposure. Determination of the hemoglobin-adducts has the advantage over monitoring MDA excretion in the urine because not only the current exposure but repeated exposures dated back can be determined.

After occupational contact with MDA concentrations below 100 µg MDA/m³ a dose-dependent increase of MDA in urine and the erythrocytic Hb adduct has been observed (Greim & Lehnert, 1995). The data show a good correlation between the MDA excretion in urine and the Hb adducts in erythrocytes. However, there is no linear correlation between the air values and the biological values.

Schuetze et al. (1995) published the results of biomonitored workers exposed to low levels of MDA. Adducts and metabolites were analyzed by gas chromatography-mass spectrometry after hydrolysis, extraction and derivatization. Hb adducts of MDA were detected in 31 out of the 33 MDA workers and both MDA and N-acetyl-MDA (AcMDA) were found in 20 of these individuals. In the urine of workers exposed to MDA both MDA and AcMDA were found in all samples, with the exception of five where only MDA was detected. Acid hydrolysis of the urine samples yielded an approximately 3-fold higher concentration of MDA than the sum of MDA and AcMDA found after base hydrolysis. MDA but not AcMDA found in urine and in Hb correlate well, except for three outliers. In one worker the Hb adduct level of MDA was very low compared to the urine levels. Two workers had very high levels of MDA as Hb adducts but very low levels as urine metabolites. The former case indicates that the workers were recently exposed

to higher levels of MDA. The latter case suggests a relatively low recent exposure. The air levels of MDA, monitored using personal air monitors, were below the detection limit. Thus, this study shows the limited value of monitoring air concentration and supports the need for biological monitoring.

Conclusion

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.

4.1.2.2 Acute toxicity

Animal data

Most of the animal tests on acute toxicity are not performed with pure MDA but with technical products containing MDA or with test substances not precisely defined. The tests performed with pure MDA demonstrate the substance to be harmful or clearely toxic depending on the animal species tested: mice, guinea pigs, and rabbits exhibit moderate toxic effects after oral application of MDA (Fairhurst et al., 1993). The oral LD50 of MDA for rats is found in the range of 350-450 mg/kg body weight (Bayer, 1974, and BASF, 1975). Damage to the liver and kidneys has been reported to be the most prominent toxic effect occurring at doses of 100 mg/kg and above.

The acute hepatotoxicity of orally administered MDA was characterized in rats, indicating dose- and time-related toxicity classed as multifocal, cholangiolitic hepatitis, the lesions of which are distributed in portal and midzonal regions of liver lobules. Male Sprague-Dawley rats were fasted for 24 hours before and after receiving several doses within 25-225 mg/kg body weight (2 ml/kg volume each). At 24 hours after treatment the common bile duct was cannulated, and bile was collected for 30 min. The rats were then exsanguined and blood collected. Oral administration of the substance caused a dose-dependent change in all markers of liver injury: The threshold for toxicity was between 25 and 75 mg/kg substance. Methylene dianiline caused concomitant changes in all markers of liver injury measured, including serum ALT, bile flow, serum bilirubin concentration, GGT activity, and liver weight. Liver sections from animals that received a dose of 100 mg/kg had multifocal lesions consisting of hepatocellular necrosis with hemorrhage and moderate neutrophil infiltration. The necrosis involved segments of periportal hepatocytes but did not surround portal tracts. Frequently, the parenchymal insult extended into the midzonal regions of hepatic lobules. The lesions associated with the portal triad consisted of bile neutrophil infiltration. A segmental necrotizing vasculitis of the portal vein was also evident. The earliest change identified with the hepatotoxicity of methylene dianiline was bile ductular necrosis, and histologic markers of liver injury continued to increase in severity over the course of 16 hours. Histologic analysis of livers from animals receiving corn oil vehicle demonstrated normal hepatic histology with no apparent lesions (Bailie et al., 1993).

Cats and dogs appear to be more sensitive than rats to the effects of single oral exposure to MDA. In briefly reported studies, 1/3 cats died after oral application of 25 mg/kg body weight and 1/3 dogs died after application of 50 mg/kg body weight MDA. Liver and kidney damage was noted at 10 mg/kg and above, and doses of 25-100 mg/kg produced blindness due to retinal atrophy in cats (BASF AG, 1961).

The inhalative LC_{50} for rats is demonstrated to exceed the highest possible concentration of MDA in air at room temperature: no mortalities were caused by a 4-hour single dose of 0.837 mg/l applied to 18 rats, exposing only the snouts and nostrils to a dust containing 66% particles at <7 micron. The rats showed exophthalmus, tremors, curved hunched body position, and ruffled fur, but recovered within 2 days (CIBA-GEIGY, 1976). In an inhalation risk test 3 rats were subjected to an atmosphere saturated with MDA by heating a bath of the compound to 200°C; all rats survived, showing moderate congestion of lungs and testes at necropsy (Dow Chemical Company, 1954a).

Dermal application of 2500 mg/kg body weight of a 50% solution of MDA in water caused no mortalities and no clinical signs in 20 rats. But 1000 mg/kg of a 50% solution of MDA in dimethylsulfoxide killed 5/10 female rats within 7 days, demonstrating apathy, hyperchromodacryorrhea, and jaundice as clinical signs (BASF AG, 1976).

Human data

The most notable instance of MDA poisoning was the so called „Epping Jaundice“, in which 84 people living in the Epping area, England, in 1965 suffered ill effects caused by eating bread baked with a flour contaminated by MDA (Kopelman et al. 1966a, 1966b). From analysis of the MDA content of bread samples it has been estimated that the dose of MDA received by these individuals was about 3 mg/kg (Fairhurst et al., 1993).

Symptoms appeared within hours to a few days of eating the bread; they were somewhat variable, but in most cases comprised upper abdominal pain, followed by aches and jaundice. Serum clinical chemistry measurements indicated elevated levels of bilirubin, alkaline phosphatase and aspartate aminotransferase. Liver biopsy revealed damage to the parenchyma and the biliary tree. In the early stages the characteristic lesion was inflammation, which progressed later to centrilobular cholestasis and hepatocellular necrosis and degeneration. There were no fatalities, all patients recovering within a period of several weeks.

Between 1966 and 1972 acute febrile illness associated with jaundice and rash developed in 12 young male workers who added powdered MDA to an epoxy resin formulation in a hot roller mill. Experience before and after the provision of respiratory protection equipment suggested that percutaneous absorption was the primary route of exposure in these cases. A further case was also reported: an employee of another company contracted to pulverize the flake form of MDA. Hepatitis developed within 3 days of commencing this type of work. In all these cases the subjects appeared to make a complete recovery and returned to work within 10 weeks of the onset of symptoms. When re-examined 9 months to 5.5 years later, all were apparently in good health (McGill and Motto, 1974).

In another case report of accidental drinking of an unknown quantity of a solution of MDA in potassium carbonate and butyrolactone (Roy et al., 1985), myocardial effects (ECG chances, bradycardia, hypotension) were indicated. Furthermore, jaundice with elevated serum

aminotransferase and bilirubin levels, haematuria and glycosuria were reported. The particular, persistent retinal damage in the eyes were also noted.

A further acute oral intoxication with MDA is reported by Tillmann et al. (1997). Six participants of a technoparty (1 female, 5 males, ages 17-25) showed severe colicky abdominal pain and subsequently developed symptoms of hepatotoxicity after ingestion of an alcoholic beverage spiked erroneously with MDA instead of methylendioxyamphetamine. All of them showed similar clinical symptoms, with an identical time course. Acute jaundice developed within 2 days after ingestion. Enzymes indicating cholestasis increased steadily over 7 days and reached peak values of 800 U/l (AP) and 380 U/l (GGT), whereas transaminases remained moderately elevated. Between days 5 and 7, all patients became febrile for one day, their body temperatures rising up to 40°C. There was no evidence for hemolysis or an infectious hepatitis. Toxicological analysis revealed the presence of MDA at a concentration of 130 mg/l in one of two urine extracts examined.

An Australian journal reports the case of 6 workmen engaged in laying an epoxy resin based floor: Four of these men developed an acute hepatic illness after a single exposure, in two of them recurring on re-exposure to MDA a few months later. Again they were most severely affected with nausea, myalgia, pain in the chest and abdomen, and showed dark urine. Liver function tests gave grossly abnormal results. One of these man, when examined after 14 months, and after a further 4 months, still complained of a variety of symptoms, and his liver was palpable (Bastian, 1984). In a further case report on absorption of MDA through the skin of workers, exhibition and severity of jaundice was said to be definitely related to the degree of exposure: There were 11 cases of jaundice within the same factory, exposure ranging from 1 day to 3 weeks with skin absorption as major route of entry into the body (Dunn and Guirguis, 1979).

In a last case a young man suffered an acute exposure to MDA dust with oral, dermal, and inhalative absorption of the substance due to an air filter malfunction: The next morning he had severe supraumbilical pain, and proritic macular rash encircling both forearms up to sleeve level. He exhibited jaundice and electrocardiogram abnormalities suggesting myocardial injury, both effects resulting from the MDA exposure. After 3 months the clinical asymptomatic patient still gave ECG evidence of myocardial residua, and after 1 year the ECG was normal (Brooks et al., 1979).

Conclusion

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 in humans.

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 LC_{50} for rats 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, liver and kidney damage and blindness due to retinal atrophy being the most severe effects.

On the basis of these acute toxicity data MDA is classified as “toxic”, risk phrases R39/23/24/25

4.1.2.3 Irritation

Animal data

No oedema and no (International Isocyanate Institute, unpublishhed report 1978a) or only slight (Industrial BIO-TEST Laboratories, unpublished report 1973) erythema reactions were observed on intact rabbit skin up to 48 hours after patch removal following a 24-hour application of 500 mg moistened MDA under occlusion. Little enhancement of the reaction was seen with application to abraded skin.

Only a mild eye reaction was observed in rabbits following instillation of 100 mg MDA into the conjunctival sac. The effects reversed within 3-7 days after instillation of the substance (Industrial Biotest Laboratories, unpublished report 1973; International Isocyanate Institute, unpublished report 1978a).

Human data

Data on local irritating effects to skin and eyes of humans are not available.

Conclusion

Human data on local irritation 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 irritation pro-perties.

4.1.2.4 Corrosivity

Animal data

MDA has proven to exhibit no corrosive effects on skin and eyes of rabbits (Industrial BIO-Test Laboratories, unpublished report 1973; International Isocyanate Institute, unpublished reports 1978b).

Human data

Data on corrosive effects to skin and eyes of humans are not available.

Conclusion

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. According to EU legislation, MDA is not to be classified because of local corrosive properties.

4.1.2.5 Sensitisation

Animal data

The potential of MDA to produce delayed contact hypersensitivity in guinea pig was evaluated with the Guinea Pig Maximisation Test. The study was performed with 15 animals per group and

using a 5% concentration at each induction phase and a 2% concentration at challenge, 3/15 (20%, mild) of the test group animals showed a skin reaction to MDA at challenge.

The test concentrations used were selected on the basis of the systemic toxicity of MDA (Thorgeirsson, 1978). Results from a guinea pig skin hypersensitization test, a slightly modified version of the Landsteiner-Draize technique, were considered to be positive on the basis of the increase of size and redness around the site of the injections in the test group. In this non validated test a total of 10 intradermal injections were made during the induction phase followed by one intradermal injection two weeks later during challenge. The concentration was 0.1% MDA in polyethyleneglycol. Ten animals were used in each the treated and control group (Dunn, 1978).

A further study has been conducted using a "repeated insult" technique, a modification of the Sterner technique involving nine topical applications of 1% MDA in Dowanol 50B during the induction phase and of a "challenge"-dose. When tested on the skin of guinea pigs using a "repeated insult" technique, MDA did not cause a sensitization reaction in any of the nine test animals (Dow Chemical Company, 1954b).

Human data

There is convincing evidence that MDA can cause skin sensitization in humans. A considerable number of individuals have been shown to exhibit a positive skin reaction on challenge with MDA in skin sensitization tests, including reaction to cross-sensitizing groups (para-group sensitivity).

From 8247 patients tested in the years from 1975 to 1984 in standard patch test showed 7.1-15% contact allergy to MDA (Gailhofer and Ludvan, 1987).

In an other study Gailhofer and Ludvan, (1989) examined the significance of positive patch test reactions to 0.5% MDA. Data of 202 MDA-positive patients concerning age, sex and profession, type, localisaton and duration of eczema and combined allergens were evaluated. The results were compared with those of 3397 consecutive, unselected, contact dermatitis patients with negative reactions to MDA. Van Joost et al. (1987) reported a case of skin reaction induced by MDA in a man who cleaned a gutter in a chemical plant which contained MDA. He developed an extensive red, itchy, papular, and vesicular eruption, with a toxic/allergic appearance involving the face, neck and wrists. A broad spectrum of reactions was obtained, apparently based on cross-sensitizing groups (para-group sensitivity). All test concentrations of MDA revealed a positive reaction. Emmet (1976) reported a case of two women employed in a small polyurethane moulding plant who developed extensive pruritic, papular, and/or vesicular eruption on face and neck, when moulding polyurethan plastic. Patch tests gave positive reactions to prepolymers based on methylene bis (4-cyclohexylisocyanate), and also to MDA which was used as a catalyst.

Patch testing indicated that a large number of patients with contact dermatitis were sensitized to MDA. Primary contact dermatitis due to hair cosmetics was diagnosed in 52 from a total of 8230 patients with eczematous dermatitis. Positive patch tests were obtained in 34 cases, of which 15 were positiv patch-tested with MDA. The remaining 18 cases were considered as likely instances of contact irritation (Angelini et al., 1985).

Of 2490 patients tested, 212 gave a positive result to an MDA patch test, and 130 of these were also positive to p-phenylenediamine (Romaguera et al., 1981). In another investigation revealed a high incidence of sensitization with several common contact allergens, after standard patch tests.

When 362 patients with hand dermatitis were patch-tested with MDA, 17 gave positive reaction to the substance (Agrup, 1968).

From 445 patients with contact dermatitis gave 13 (2.9%) a positive reaction to MDA (De Agostini et al., 1987). In a joint study MDA was tested at six European clinics. A total of 2772 patients were patch-tested with 1% MDA in white petrolatum. 136 patients (4.9%) showed positive reactions (Breit, 1969).

In 1988, 576 consecutive patients of the Allergology Center in Italy were tested with the standard series: 22 (3.8%) positive patch-test results to MDA were noted. MDA was the fourth most common allergen after nickel, cobalt and potassium dichromate (Massone et al., 1990). 4140 patients from eight skin hospitals were patch tested. A sensitization was found in 47% of the people tested. 3.3% of 4140 patients with contact dermatitis gave positive patch tests with MDA (Schnuch et al., 1993).

There is a single case report of a worker handling an MDA-containing insulating material who developed an apparent skin photosensitivity to MDA, observed during diagnostic photopatchtesting. A 39-year-old telephone service installer, skin type IV, who works outdoors climbing telephone poles, developed an erythematous, pruritic dermatitis. This occurred on his uncovered arms and forearms, but not on his hands which were covered by gloves, in the summer month, and cleared when he was not working. Phototesting revealed a decreased minimal erythema dose, and no abnormal reaction or erythema to UVA. Photopatch tests were positive for MDA (Le Vine, 1983).

Conclusion

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-reactions to para-groups. Based on human data MDA is already classified as "sensitizing" and labeled with R 43 (may cause sensitization by skin contact).

4.1.2.6 Repeated dose toxicity

Animal data

Oral route

In a subchronic study which was accepted as valid (validity restricted by missing ophthalmo-logy examination). MDA (>99%) was administered in the drinking water for 3 months to 80 male rats and 80 female rats (strain: Tif:RAlf (SPF)) at doses of 0, 80, 400, and 800 ppm (equivalent to approximately 7.5, 23 and 31 mg/kg bw/d in males and 8, 22 and 32 mg/kg bw/d in females) (Ciba-Geigy, 1982). 20 out of 80 animals of each sex and each group were used for a 4-week recovery period. Laboratory investigations were carried out in 10 rats of each sex and group after completion of the treatment and after recovery period. An autopsy was done on 20 animals at the end of the test period and on 10 animals after recovery. One high dose female was sacrificed after the 53rd day of treatment with trembling and in a emaciated condition. Rats receiving 400 and 800 ppm MDA showed depressed food consumption, water consumption and body weight gain in males and females during the test period and at the end of the treatment. Water und food uptake normalised during recovery, whereas body weight did not recover in the recovery period.

No clinical signs were observed in the low dose groups. Anemia was seen in males and females of the mid and high dose groups at the end of treatment and after recovery. The number of RBC was decreased, the concentrations of hemoglobin and hematokrit were reduced, in response to this MCV, MCH and the number of reticulocytes were elevated. In high dose animals, the number of leukocytes were higher than in control groups, the relative amount of neutrophils increased in high dose males and females at the end of treatment and in males of the mid and high dose groups of the recovery groups. High dose females had lower percentages of lymphocytes at the end of the test period. The prothrombin time was prolonged in high dose males and females of the high dose group. Methemoglobin levels were not determined in this study.

Elevated serum concentrations of alkaline phosphatase, ALAT, ASAT, urea, bilirubin, cholesterol were observed in males and females of the mid and high dose groups at the end of the test period. After recovery the concentrations of alkaline phosphatase, ASAT (males only) and urea remained still elevated. Total proteins had higher concentrations in males of the mid and high dose groups at the end of treatment and afterwords decreased at the end of recovery in males and females of the mid and high dose groups. Levels of potassium were decreased in mid and high dose males at the end of test period and increased in mid and high dose females after recovery. No treatment-related changes were observed in urinalysis.

Corresponding to the lower body weight in males and females of the mid and high dose group the absolute weights of several organs were lower than controls at the end of treatment and recovery influencing also the relative organ body or brain ratios.

Rats treated with 800 ppm developed a hyperplasia of small biliary ducts with initial fibrosis in the peripheral parts of the liver lobules, a hypertrophy of the thyroid follicular epithelial cells and diffuse hyperplasia of the glandular structures with marked colloid depletion. At the end of the recovery period the liver lesions persisted and the thyroid stimulation was much less pronounced. Only 3/10 males and 2/10 females showed slight stimulation of the follicular epithelium. Rats receiving 400 ppm MDA displayed similar histopathological changes of a less severe nature. After recovery liver lesions persisted, but no thyroid changes were noted.

One male rat of the high dose group and one male and one female of the mid dose groups showed a focal nodular hyperplasia of the thyroid.

In the 80 ppm group no liver lesions were noted, but a slight stimulation of the follicular epithelium in the thyroids was observed in 2/20 males and 2/20 females.

Whereas nephrocalcinosis was evident in all females of treatment and control groups, mineralisation was seen in all males of the mid dose group and in 21 of 30 males of the high dose groups. One male of the 80 ppm group and none of the control males showed kidney mineralisation.

A NOAEL could not be derived from this study. The LOAEL (due to the thyroid lesions observed) is 80 ppm (equiv. to 7.5 mg/kg bw/d in male rats and 8 mg/kg bw/d in female rats).

Another study was performed in B6C3F1 mice and F344/N rats receiving MDA as the dihydrochloride in drinking water for 14 days resp. 90 days (NTP, 1983). In the 14-day study five rats/sex/group received 0, 200, 400, 800, 1600, and 3200 ppm (equivalent to approx. 0, 17.6, 32.8, 36.5, 78.4, 89.2 in male rats, and 0, 16.6, 33.2, 51.2, 80, 128 mg/kg bw/d in female rats, calculated on an assumed water uptake of 100 g/kg bw/d, taking into account the drastical reduce

of water consume up to 72% in males and 60% in females). Five mice/sex/group received the same MDA concentrations in the drinking water (equivalent to approx. 0, 31.8, 77.6, 135.6, 170.4, 100.8 mg/kg bw/d in male mice, and 0, 29.7, 57, 102, 132, 100.8 mg/kg bw/d in female mice, calculated on an assumed water uptake of 150 g/kg bw/d, taking into account the reduced water consume up to 79% in both sexes). Water consumption was lowered in all dosed rat groups and in male mice that received 1600 ppm or more and in female mice at 800 ppm or higher. Mean body weight gain was depressed dose-related in all rat groups and in mice that received 800 ppm or more. In some rats receiving 1600 or 3200 ppm, crater-like foci with black content in the cardiac part of the stomach were noted. No premature deaths occurred in rats. Survival was reduced in some mice at 800 ppm or higher, all mice died at 3200 ppm. No compound-related lesions were identified in mice at necropsy. Hematology, clinical biochemistry and histopathological examinations were not performed in any species. A NOAEL was not determined in the rat study, whereas in mice the NOAEL was 400 ppm (equiv. to 77.6 mg/kg bw/d in males, resp. 57 mg/kg bw/d in females).

In the 90-day studies 10 mice/sex/group were treated with 0, 25, 50, 100, 200, and 400 ppm (equiv. to approx. 0, 2.5, 5.7, 11.4, 26.5, 54.9 mg/kg bw/d for male mice, 0, 3.5, 7.6, 14.4, 25.9, 52 mg/kg bw/d for female mice) and 10 rats/sex/group received 0, 50, 100, 200, 400, and 800 ppm (equiv. to approx. 0, 3.8, 7.1, 13.2, 25.7, 38.7 mg/kg bw/d in male rats and 0, 3.7, 7.1, 12.7, 20.4, 44.4 mg/kg bw/d in female rats). This study did not include parameters of hematology and clinical biochemistry, but full histopathological examination of control animals and high dose animals was done. Liver, pituitary and thyroid of rats receiving 400 ppm, and liver and thyroid of rats receiving 200 ppm were also examined histologically. No animal died. The mean final body weight was depressed in male rats receiving 800 ppm and in female rats receiving 400 ppm. Water consumption was depressed 10% or more in both sexes of rats receiving 200 ppm MDA or more. In a dose-related fashion in rats getting 400 or 800 ppm bile duct hyperplasia and an adenomatous goiter was observed. Some rats receiving 400 ppm and one male rate in the 800 ppm group developed thyroid follicular hyperplasia.

In all male rats and 5/9 female rats getting 800 ppm a pituitary basophil hypertrophy was found. In mice, mean body weight was depressed in males (200 ppm) and in females (400 ppm). Water consumption of dosed male mice was greater than that in controls and in female mice it was comparable to controls. Bile duct hyperplasia was found in 5/10 male mice and in 4/10 female mice that received 400 ppm. Adenomatous goiters less severe than that observed in high dose rats were observed in one high dose male and female mouse. The NOAEL in both studies was identified to be 100 ppm (equivalent to 11.4 mg/kg bw/d in male mice and 14.4 mg/kg bw/d in female mice, the NOAEL in rats was 7.1 mg/kg bw/d in males and 7.5 mg/kg bw/d in females).

In a 14-day study (BASF 1977a), 10 male and female Sprague-Dawley rats were treated by gavage with 0,25 mg and 50 mg/kg bw/d of MDA on 5 days/week. Anemia with decreased numbers of red blood cells and reduced levels of hemoglobin and hematokrit and increased numbers of leukocytes were registered in high dose males and females. In rats of this dose group clinical chemistry revealed an increase of serum enzymes (ALAT, alkaline phosphatase), total proteins (males only), total lipids and total bilirubin. Levels of calcium increased and anorganic phosphorus levels were decreased. Low dose animals had only lower values of total lipids and increased concentrations of alkaline phosphatases. High dose males and females showed elevated organ weights (abs/rel) of the liver, kidneys, spleen and thyroid. Mean liver weight was also increased in 25 mg-females.

Urinalysis yielded effects in females of both dose groups. Isolated renal cells and cylinder in the urinary sediment were evident. Histopathology showed dose related mild-moderate lesions in both dose groups consisting in proliferation of bile ducts with initial fibrosis and inflammatory reactions of the liver, enlargement of the spleen due to extramedullary hematopoiesis, hyperplasia of of the thyroid epithelium. Minimal renal tubular cell desquamation was evident in the kidneys of 3 control males, 4 males and 1 female at 25 mg/kg and 6 males and 1 female at 50 mg/kg. The low dose of 25 mg/kg represented the LOAEL of this study, a NOAEL was not derived.

The livers of male Wistar rats fed in groups of 3-8 animals/dose with a diet containing 0 or 1000 ppm MDA (≅70 mg/kg bw/d) for 8 weeks (plus recovery of 8, 16, 24, 32 weeks), 16-weeks (plus recovery of 8, 16, and 24 weeks), 24 weeks (with recovery of 8 and 16-weeks), 32-weeks (plus 8 weeks of recovery) or 40 weeks (without recovery) were examined at the end of the treatment and recovery periods (Fukushima et al., 1979). A proliferation of bile ducts, oval cell infiltration, fibrosis and hepatocellular necrosis of the livers were seen. The hepatic parenchym was replaced by proliferating bile ducts and portal cirrhosis developed. The severity of the lesions gradually increased with the treatment periods and regressed with prolongation of the observation time, but did not achieve complete reversibility.

Histopathology revealed a periportal proliferation of bile ducts, oval cell infiltration, focal necrosis and fatty change of hepatocytes and fibrosis. Liver lesions showed a gradual increase from mild severity after 8 weeks of treatment to marked severity with longer treatment duration, the lesions were most prominent at the end of the treatment duration and showed regression during recovery time. At 40 weeks of treatment, the hepatic parenchyme was replaced by proliferating bile ducts and portal cirrhosis. The activity of ASAT was increased in rats at study termination at weeks 8, and 16, levels were normalized within one week of recovery. Only at the end of 8 weeks of treatment higher activities of ALAT and alkaline phosphatase were seen. Increased levels of gamma-glutamic transpeptidase was observed at the end of all treatment periods, levels showed a tendency to normalization during recovery.

MDA-related toxic effects in the liver and thyroid were also seen in 2-year studies on F344 rats and B6C3F1 mice (NTP, 1983, see Table in 4.1.2.8). Rats and mice treated with 150 and 300 ppm MDA in drinking water (equivalent to 9 and 16 mg/kg bw/d for male rats and 10 and 19 mg/kg bw/d for female rats, 25 and 57 mg/kg bw/d for male mice and 19 and 43 mg/kg bw/d for female mice) showed increased incidences of nonneoplastic liver changes.

Nonneoplastic lesions observed at the end of treatment including unspecified dilatation (males only), fatty metamorphosis and focal cellular change were observed in rats of each dose groups (without a clear dose relationship). Liver cell degeneration was evident in most male mice of both dose groups and in 7/50 high dose females. An increase of cystic and hyperplastic follicular cell changes were seen in the thyroid of the rats, follicular cell hyperplasia occurred in mice. In both species thyroid effects were evident with a slightly elevated frequency in the low dose groups of male and female rats and of male mice compared to the control groups, alterations occurred more frequently in all high dose groups of each species. Mineralisation of the kidney was seen in increased incidences in high dose male rats. In male and female mice higher incidences of renal nephropathy in the mid and high dose groups and papillary mineralisation in high dose group than in controls were observed.

Liver and thyroid changes were consistent to MDA-related effects observed in other studies in rats and mice. A clear dose relationsship of the liver and thyroid changes was lacking.

However this may be explanable due to simultaneous or overlapping processes of degeneration/preneoplastic changes and tumor growth. The LOAEL of nonneoplastic lesions, derived from toxic liver effects were estimated to be 150 ppm in rats and mice (equiv. to 9, resp. 10 mg/kg bw/d in male, resp. female rats, and 25 resp. 19 mg/kg bw/d in male, resp. female mice). A NOAEL was not estimated in this study.

Other application routes

Leong et al. (1987) investigated the effect of inhaled aerosols of MDA in polyethylene glycol 200 (PEG) solution in male guinea pigs of albino Hartley strain and pigmented guinea pigs of mixed variety. The study was not reliable with respect to toxic effects on the respiratory tract (only few organs were investigated, no histopathology on the upper respiratory tract). Although an effect of MDA (0.44 mg/l) occurred in this 14-day inhalation study (4 h/d, 5 d/wk) in the eyes of eight exposed animals (the retinas of all animals showed a degeneration of the inner and outer segments of the photoreceptor cells and the pigmented epithelial cell layer, not due to an interaction with melanin).

To determine the maximum tolerated dose, Holland et al. (1987) reported that 4/9 female and 1/9 male C3Hf/Bd mice died after a 14-day dermal exposure (5 d/week) to 50 µl of 1 10% (w/v, corresponding to approx. 100-150 mg/kg bw/d) MDA solution in methanol. when acetone was the solvent, 3/10 females and 3/10 males died within two weeks.

No valid repeated dose study with inhalation and dermal application route was available.

Summary on nonneoplastic lesions

Primary target organs in rats and mice after repeated oral exposure to MDA are the liver and the thyroid. Main effects were liver cell degeneration in the mouse at doses from 25 mg/kg bw/d (150 ppm, 2-year study, NTP, 1983), bile duct hyperplasia in rats at 20.4 mg/kg bw/d or higher (14-d or 90-d studies, Ciba-Geigy, 1982, BASF, 1977a, NTP, 1983) and bile duct hyperplasia in mice receiving 52 mg/kg bw/d (400 ppm, 90-d study, NTP, 1983). Elevated liver transaminase activities were observed in rats which received doses of 22 mg/kg bw/d or higher in subacute or subchronic tests (Ciba-Geigy, 1982, BASF, 1977a). In rats, liver lesions were not or not fully reversible (Ciba-Geigy, 1982, Fukushima et al., 1979), no data on recovery of liver effects were available in mice. The severity of microscopic lesions observed in the rat liver were reported to increase with the dosage (90-d studies, NTP, 1983, BASF, 1977a).

In the thyroid, the prominent effect of MDA treatment was follicular cell hyperplasia/hypertrophy and diffuse glandular hyperplasia with colloid depletion occurring at dose levels from 7.5 mg/kg bw/d (90-d study, Ciba-Geigy, 1982) or 9 mg/kg bw/d (2-year study; NTP, 1983). In mice, thyroid follicular cell hyperplasia was also observed in 2-year study (NTP, 1983) in males treated from 25 mg/kg bw/d and in females at 43 mg/kg bw/d. Adenomatous goiter was observed in a male mouse receiving 54.9 mg/kg bw/d and a female mouse receiving 52 mg/kg bw/d on 90 days (NTP, 1983).

Comparing the effect levels inducing thyroid lesions in the long term studies (NTP, 1983), rats seem to be more sensitive than mice without any clear sex preference, and male mice showed a higher sensitivity than female mice. Although a dose-relationship was not obviously present for liver effects in rats of the 2-year study, sensitivity for liver damage seemed to be higher in rats than in mice and male mice were more sensitive than females. The similarities in the target organ

sensitivity may lead to the assumption that the thyroid effects were possibly associated to the effects on the liver.

Furthermore hemotoxic effects indicated by anemia and extramedullary hemopoiesis in the spleen were evident from 90-day studies in rats at MDA concentrations equivalent to 22 mg/kg bw/d (Ciba-Geigy, 1982). Increased splenic hemopoiesis was also reported in the 14-day rat study at dosages from 25 mg/kg bw/d (BASF, 1977a), depressed red cell parameters were seen at 50 mg/kg bw/d of MDA. Microscopic lesions indicating anemia was not found in the mouse studies available, red cell parameters were not examined. Methemoglobin levels were not examined in any of the repeated dose studies cited. However, methemoglobinemia was found in cats which received single oral MDA doses or 4 times 8-hours applications of MDA solutions on the dermis (Hofmann et al., 1966, cited in BUA, 1994).

Some studies gave indications that MDA has nephrotoxic properties. Mild renal and urinary findings in some rats treated by gavage administration were reported to be related to subacute MDA treatment (BASF, 1977a). Results from subacute and subchronic drinking water studies did not endorse nephrotoxicity, possibly due to the different application routes. In long term studies, there was a higher rate of kidney mineralisation in treated male rats (Ciba-Geigy, 1982, NTP, 1983). In male and female mice, a higher rate of nephropathy was registered in both dosed groups and a higher rate of papillary mineralisation did occur at the high dose level (NTP, 1983).

At present no adequate test on the effects after repeated inhalative exposure exists, in a 14-day inhalation study nonreliable to its inhalation testing procedures guinea pigs developed retina degeneration. MDA was not investigated to its effects after repeated dermal application.

NOAEL/LOAEL

Repeated dose oral studies - rat

The LOAEL representing the most sensitive adverse (nonneoplastic) effect after repeated oral application was derived from the Ciba-Geigy study (1982) which was accepted as valid. It was 7.5 mg/kg bw/d in male rats and 8 mg/kg bw/d in female rats. This LOAEL is corresponding to the level of LOAEL from the 2-year study on rats on nonneoplastic effects (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 the long term study was considered to be the most appropriate value for quantitative risk assessment. From the studies available no NOAEL could be derived for the rat.

Repeated dose oral studies - mouse

The database of MDA-related toxic effects on mice was less than that in rat, because only few drinking water studies existed. A NOAEL can be derived from the 90-day study (NTP, 1983), which was 11.4 mg/kg bw/d in male mice and 14.4 mg/kg bw/d in female mice.

Human data

Little information with limited validity is available on the toxic effect after repeated exposure to humans. Bastian (1984) reported four cases of acute intoxications with MDA in workers resulting in an acute hepatic illness. In two of these men the illness recurred on re-exposure a few months later and their reconvalescence period was prolonged.

Clinical hepatitis related to MDA exposure was reported in a letter to the editor from Williams et al. (1974). Six cases out of 300 men who applied epoxy resins as a surface coat at a plant construction site showed elevated serum transaminases and bilirubin. The liquid epoxide was mixed with a dry powder containing methylenedianiline (no further details available).

Classification

Rat liver and thyroid lesions as well as the anemia were considered to represent severe health effects which occurred below the critical dose level of 50 mg/kg bw/d for the oral 90-day test. Also, premature deaths in mice receiving oral doses from 78 mg/kg bw/d MDA for 14 days efforts the R 48/22.

According to the severe health effects which occurred after repeated dose administration MDA is classified as "harmful", risk phrase R48/20/21/22.

4.1.2.7 Mutagenicity

All genotoxicity tests were conducted with pure MDA or MDA dihydrochloride (not with technical-grade MDA). In all reports (except the SCE in vivo assay) test methodologies and description of data were adequate. However, some findings did not allow clear conclusions. An overview on genotoxicity data is given in **Table 4.6**.

Bacterial systems

With S-9 mix, bacterial mutation tests were positive in a dose-dependent manner in Salmonella typhimurium strains TA100 and TA98 in doses ranging from 3.0 to 333 ug/plate (Zeiger et al., 1988; rat and hamster liver S-9 mix) or in doses from 30 ug/plate upwards (BASF, 1977; rat liver S-9 mix). Without S-9 mix, negative results were observed in both studies.

In vitro systems with mammalian cells

A chromosomal aberration test with CHO cells was positive with S-9 mix and equivocal without (Gulati et al., 1989). With S-9 mix, 3 experiments were performed with 2 h exposure and 13.5 h to 15.0 h sampling; in the dose range 500 to 1000 µg/ml aberration frequencies ranging from 14.0% to 85.0% were induced. Without S-9 mix, 2 experiments were performed with 2 h exposure and 15 h or 18 h sampling; one trial was negative for doses up to 500 µg/ml; in the second trial doses up to 600 µg/ml were negative and an increased aberration frequency of 15% was found for the highest tested dose of 800 µg/ml. Since cytotoxicity data are lacking, the findings cannot be interpreted adequately. It seems that clastogenic effects were limited to doses with strong cytotoxic effects.

In a mouse lymphoma assay which was done only without metabolic activation a weak positive result was obtained (McGregor et al., 1988). Three experiments were performed; in 2 of them 2- to 3-fold increases of mutant frequencies were induced by the highest tested doses of 500 µg/ml or 700 µg/ml; 1000 µg/ml were totally cytotoxic.

A test for induction of sister chromatid exchanges (SCE) was marginally positive with and without S-9 mix; data on cytotoxicity were not given (Gulati et al., 1989). With S-9 mix, one experiment was performed with 2 h exposure and 24 h sampling; in doses ranging from 160 to 1600 µg/ml marginal increases of SCE frequencies were found; the maximum effect was ca.

1.3-fold as compared to the negative control. Without S-9 mix, two experiments were performed with 2 h exposure; in the first experiment with 24 h sampling, for doses ranging from 16 to 160 µg/ml marginal increases of SCE frequencies were found, the maximum effect was ca. 1.4-fold as compared to the negative control; in a second experiment prolonged sampling times were included, again marginal increases of SCE frequencies were found.

Tests for induction of DNA excision-repair (unscheduled DNA synthesis, UDS) in primary rat hepatocytes led to controversial findings, although - with the exception of rat strains - similar experimental conditions were used with an autoradiographic methodology and analysis of net nuclear grains. Mori et al. (1988) reported on a clear and dose-dependent effect for doses ranging from 1.0 to 100 µmol/l (19.8 to 19800 µg/ml) with hepatocytes from male ACI/N rats; a dose of 1000 µmol/l was totally cytotoxic. According to Shaddock et al. (1989) there was no effect with hepatocytes from Sprague-Dawley rats for doses up 100 µg/ml; higher doses could not be analysed due to toxicity. With hepatocytes from rats which were induced by Aroclor or phenobarbitone very weak effects were observed for doses from 25 to 100 µg/ml.

In vivo systems with mammals

In two investigations on the potential of MDA for induction of micronuclei in vivo, weak effects were obtained after i.p.-administrations of high doses.

In two bone marrow experiments with 5 male B6C3F1 mice per group, 3 daily doses of 9.3, 18.5 or 37.0 mg/kg led to increased micronucleus frequencies which were less than 2-fold (0.23 to 0.35%) as compared to concurrent negative controls (0.17 and 0.19%) (Shelby et al., 1993). Micronucleus frequencies in treated animals were within the range of negative control values obtained for the 49 chemicals which were tested in the described investigation.

In experiments with reticulocytes of CD-1 mice again weak effects were obtained (Morita et al., 1997). In two experiments with single treatment, a weak but dose-dependent increase was observed in one experiment (doses 28 to 112 mg/kg) and a marginal increase in the other (28 to 140 mg/kg). Two daily doses ranging from 22.8 to 90 mg/kg were negative. In all three experiments highest doses were near to LD_{50} values.

In vivo UDS tests with liver cells from male Fischer-344 rats or B6C3F1 mice were negative (Mirsalis et al., 1989). Oral doses (gavage) up to the LD_{50} range were used (rats, 20, 80, 350 mg/kg; mice, 50, 200, 500, 1000 mg/kg); sampling times were 2 and 12 h after treatment.

In an in vivo bone marrow SCE test with male Swiss mice marginally increases in SCE frequencies were obtained after intraperitoneal administration of 9 and 18 mg/kg (Parodi et al., 1983). The maximum SCE frequency was 1.4-fold as compared to the concurrent negative control group. The investigation suffers from methodological insufficiencies (only 3 animals with 15 to 20 analysed cells per group, no toxicity data) and the 'effect' might well be unspecific.

An in vivo alkaline elution assay with liver DNA from Sprague-Dawley rats led to a positive result (Parodi et al., 1981). Single intraperitoneal administrations of the LD_{50} dose 74 mg/kg (0.37 mmol/kg) induced clear increases in DNA fragmentation 4 h and 24 h after treatment. Since elution was run under pH 12.3, primarily single and double strand breaks in DNA were detected (not alkali-labile sites).

In order to evaluate the DNA-binding capacity of MDA, radiolabeled (^{3}H)MDA was administered intraperitoneally to groups of 6 male Wistar rats at single doses of 5.6 and 116.5 µmol/kg (corresponding to 1.1 and 23.1 mg/kg; Schütze et al., 1996). In the liver relatively low covalent binding indices of 1.05 (low dose) and 2.3 (high dose) were determined [CBI = (µmol of MDA bound / mol of DNA) / (mmol of MDA applied / kg bodyweight)].

Conclusion

MDA induces gene mutations in bacteria. In mammalian cell cultures in the presence of an exogenous metabolisation system, MDA is an inducer of chromosomal aberrations. 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 (UDS) tests 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. On the other hand, there is no sufficient evidence to place the substance in category 2. Therefore, according to the classification criteria MDA has been classified as category 3 mutagen.

Table 4.6 Overview on genotoxicity data of MDA

Test system	Negative effects	Questionable or weak effects	Positive effects	Reference
Bacterial gene mutations test	without S-9 mix		dose-dependent effect with S-9 mix	BASF, 1977; Zeiger et al., 1988
Chromosomal aberration test in vitro		CHO cells without S-9 mix negative after 2-h exposure to doses up to 600 µg/ml, positive in 1 expt. at 800 µg/ml; no toxicity data	CHO cells with S-9 mix after 2-h exposure to 500 - 1000 µg/ml	Gulati et al., 1989
Mouse lymphoma assay		without S-9 mix 2- to 3-fold increases in 2 out of 3 expts. at highest analysable doses of 500 or 700 µg/ml; no toxicity data		McGregor et al., 1988
SCE test in vitro		in CHO cells with and without S-9 mix marginal increases (up to 1.4-fold), doses 160-1600 (+S9), 16-160 µg/ml (-S9)		Gulati et al., 1989
UDS test in vitro (DNA repair test)		controversial findings for rat hepatocytes: dose-dependently positive in one investigation, negative and marginal effects in another		Mori et al., 1988; Shaddock et al., 1989
Micronucleus test in vivo (bone marrow)		weak effects (<2-fold) in male mice after 3 i.p.-adm. of 9.3 to 37.0 mg/kg, no dose-dependency		Shelby et al., 1993
Micronucleus test in vivo (peripheral blood)		equivocal effects in male mice after 1 or 2 i.p.-adm. of 22.5 to 140 mg/kg		Morita et al., 1997
UDS test in vivo (DNA repair test)	rodent liver cells, single oral exposure, doses up to 350 mg/kg (rats) or 1000 mg/kg (mice)			Mirsalis et al., 1989
SCE test in vivo		marginal effects (up to 1.4-fold) in bone marrow cells of male mice after i.p.-doses of 9 or 18 mg/kg; low reliability, methodological insufficiencies		Parodi et al., 1983
Alkaline elution assay in vivo (DNA strand breaks)			rat liver cells, i.p.-dose of 74 mg/kg (=LD_{50}), sampling times 4 and 24 h	Parodi et al, 1981
DNA-binding assay in vivo		low binding capacity in rat liver cells, single i.p.-doses of 1.1 and 23.1 mg/kg		Schütze et al., 1996

4.1.2.8 Carcinogenicity

Experimental animal data

In two-year studies in F344 rats and B6C3F1 mice (NTP, 1983: Weisburger et al., 1984; Lamb et al., 1986), 150 and 300 ppm MDA administered in drinking water (equiv. to 9 and 16 mg/kg bw/d for male rats and 10, resp. 19 mg/kg bw/d for female rats, 25, resp. 58 mg/kg bw/d for male mice, and 19, resp. 43 mg/kg bw/d for female mice) was clearly carcinogenic, producing thyroid and liver tumors in both species. Survival was comparable among all groups. High dose female rats had lower mean body weights than those of the controls. No consistent effects on body weights were identified in the low dose females or either in dosed group of males. The average daily water consumption per rat by low- and high dose rats was 87% and 75% that of the controls for males and 93% and 82% for females. No compound-related clinical signs were observed. No significant differences in survival were observed between any groups of either sex of rats.

In rats, the incidence of thyroid follicular cell carcinoma was significantly higher in high dose males than in controls (**Table 4.7**). High dose female rats showed a significant higher rate of follicular cell adenomas than in the controls. Neoplastic nodules in the liver showed a significantly higher incidence in low and high dose males than in controls. One bile duct adenoma was found in one high dose male rat. Transitional cell papillomas of the urinary bladder were found in 2/50 low dose and 1/50 high dose rats.

In mice, the incidences of follicular cell adenomas gained significance in high dose males and females (**Table 4.8**). Hepatocellular carcinomas were significantly higher in males of each dose group and in high dose females. Hepatocellular adenomas occurred with significant higher incidence in high dose females.

Cystic and/or hyperplastic follicular thyroid lesions were increased in high dose female rats and mice of each sex. Rats and mice of each dose group showed toxic liver effects. An increased incidence of kidney nephropathy was evident in both dose groups in mice, high dose male rats showed a higher incidence of renal mineralisation (see 4.1.2.6).

Table 4.7 Number of rats with non-neoplastic and neoplastic lesions in the thyroid and liver

Sex		**Males**			**Females**	
Dose in ppm	**0**	**150**	**300**	**0**	**150**	**300**
Thyroid:						
Follicular cysts	1/49	2/47	3/48	0/47	3/47	7/48
Follicular cell hyperplasia	1/49	2/47	3/48	1/47	3/47	8/48
Follicular cell adenoma	1/49	4/47	3/48	0/47	2/47	17/48*
Follicular cell carcinoma	0/49	0/47	7/48*	0/47	2/47	2/48
C-Cell adenoma	0/49	0/47	0/48	0/47	3/47	6/48
Liver:						
Unspecified dilatation	1/50	6/50	10/50			
Fatty metamorphosis	14/50	28/50	33/50	7/50	20/50	11/50
Focal cellular change	14/50	38/50	36/50	5/50	17/50	10/50
Neoplastic nodules	1/50	12/50*	25/50*	4/50	8/50	8/50

*Tumor incidences indicated as statistically significant; no statistics available on the nonneoplastic lesion

Table 4.8 Number of mice with non-neoplastic and neoplastic lesions in the thyroid and liver

Sex		Males			Females	
Dose in ppm	0	150	300	0	150	300
Thyroid:						
Follicular cell hyperplasia	0/47	3/49	18/49	0/50	0/47	23/50
Follicular cell adenoma	0/47	3/49	16/49*	0/50	1/47	13/50*
Follicular cell carcinoma	0/47	0/49	0/49	0/50	0/47	2/50
Liver:						
Liver cell degeneration	0/50	40/50	30/50	0/50	0/50	7/50
Liver cell adenoma				3/50	9/50	12/50*
Liver cell carcinoma	10/49	33/50*	29/50*	1/50	6/50	11/50*

*Tumor incidences indicated as statistically significant; no statistics available on the nonneoplastic lesion

A number of other studies on carcinogenicity in rats and mice have been reported, however they were not well performed or documented (Steinhoff and Grundmann, 1970; Schoental, 1968; Griswold et al., 1968).

Human data

Data on the carcinogenic potency in humans are of limited quality (e.g. no data on confounding factors, no data on exposure to other substances).

In a Swedish retrospective study Selden et al., (1992) tried to investigate the state of health of 197 power generator workers, who were exposed to MDA between 1963 and 1968. Neither the concentration of MDA nor the exposure route and time of exposure was registered. The number of the finally examined persons was not mentioned. Although one case of bladder cancer occurred in this group, they concluded that there was no statistically significant evidence of an increased overall or bladder cancer risk compared to the total population.

Liss and Giurguis (1994) followed a group of 10 workers exposed to MDA for 7 days to 2.5 months between 1967 and 1976. The concentration supposed to be inhaled ranged from 0.04-3.11 mg/m3. After developing an acute jaundice the workers left the factory, 23 years after intoxication in one of the workers bladder cancer was diagnosed. For the average latency period for aromatic amine-induced cancers has been suggested to be about 20 years, occurrence of bladder cancer has been observed in other persons occupationally exposed to MDA, and because of animal datas they concluded, that these finding adds weight to the suggestion that MDA is carcinogenic in humans.

On instruction of the U.S. National Institute for Occupational Safety and Health (NIOSH) Liss and Chrostek (1983) conducted a follow-up investigation of 179 white male deaths among employees with potential exposure to epoxy resins and amine hardeners who had ever worked for more than 1 month in areas with potential exposure to MDA. 46 persons of this group died with malign neoplasms. The proportional mortality rate amongst these persons revealed a statistically significant excess for cancer of large intestine, cancer of bladder, lymphosarcoma and reticulo-sarcoma compared to the whole population. In a proportional cancer mortality ratio analysis only the excess of bladder cancer remained significantly elevated. On the basis of these findings NIOSH suggests an association between bladder cancer and work in areas with past or present potential exposure to MDA.

Summary

Various reports of limited reliability describing effects after repeated exposures of humans showed a coincidence of bladder cancers and work in areas with exposure to MDA.

Considerations on the mechanism of action

MDA obviously influences the function of the thyroid gland resulting in hypothyroidism. Some of the induced adverse effects, e.g. the depressed food consumption, lower body weight gain, effects on red cells, lymphocytes, and clotting parameters were explainable as secondary responses. However, the mechanisms by which MDA produced the nonneoplastic and neoplastic lesions are still unknown. At present, there are no data on the thyroid and pituitary hormone status. Besides of the thyroid effects, the mechanism of liver tumor development remains unclear, too. Cell injury may give indications on a nongenotoxic mechanism, however it is still unproved. Therefore, based on the results of carcinogenicity studies in animals and the results of genotoxicity studies and 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-stimulation (thyroid) effects for the moment it has to be assumed that a genotoxic mechanism is involved.

MDA induced tumors were observed in livers and in thyroid of male and female rats and mice. This coincidence may lead to an assumption that theoretically thyroid tumors may be associated to liver tumors. Until now the pathomechanism of tumor growth in the thyroid is not investigated. It is not known whether MDA acts indirectly on the thyroid, e.g. inducing microsomal enzymes of the liver cell resulting in an increased glucuronidation and a secondary chronic stimulation of the thyroid, or whether MDA may act directly on the follicular cell. At present there are no data which give reasons for a species specific phenomenon. Tumor induction after cell injury in the liver may be interpreted to give indication for a nongenotoxic mechanism of action. On the other hand there are positive genotoxic data in vitro and in vivo. Therefore a genotoxic mechanism can not be excluded for the tumor response of each target organ.

At present there are no data which give reasons to assume a species specific mechanism. Considering the tumor types, thyroid follicular adenomas/carcinomas and liver cell adenomas/carcinomas are tumors which occur in rats, mice and man with similar cellular morphology and growth pattern. Spontaneous thyroid tumors in rats were infrequent, incidences ≤1% for follicular cell adenomas or carcinomas were reported for untreated male and female F344 rats (Boorman and Elwell, 1996). None of the rat control groups of this study had thyroid follicular tumors except one out of 49 males with a follicular cell adenoma. Also, it is known that B6C3F1 mice have low spontaneous rates of thyroid follicular adenomas (≤1%) and of follicular carcinomas (≤0.5%) (Heath, 1996). No tumor was observed in the thyroid of the control mice of the carcinogenicity study on MDA.

In general, chemical induced thyroid carcinogenesis are considered to have relevance for the risk evaluation on human health. Species-related quantitative differences in substance-induced thyroid hormonal responses should be well investigated to claim that rodents are more sensitive than humans. As no specific data on disturbances on thyroid hormone homeostasis were known for MDA exposed rats, mice or other species, risk assessment should be based on a conservative position. The absence of equivalent human data is not suitable to negate positive animal findings. MDA induces thyroid tumors in rats and mice and may also pose a carcinogenic hazard for the human thyroid. Similarly, liver tumors in rats and (because of higher spontaneous tumor rates to lower extent) also liver tumors in mice were considered to have potential relevance for humans.

The consistency of findings between two rodent species is an additional argument to postulate a relevant carcinogenic potential.

From the cancer study in rats (NTP, 1983), where 2 low dose and 1 high dose rat developed bladder tumors, it can not surely be excluded that these tumors were associated to MDA-treatment: bladder transitional cell papillomas were reported to be vary rare in untreated animals. The incidence of bladder tumors did not show dose relationship, and there were no cases in the control groups of the study. Human data have led to a suggestion that bladder cancer may be associated to occupational MDA-exposure, but no clear conclusion could be drawn from human data. Together with the rat data, biological plausibility was not sufficient to conclude that MDA induce bladder tumors.

Another extremely rare tumor, a bile duct adenoma was observed in 1/50 high dose rat of the NTP cancer study. Although the incidence is very low, the authors discussed a possible association to the MDA treatment. This tumor was not observed in 3 633 control rats of this strain in the NTP Bioassay Program and the bile duct hyperplasia may be discussed as the corresponding preneoplasia.

Conclusion

MDA is carcinogenic in experimental animals. Longterm 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 the presence of a carcinogenic activity in humans. The available data are not sufficiently to justify the evaluation as an human carcinogen according to the criteria of the Directive 67/548/EEC. However, they warrant the classification of a carcinogen of category 2.

4.1.2.9 Toxicity for reproduction

Animal data

Fertility impairment: no data available

Developmental toxicity: no valid data available

Human data

No data available

Other information

Data from a subchronic study (3 months drinking water study in rats, Ciba-Geigy, 1982) were also considered. However, in view of the fact of severely reduced body weight of less than 50% compared to the controls and of drastically reduced waterintake (resp. substance-intake) in the mid and higher dose groups in this study, informations concerning gonads (e.g. reduced weight) are not considered of special value for the evaluation of possible effects on reproductive organs.

There is insufficient information on a possible toxic potential of MDA concerning reproduction.

4.1.2.10 Risk characterisation

General aspects

MDA is used industrially as an intermediate product. Use of the substance itself or as a component of consumer products is unknown. Exposure of the general population is not asssumed to exist. However, in case of using products, colored with the recently notified azodye Cartasol Yellow an exposure of consumers cannot be excluded due to the possibility of liberation of MDA. In addition, there may be a potential exposure to MDA for uremic patients or patients who receive frequent blood transfusions from gamma-ray irradiated polyurethane-containing medical devices.

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. 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.

Human data on local irritation or corrosion caused by MDA are not available. In rabbits, slight irritation to the skin and mild irritation to the eyes and no local corrosive effects are demonstrated.

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.

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. A 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 the subchronic Ciba-Geigy study (1982). 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. A NOAEL can be derived from the 90-day study (NTP, 1983), 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.

MDA causes concern for man owing to possible mutagenic effects. There is evidence from an in vivo micronucleus test (although only weakly positive) which is supported by the induction of DNA fragmentation in vivo and chromosomal aberrations in vitro.

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. The results from the reports on human exposure did not show clearly a carcinogenic activity in humans.

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 tumours in rats and mice is a consequence of chronic tissue-damaging (liver) or tissue-stimulating (thyroid) effects a genotoxic mechanism cannot be excluded.

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

4.1.2.11 Workers

4.1.2.11.1 Toxicological endpoints relevant for workplace risk assessment

Introductory remarks

MDA is absorbed via the oral, dermal and inhalation route. As to the extrapolation steps a central tendency estimate is intended. A higher sensitivity of a subpopulation (intraspecies variability) is possible.

Acute toxicity

The inhalative LC_{50} (4 h) in rats is higher than 0.837 mg/l (837 mg/m^3). After dermal exposure 50% of rats died at 1 000 mg/kg with DMSO as vehicle. No rats died at 2500 mg/kg with water as vehicle. LD_{50} (oral) in rats is found in the range of 350 - 450 mg/kg with damage to the liver and kidney at doses of 100 mg/kg and above. In another study of acute oral toxicity in rats a threshold for liver effects was found between 25 and 75 mg/kg. At 100 mg/kg liver necrosis was observed. In humans 3 mg/kg (estimated acute oral dose) resulted in hepatocellular toxicity (e.g. necrosis and degeneration). A NOAEL was not determined. A quantitative comparison of rat and human data is complicated by the different way of administration (gavage versus diet (bread)) and the missing dose response relationship of the human data. But it might be assumed that one order of magnitude lies between the effect levels of rats and humans for acute oral liver toxicity. As a quantitative estimate a 10-fold higher sensitivity of humans is assumed. Since there are no quantitative human data as to the dermal and inhalation exposure, the evaluation of dermal and inhalation toxicity should be based on oral human data.

Inhalation (estimation of NAEC)

Starting with the LOAEL of 3 mg/kg (human, oral, acute) the following extrapolation is performed. For a route-to-route extrapolation a body weight of 70 kg, a respiratory volume of 10 m^3/8 h and an equivalent inhalatory and oral uptake are assumed. A LAEC (human, inhalation, acute) in the range of 21 mg/m^3/8 h with liver toxicity is calculated. For a LAEC/NAEC-extrapolation a default factor of 1/3 is used. A NAEC (human, inhalation, acute) in the range of 7 mg/m^3/8 h is estimated. However, concerning the LAEC/NAEC-extrapolation it has to be mentioned, that a dose-response relationship in humans is not available and the effects at 3 mg/kg were marked. So it is not excluded, that the factor of 1/3 is not sufficient.

Dermal (estimation of NAEL)

Starting with the LOAEL of 3 mg/kg (human, oral, acute) the following extrapolation is performed. For a route-to-route extrapolation the data from rat acute toxicity (oral/dermal) are compared to estimate the relation of oral and dermal absorption. The oral LD_{50} for rats is found in the range of 350 - 450 mg/kg. Toxicity after dermal exposure seems to depend on the vehicle. A LD_{50} in the range of 1 000 mg/kg can be estimated for a vehicle that supports dermal absorption and a value higher than 2 500 mg/kg for a non-supporting vehicle. For a route-to-route extrapolation the factor ">2" is assumed. Supposing that this is also relevant to humans (body weight: 70 kg) the LOAEL of 3 mg/kg (human, oral, acute) is equivalent to a dose higher than 420 mg/person (LAEL, human, dermal, acute). For a LAEL/NAEL-extrapolation a factor of 1/3 is used. A NAEL (human, dermal, acute) higher than 140 mg/person is estimated.

Irritation/Corrosion

Inhalation

No data available; not suspected to be a respiratory tract irritant

Dermal

No skin/eye irritant (not corrosive)

Sensitization

Inhalation

No data available concerning respiratory sensitization

Dermal

MDA is considered as a skin sensitizer (mainly based on human data)

Repeated dose toxicity

Because of the lack of other relevant data acute human data and results of a 2-year oral rat study are used for an estimate of chronic inhalatory and dermal toxicity in humans. Several studies in rats and mice revealed the liver and the thyroid as the main target organs. Based on a 2-year oral rat study (liver and thyroid effects) a LOAEL of 9 mg/kg/d was determined (see 4.1.2.6). A NOAEL was not found. A comparison with the acute human toxicity data (marked liver toxicity at 3 mg/kg) shows the higher sensitivity of humans mentioned under "Acute toxicity".

Inhalation (estimation of NAEC)

Starting with the LOAEL of 9 mg/kg/d (rat, oral, chronic) the following extrapolation is performed. For a species extrapolation the factor of 1/10, derived from the acute oral data (rat and human), is used to calculate a LAEL (human, oral, chronic) in the range of 0.9 mg/kg/d. For a route-to-route extrapolation a body weight of 70 kg, a respiratory volume of 10 m^3/8 h and an equivalent inhalatory and oral uptake are assumed. A LAEC (human, inhalation, chronic) in the range of 6 mg/m^3/8 h is calculated. For a LAEC/NAEC-extrapolation a factor of 1/3 is used. A NAEC (human, inhalation, chronic) in the range of 2 mg/m^3/8 h is estimated.

For reasons of comparability the NAEC without consideration of the anticipated higher human sensitivity is calculated as well: a NAEC in the range of 20 mg/m^3/8 h results. This NAEC is 10 - fold higher than the adjusted NAEC of 2 mg/m^3/8 h, the latter being considered more relevant and therefore used for risk assessment.

Dermal (estimation of NAEL)

Starting with the LOAEL of 9 mg/kg/d (rat, oral, chronic) the following extrapolation is performed. For a species extrapolation the factor of 1/10, derived from the acute oral data (rat and human), is used to calculate a LAEL (human, oral, chronic) in the range of 0.9 mg/kg/d. For a route-to-route extrapolation the factor >2 is used as described under "Acute toxicity (Dermal)" leading to a LAEL (human, dermal, chronic) >1.8 mg/kg/d. For a body weight of 70 kg results a LAEL (human, dermal, chronic) >130 mg/person/d. For a LAEL/NAEL-extrapolation a factor of 1/3 is used. A NAEL (human, dermal, chronic) >40 mg/person/d is estimated.

For reasons of comparability the NAEL without consideration of the anticipated higher human sensitivity is calculated as well: a LAEL >400 mg/person/d results. This LAEL is 10-fold higher than the adjusted NAEL of >40 mg/person/d, the latter being considered more relevant and therefore used for risk assessment.

Mutagenicity

Following the conclusion of chapter 4.1.2.7 MDA has a mutagenic potential to mammalian cells. Small increases of micronuclei were observed in mouse bone marrow cells with repeated intraperitoneal administrations of doses probably near to the LD_{50}.

Carcinogenicity

There is no clear evidence of carcinogenicity in humans. The carcinogenicity of MDA was demonstrated in drinking-water studies on rats and mice. MDA caused thyroid and liver tumours in both species. The T25-value of 8.4 mg/kg/d describes the carcinogenic potency in animals (continuous life time exposure) (Dybing et al., 1997). It was calculated for MDA-dihydrochloride (molecular weight: 269.2 g/mol). For MDA (molecular weight: 198.3 g/mol) a T25 of 6.2 mg/kg/d results. The mechanism of tumor formation is discussed in chapter 4.1.2.8. On the one hand the carcinogenicity studies may be interpreted to indicate a nongenotoxic mechanism of action based on nonneoplastic effects. But considering on the other hand the genotoxicity data it has to be assumed that a genotoxic mechanism without a threshold for tumor formation is involved.

Inhalation

The T25-value (6.2 mg/kg/d) is extrapolated to a modified value assumed to be relevant to humans (workplace time schedule, inhalation) by the following steps. Based on the assumption,

that a 10-fold higher sensitivity of humans concerning carcinogenicity has to be regarded a value of 0.62 mg/kg/d is calculated for humans. For a route-to-route extrapolation a body weight of 70 kg, a respiratory volume of 10 m^3/8 h and an equivalent inhalatory and oral uptake are assumed. A value of 4.3 mg/m^3 results. A final adjustment to workplace conditions is done below (constants are taken from DECOS, 1995).

$$4.3\ \text{mg/m}^3 \cdot \frac{75\ \text{years} \cdot 52\ \text{weeks} \cdot 7\ \text{days}}{40\ \text{years} \cdot 48\ \text{weeks} \cdot 5\ \text{days}} = \text{ca. } 12\ \text{mg/m}^3$$

A modified T25-value (inhalation, workplace time schedule) in the range of 12 mg/m^3 is estimated.

For reasons of comparability the modified T25-value without consideration of the anticipated higher human sensitivity is calculated as well: a value in the range of 120 mg/m^3 results. This value is 10-fold higher than the modified T25-value of 12 mg/m^3. There are uncertainties as to the use of a species factor derived from acute toxicty, but there are at present no clear reasons excluding a higher sensitivity of humans concerning carcinogenicity.

Since it has to be assumed that a genotoxic mechanism is involved a linear dose response cannot be excluded.

Dermal

The T25-value (6.2 mg/kg/d) is extrapolated to a modified value assumed to be relevant to humans (workplace time schedule, dermal) by the following steps. Based on the assumption, that a 10-fold higher sensitivity of humans concerning carcinogenicity has to be regarded a value of 0.62 mg/kg/d is calculated for humans. For a route-to-route extrapolation the factor >2 is used as described under "Acute toxicity (Dermal)". For a body weight of 70 kg results a value >90 mg/person/d. A final adjustment to workplace conditions is done below (constants are taken from DECOS, 1995).

$$>90\ \text{mg/person/d} \cdot \frac{75\ \text{years} \cdot 52\ \text{weeks} \cdot 7\ \text{days}}{40\ \text{years} \cdot 48\ \text{weeks} \cdot 5\ \text{days}} = > 250\ \text{mg/person/d}$$

A modified T25-value (dermal, workplace time schedule) of >250 mg/person/d is estimated.

For reasons of comparability the modified T25-value without consideration of the anticipated higher human sensitivity is calculated as well: a value of >2500 mg/kg/d results. This value is 10-fold higher than the modified T25-value of >250 mg/kg/d. There are uncertainties as to the use of a species factor derived from acute toxicty, but there are at present no clear reasons excluding a higher sensitivity of humans concerning carcinogenicity. Since it has to be assumed that a genotoxic mechanism is involved a linear dose response cannot be excluded.

Reproductive toxicity

There are no specific studies on developmental toxicity or fertility impairment. The data from repeated dose toxicity are not considered to be relevant for the assessment (see 4.1.2.9).

Summary of effects relevant for workplace risk assessment

Table 4.9 Summary of effects relevant for workplace risk assessment

	Inhalation	Dermal
Acute toxicity	extrapolated NAEC: 7 mg/m³ extrapolated LAEC: 21 mg/m³ liver toxicity	extrapolated NAEL: > 140 mg/person extrapolated LAEL: > 420 mg/person liver toxicity
Irritation	no data: not suspected to be a respiratory tract irritant	not classified as irritating to skin or eyes
Corrosivity	---	not corrosive
Sensitization	no data concerning respiratory sensitization	skin sensitizer
Repeated dose toxicity (systemic)	extrapolated NAEC: 2 mg/m³ extrapolated LAEC: 6 mg/m³ liver and thyroid toxicity	extrapolated NAEL: > 40 mg/person/d extrapolated LAEL: > 130 mg/person/d liver and thyroid toxicity
Repeated dose toxicity (local)	not considered to be a respiratory tract irritant	not classified as 'irritating to skin or eyes'
Mutagenicity	suspected to be mutagenic	
Carcinogenicity	carcinogenic	
	extrapolated "T25" (workplace time schedule): 12 mg/m³	extrapolated "T25" (workplace time schedule): > 250 mg/person/d
Fertility impairment Developmental toxicity	incomplete data base	

4.1.2.11.2 Occupational risk assessment

For the purpose of risk assessment it is assumed that inhalation of dust and skin exposure are the main routes of exposure. Oral exposure is not considered to be a significant route of exposure under normal working practices.

Acute toxicity

Risk assessment for acute health effects directly relies on human experience. In humans the estimated oral dose of 3 mg/kg resulted in liver toxicity.

Inhalation

For acute inhalation exposure a NAEC in the range of 7 mg/m^3 (8 h) is estimated. At 21 mg/m^3 acute inhalation exposure is anticipated to result in acute liver toxicity in humans. The maximum level of exposure is calculated to be 0.1 - 1.25 mg/m^3 (EASE) for the production of preparations in the industrial area resulting in a MOS of 6 to 70. This acute risk situation is considered to be a borderline situation for no "concern „.

Conclusion ii)

Dermal contact

For acute dermal exposure a NAEL of greater than 140 mg/person was estimated. A total dermal dose of greater than 420 mg/person is anticipated to result in liver toxicity. These data are compared with the exposure information (see table at the end of chapter 4.1.1.4).

Because investigations of dermal exposure have shown that glove materials used do not provide complete protection and information about the suitability of these materials which are recommended by the producers is not available, dermal exposure of a relevant level is assumed for all applications even with PPE. The exposure calculations by the EASE model are used for risk assessment purposes. For skilled trade applications the highest dermal exposure values are calculated. The standard of hygiene in skilled trade, e. g. on building sites is assumed to be low: protective gloves are not always worn and not regularly changed (MOS: >0.05 - 0.3). This risk situation is the most critical one and clearly of concern. If a worker is dermally exposed to such high levels, acute liver toxicity is anticipated.

In the chemical industry PPE is highly accepted. Because it is not proved that protective gloves are of suitable material. MOS-values of >0.3 - 3.3 cannot be excluded. This situation is critical too. For all other workplace scenarios acute dermal exposure is of concern as well.

Conclusion iii)

Irritation/Corrosivity

Inhalation

There are no data available concerning respiratory tract irritation. MDA is not suspected to be a respiratory tract irritant. With regard to this toxicological endpoint inhalation exposure is not of concern.

Conclusion ii)

Dermal contact

MDA is not classified as irritating to skin or eyes. Dermal exposure of workers is therefore not anticipated to result in irritant effects.

Conclusion ii)

Sensitization

Dermal contact

MDA is considered to be a human skin sensitizer. There are no valid data on its sensitization potency. Estimates of dermal exposure without PPE for different exposure scenarios clearly demonstrate that there may be a substantial risk of skin sensitization resulting in contact allergies. Because investigations have shown that glove materials used do not provide complete protection and information on suitability of glove materials is not available, relevant dermal exposure and contact allergies are expected even with use of PPE.

Conclusion iii)

Inhalation

There are no data available on respiratory sensitization. For preliminary risk assessment inhalation exposure is not suspected to result in respiratory tract sensitization.

Conclusion ii)

Repeated dose toxicity (systemic)

The relevant information (exposure, toxicity, MOS) is listed in **Table 4.10**.

Table 4.10 MOS values [repeated dose toxicity (systemic)] of MDA

		Inhalation				Dermal contact				
Exposure scenario	**Duration and frequency**	**Shift average value [mg/m³]**	**NAEC [mg/m³]**	**MOS (extrap.)**	**Conclusion**	**Shift average value [mg/cm²/d]**	**Shift average value [mg/p/d]**	**NAEL [mg/p/d]**	**MOS (extrap.)**	**Conclusion**
Chemical industry										
Manufacturing and further processing as a chemical intermediate (methylene diphenyl di-isocyanate, MDI) activity: drumming, transfer, cleaning, maintenance										
- Dust	shift length, daily	0.52[1]	2	4	iii	0.1 - 1[2]	42 - 420	> 40	> 0.1 - 1	iii
- Vapour	shift length, daily	very low[3]	2	very high	ii	0.06 - 0.6[2]	25 - 252	> 40	> 0.2 - 2	iii
Production of preparations activity: drumming, transfer, cleaning, maintenance										
Imid preparations, max. 10 % MDA										
- Dust (powder)	batch processing, 2hours/daily	0.05-0.125[2]	2	16-40	ii	0.01-0.1[2]	4-42	> 40	> 1-10	iii
Curing formulations, max. 60 % MDA										
- Dust	batch processing, 2hours/daily	lower than above[3]	2	> 16-40	ii	0.06-0.6[2]	25-252	> 40	> 0.2-2	iii
max 5 % MDA										

Table 4.10 continued overleaf

Table 4.10 continued

		Inhalation				Dermal contact				
Exposure scenario	**Duration and frequency**	**Shift average value [mg/m³]**	**NAEC [mg/m³]**	**MOS (extrap.)**	**Conclusion**	**Shift average value [mg/cm²/d]**	**Shift average value [mg/p/d]**	**NAEL [mg/p/d]**	**MOS (extrap.)**	**Conclusion**
Industrial area										
- Dust	batch processing, 2hours/daily	lower than above[3]	2	> 16-40	ii	0.005-0.05[2]	2-21	> 40	> 2-20	iii
Manufacturing of formulations using powdery MDA activity: transfer, weighing, filling, drumming										
- Dust	batch processing, 2hours/daily	0.6[1]	2	3	iii	0.1 - 1[2]	42 - 420	> 40	> 0.1 - 1	iii
Formulating putties using liquid MDA (approx. 60 %)										
- Vapour		very low[3]	2	very high	ii	0.06 - 0.6[2]	25 - 252	> 40	> 0.2 - 2	iii
Production of preparations activity: drumming, transfer, cleaning, maintenance										
Imid preparations max. 10 % MDA										
- Dust (powder)	batch processing, 2hours/daily	0.1- 1.25[4]	2	1.6 - 20	iii	0.01 - 0.1[2]	4 - 42	> 40	> 1 - 10	iii
Curing formulations max. 60 % MDA										
- Dust	batch processing, 2hours/daily	0 - 0.75[4]	2	> 3	iii	0.06 - 0.6[2]	25 - 252	> 40	> 0.2 - 2	iii
max. 5 % MDA										

Table 4.10 continued overleaf

Table 4.10 continued

		Inhalation				Dermal contact				
Exposure scenario	**Duration and frequency**	**Shift average value [mg/m³]**	**NAEC [mg/m³]**	**MOS (extrap.)**	**Conclusion**	**Shift average value [mg/cm²/d]**	**Shift average value [mg/p/d]**	**NAEL [mg/p/d]**	**MOS (extrap.)**	**Conclusion**
- dust	batch processing, 2hours/daily	0 - 0.08[4]	2	> 25	ii	0.005 - 0.05[2]	2 - 21	> 40	> 2 - 20	iii
Mixing curing formulations (max. 60 % MDA) with resin for epoxies activity: transfer, weighing, filling										
- Dust	short term (0.5 h), daily	0 - 0.2[4]	2	> 10	ii	0.06 - 0.6[2]	50 -504	> 40	> 0.1 - 1	iii
- Vapour	short term (0.5 h), daily	very low[3]	2	very high	ii	0.06 - 0.6[2]	50 -504	> 40	> 0.1 -1	iii
Handling of formulations containing MDA and epoxid resins (4.5 - 30 %)										
- Vapour	shift length, daily	very low[3]	2	very high	ii	0.03 - 0.3[2]	25 - 252	> 40	> 0.2 -2	iii
Mixing curing formulations (max. 5 % MDA) with resin for polyurethanes activity: transfer, weighing, filling										
- Dust	short term (0.5 h), daily	0 - 0.02[4]	2	> 100	ii	0.005 - 0.05[2]	4.2 - 42	> 40	> 1 - 10	iii
Handling of formulations containing MDA and polyurethane (2 - 3 %)										

Table 4.10 continued overleaf

Table 4.10 continued

		Inhalation				Dermal contact				
Exposure scenario	**Duration and frequency**	**Shift average value [mg/m³]**	**NAEC [mg/m³]**	**MOS (extrap.)**	**Conclusion**	**Shift average value [mg/cm²/d]**	**Shift average value [mg/p/d]**	**NAEL [mg/p/d]**	**MOS (extrap.)**	**Conclusion**
- Vapour	shift length, daily	very low[3]	2	very high	ii	0.003 - 0.03[2]	2.5 -25	> 40	> 2 - 16	iii
Handling of formulations containing MDA (0.1-10 %) and imid resins activity: weighing, filling										
- Dust (powder)	short term (0.5 h), daily	0.03 - 0.3[2]	2	7 - 67	iii	0.01 - 0.1[2]	8.4 - 84	> 40	> 0.5 - 5	iii
- Vapour	shift length, daily	very low[3]	2	very high	ii	0.01 - 0.1[2]	8.4 - 84	> 40	> 0.5 - 5	iii
Skilled trade										
Mixing formulations containing MDA (9 - 60 %) with epoxid resins activity: transfer, weighing, filling, drumming										
- Dust	short term (0.5 h), not daily[5]	0 - 0.2[4]	2	> 10	ii	0.6 - 3[2]	504 - 2 520	> 40	> 0.02 - 0.08	iii
Handling of formulations containing MDA and epoxid resins (4 - 30 %)										
- Vapour	duration and frequency not known, assumed: not daily[5]	very low[3]	2	very high	ii	0.3 - 1.5[2]	252 - 1 260	> 40	> 0.03 - 0.16	iii

[1]Workplace measurements
[2]EASE
[3]Expert judgement
[4]EASE (without LEV)
[5]Information about frequency of exposure not available

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

For inhalation risk assessment an extrapolated NAEC in the range of 2 mg/m^3 was calculated. The NAEC is compared with the exposure information. For details see **Table 4.10**. The critical scenarios with repeated inhalation exposure of workers are in the chemical industry (MOS 4) during production and in the industrial area during manufacturing of formulations (MOS 3), drumming of powdery imid preparations (10% MDA) and curing formulations (60% MDA) (MOS 1.6 - 20, >3), handling of powdery imid preparations (MOS 7 - 67). These MOS values are considered of concern.

It has to be mentioned that the MOS without consideration of the anticipated higher human sensitivity is greater than the extrapolated MOS used for risk characterisation.

Conclusion iii)

Dermal contact

For dermal risk assessment an extrapolated NAEL of greater than 40 mg/p/d was calculated. Repeated dermal exposure is assumed in the chemical industry, in all industrial applications even in case of use of PPE (see chapter 4.1.1.2). MOS-values in the range of_>0.1 - 1 to >2 - 20 are calculated. For skilled trade applications intermittent exposure is assumed. However, because shift average values are rather high, conclusion iii is drawn. For details see **Table 4.10**. These MOS are considered to be of concern. In case of relatively low MOS-values chronic liver toxicity is anticipated to occur.

It has to be mentioned that the MOS without consideration of the anticipated higher human sensitivity is 10 times the MOS (extrap.).

Conclusion iii)

Combined exposure

Systemic health effects due to combined exposure have to be assessed in addition to route - specific risk assessment.

Combined exposure is calculated by the formula:

$$\frac{1}{MOS_{comb.}} = \frac{1}{MOS_{inh.}} + \frac{1}{MOS_{derm.}}$$

The results of the calculations for combined exposure are presented in the following **Table 4.11**.

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. For details see **Table 4.11**.

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

Table 4.11 Combined exposure [repeated dose toxicity (systemic)]

Exposure scenario	$MOS_{inhalativ}$*	MOS_{dermal}*	$MOS_{combined}$
Chemical industry			
Manufacturing and further processing as a chemical intermediate (methylene diphenyl di-isocyanate, MDI)			
– Dust	4	0.1	0.1
– Vapour	very high	0.2	—
Production of preparations			
Imid preparations, max. 10 % MDA			
– Dust	16	1	0.9
Curing formulations, max. 60 % MDA			
– Dust	16	0.2	0.2
max. 5 % MDA			
– Dust	16	2	1.8
Industrial area			
Manufacturing of formulations using powdery MDA			
– Dust	3	0.1	0.1
Formulating putties using liquid MDA (approx. 60 %)			
– Vapour	very high	0.2	—
Production of preparations			
Imid preparations max. 10 % MDA			
– Dust	1.6	1	0.6
Curing formulations max. 60 % MDA			
– Dust	3	0.2	0.2
max. 5 % MDA			
– Dust	25	2	1.8
Mixing curing formulations (max. 60 % MDA) with resin for epoxies resins			
– Dust	10	0.1	0.1
– Vapour	very high	0.1	—
Handling of formulations containing MDA and epoxid resins (4.5 - 30 %)			
– Vapour	very high	0.2	—
Mixing curing formulations (max. 5 % MDA) with resin for polyurethanes			

Table 4.11 continued overleaf

Table 4.11 continued

Exposure scenario	$MOS_{inhalativ}$*	MOS_{dermal}*	$MOS_{combined}$
– Dust	100	1	1
Handling of formulations containing MDA and polyurethane (2 - 3 %)			
– Vapour	very high	2	—
Handling of formulations containing MDA (0.1-10 %)and imid resins			
– Hust	7	0.5	0.5
– Vapour (paste)	very high	0.5	—
Skilled trade			
Mixing formulations containing MDA (9 - 60 %) with epoxid resins			
– Dust	10	0.02	0.02
Handling of formulations containing MDA and epoxid resins (4 - 30 %)			
– Vapour	very high	0.03	—

*Lowest MOS values of ranges are used

Repeated dose toxicity (local)

Inhalation

MDA is not considered to be a respiratory tract irritant. Repeated inhalation exposure is not anticipated to result in relevant respiratory tract irritation.

Conclusion ii)

Dermal contact

MDA is not classified as 'irritating' to skin or eyes. Repeated dermal contact at workplaces is not anticipated to result in skin irritation.

Conclusion ii)

Mutagenicity

MDA is suspected to be mutagenic. Because of lack of relevant data germ cell mutagenicity cannot be assessed. However, as long as MDA is assumed to be a genotoxic carcinogen, there is no priority for further mutagenicity testing.

For this reason **conclusion** i is not recommended. Additionally it is to be assumed that risk reduction measures for germ cell mutagens and genotoxic carcinogens will be quite similar. Therefore **conclusion iii**) seems not to be adequate.

Overall, because MDA is assumed to be a genotoxic carcinogen implying far-reaching risk reduction measures, **conclusion ii**) is formally reached for mutagenic risk assessment.

Conclusion ii)

Carcinogenicity

MDA is classified as carcinogenic. Carcinogenicity of MDA was established in rodents. The mechanism of tumour development is not clearly demonstrated. Based on corresponding discussions in chapter 4.1.2.8 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 (see chapter 4.1.3.2.1). 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 above.

For purposes of carcinogenic risk assessment a MOE (margin of exposure) is calculated. Assuming a chronic level of inhalation exposure of 0.52 mg/m^3 (chemical industry) a MOE of 23 will result. The MOE for the other exposure scenarios are calculated as well. For details see **Table 4.12**.

Assuming the involvement of a genotoxic mechanism most MOE values are of concern. 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. 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 applications, even in case of use of PPE (see chapter 4.1.1.2).

The MOE for all dermal exposure scenarios are calculated, for details see **Table 4.12**.

Table 4.12 MOE values of MDA

Exposure scenario	Duration and frequency	Shift average value [mg/m³]	T 25 [mg/m³]	MOE	Conclusion	Shift average value [mg/cm²/d]	Shift average value [mg/p/d]	T25 [mg/p/d]	MOE	Conclusion
Chemical industry										
Manufacturing and further processing as a chemical intermediate (methylene diphenyl di-isocyanate, MDI) activity: drumming, transfer, cleaning, maintenance										
- Dust	shift length, daily	0.52[1]	12	23	iiib	0,1 - 1[2]	42 - 420	> 250	> 0.6 - 6	iiib
- Vapour	shift length, daily	very low[3]	12	very high	iiia	0.06 - 0.6[2]	25 - 252	> 250	> 1 - 10	iiib
Production of preparations activity: drumming, transfer, cleaning, maintenance										
Imid preparations, max. 10 % MDA										
- Dust	batch processing, 2hours/daily	0.05-0.125[2]	12	96 - 240	iiib	0.01 - 0.1[2]	4 - 42	> 250	> 6 - 62	iiib
Curing formulations, max. 60 % MDA										
- Dust	batch processing, 2hours/daily	lower than above[3]	12	> 96 - 240	iiib	0.06 - 0.6[2]	25 - 252	> 250	> 1 - 10	iiib
max. 5 % MDA										
- Dust	batch processing, 2hours/daily	lower than above[3]	12	> 96 - 240	iiib	0.05 - 0.05[2]	2 - 21	> 250	> 12 - 125	iiib

Table 4.12 continued overleaf

Table 4.12 continued

Exposure scenario	Duration and frequency	Shift average value [mg/m³]	T 25 [mg/m³]	MOE	Conclusion	Shift average value [mg/cm²/d]	Shift average value [mg/p/d]	T 25 [mg/p/d]	MOE	Conclusion
Industrial area										
Manufacturing of formulations using powdering MDA activity: transfer, weighing, filling, drumming:										
- Dust	batch processing, 2hours/daily	0.6[1]	12	20	iiib	0.1 - 1[2]	42 - 420	> 250	> 0.6 - 6	iiib
- fFrmulating putties using liquid MDA (approx. 60 %)										
- Vapour		very low[3]	12	very high	iiia	0.06 - 0.6[2]	25 - 252	> 250	> 1 - 10	iiib
Production of preparations activity: drumming, transfer, cleaning, maintenance										
Imid preparations max. 10 % MDA										
- Dust	batch processing, 2hours/daily	0.1- 1.25[4]	12	10 - 120	iiib	0.01 - 0.1[2]	4 - 42	> 250	> 6 - 62	iiib
Curing formulations max. 60 % MDA										
- Dust	batch processing, 2hours/daily	0 - 0.75[4]	12	> 16	iiib	0.06 - 0.6[2]	25 - 252	> 250	> 1 - 10	iiib
max. 5 % MDA										
- Dust	batch processing, 2hours/daily	0 - 0.08[4]	12	> 150	iiib	0.005 - 0.05[2]	2 - 21	> 250	> 12 - 125	iiib

Table 4.12 continued overleaf

Table 4.12 continued

Exposure scenario	Duration and frequency	Shift average value [mg/m³]	T 25 [mg/m³]	MOE	Conclusion	Shift average value [mg/cm²/d]	Shift average value [mg/p/d]	T 25 [mg/p/d]	MOE	Conclusion
Mixing curing formulations (max. 60 % MDA) with resin for epoxies activity: transfer, weighing, filling										
- Dust	short term (0.5 h), daily	0 - 0.2[4]	12	> 60	iiib	0.06 - 0.6[2]	50 -504	> 250	> 0.5 - 5	iiib
- Vapour	short term (0.5 h), daily	very low[3]	12	very high	iiia	0.06 - 0.6[2]	50 -504	> 250	> 0.5 - 5	iiib
Handling of formulations containing MDA and epoxid resins (4.5 - 30 %)										
- Vapour	shift length, daily	very low[3]	12	very high	iiia	0.03 - 0.3[2]	25 - 252	> 250	> 1 - 10	iiib
Mixing curing formulations (max. 5 % MDA) with resin for polyurethanes activity: transfer, weighing, filling										
- dust	short term (0.5 h), daily	0 - 0.02[4]	12	> 600	iiib	0.005 - 0.05[2]	4.2 - 42	> 250	> 6 - 60	iiib
Handling of formulations containing MDA and polyurethane (2 - 3 %)										
- Vapour	shift length, daily	very low[3]	12	very high	iiia	0.003 - 0.03[2]	2.5 -25	> 250	> 10 - 100	iiib
Handling of formulations containing MDA (0.1-10 %) and imid resins activity: weighing, filling										

Table 4.12 continued overleaf

Table 4.12 continued

Exposure scenario	Duration and frequency	Shift average value [mg/m³]	T 25 [mg/m³]	MOE	Conclusion	Shift average value [mg/cm²/d]	Shift average value [mg/p/d]	T 25 [mg/p/d]	MOE	Conclusion
- Dust	short term (0.5 h), daily	0.03 - 0.3[2]	12	40 - 400	iiib	0.01 - 0.1[2]	8.4 - 84	> 250	> 3 - 30	iiib
- Vapour	shift length, daily	very low[3]	12	very high	iiia	0.01 - 0.1[2]	8.4 - 84	> 250	> 3 - 30	iiib
Skilled trade										
Mixing formulations containing MDA (9 - 60 %) with epoxid resins activity: transfer, weighing, filling, drumming										
- Dust	short term (0.5 h), not daily[5]	0 - 0.2[4]	12	> 60	iiib	0.6 - 3[2]	504 - 2 520	> 250	> 0.1 - 0.5	iiib
Handling of formulations containing MDA and epoxid resins (4 - 30 %)										
Vapour	duration and frequency not known, assumed: not daily[5]	very low[3]	12	very high	iiia	0.3 - 1.5[2]	252 - 1 260	> 250	> 0.2 -1	iiib

[1]Workplace measurements
[2] EASE
[3]Expert judgement
[4]EASE (without LEV)
[5]Information about frequency of exposure not available

The MOE values range is from >0.5 - 5 to >12- 125.

Most MOE-values calculated for dermal exposure are very low resulting in high concern for carcinogenicity due to dermal contact.

Conclusion iiib)

Combined exposure

Carcinogenic risks due to combined exposure (inhalation and skin contact) are to be assessed in addition to route-specific estimates. With reference to the corresponding quantitative considerations for the toxicological endpoint 'Repeated dose toxicity' for carcinogenic risks it can be concluded as well that inhalation exposure in most cases does not contribute to the overall risk for all exposure scenarios. Carcinogenic risk for combined exposure nearly exclusively is determined by the estimates of dermal exposure.

Combined exposure is calculated by the formula:

$$\frac{1}{MOS_{comb.}} + \frac{1}{MOS_{inh.}} + \frac{1}{MOS_{derm.}}$$

For details see **Table 4.13**.

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

Table 4.13 Combined exposure (carcinogenicity)

Exposure scenario	$MOE_{inhalativ}$*	MOE_{dermal}*	$MOE_{combined}$
Chemical industry			
Manufacturing and further processing as a chemical intermediate (methylene diphenyl di-isocyanate, MDI)			
– Dust	23	0.6	0.6
– Vapour	very high	1	—
Production of preparations			
Imid preparations, max. 10 % MDA			
– Dust	96	6	5.6
Curing formulations, max. 60 % MDA			
– Dust	96	1	1
max. 5 % MDA			
– Dust	96	12	11
Industrial area			
Manufacturing of formulations using powdery MDA			
– Dust	20	0.6	0.6
Formulating putties using liquid MDA (approx. 60 %)			
– Vapour	very high	1	—
Production of preparations			
Imid preparations max. 10 % MDA			
– Dust	10	6	0.3
Curing formulations max. 60 % MDA			
– Dust	16	1	0.9
max. 5 % MDA			
– Dust	150	12	11
Mixing curing formulations (max. 60 % MDA) with resin for epoxie			
– Dust	60	0.5	0.5
– Vapour	very high	0.5	—
Handling of formulations containing MDA and epoxid resins (4.5 - 30 %)			
– Vapour	very high	1	—
Mixing curing formulations (max. 5 % MDA) with resin for polyurethanes			

Table 4.13 continued overleaf

Table 4.13 continued

Exposure scenario	$MOE_{inhalativ}$*	MOE_{dermal}*	$MOE_{combined}$
– Dust	600	6	5.9
Handling of formulations containing MDA and polyurethane (2 - 3 %)			
– Vapour	very high	10	—
Handling of formulations containing MDA (0.1-10 %)and imid resins			
– Dust	40	3	2.8
– Vapour	very high	3	—
Skilled trade			
Mixing formulations containing MDA (9 - 60 %) with epoxid resins			
– Dust	60	0.1	0.1
Handling of formulations containing MDA and epoxid resins (4 - 30 %)			
– Vapour	very high	0.2	—

* Lowest MOE values of ranges are used

Reproductive toxicity

As outlined in chapter 4.1.2.9 reproductive toxicity testing is not complete (fertility impairment and developmental toxicity). Because of relevant data gaps a conclusion as to reproductive toxicity of MDA is not possible. A corresponding risk assessment cannot be performed.

MDA is classified as a carcinogenic agent. For carcinogens it should be considered whether testing is necessary at all, as many risk reduction measures are already in place. For MDA it cannot be excluded that there is a genotoxic mechanism leading to tumour development. Thus a no adverse effect level cannot be established. Although it cannot be excluded that possible reproductive toxicity of MDA is judged more relevant than carcinogenicity it is not proposed to fill this data gap since the substance is considered as a genotoxic carcinogen and knowledge of adverse effects on reproduction would as experience shows not impact on risk reduction measures.

Conclusion

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

The conclusions of the occupational risk assessment are summarized in the following table:

Table 4.14 Results of the occupational risk assessment

Exposure scenario	Acute toxicity (inhalation)	Acute toxicity (dermal)	Irritation/ Corrosivity	Sensitization (inhalation)	Sensitization (dermal)	Repeated dose toxicity (systemic, inhalation)	Repeated dose toxicity (systemic, dermal)	Repeated dose toxicity (local, inhalation and dermal)	Mutagenicity	Carcinogenicity (inhalation)	Carcinogenicity (dermal)	Reproductive toxicity
Chemical industry												
manufacturing and further processing as a chemical intermediate (methylene diphenyl di-isocyanate, MDI)												
- dust		iii			iii	iii	iii			iiib	iiib	
- vapour		iii			iii		iii				iiib	
production of preparations												
- imid preparations, max. 10 % MDA		iii			iii		iii			iiib	iiib	
- curing formulations, max. 60 % MDA		iii			iii		iii			iiib	iiib	
- max. 5 % MDA		iii			iii		iii			iiib	iiib	
Industrial area												
manufacturing of formulations using powdery MDA		iii			iii	iii	iii			iiib	iiib	
formulating putties: using liquid MDA (approx. 60 %)		iii			iii		iii				iiib	
production of preparations												
- imid preparations, max. 10 % MDA		iii			iii	iii	iii			iiib	iiib	
- curing formulations, max. 60 % MDA		iii			iii	iii	iii			iiib	iiib	
- max. 5 % MDA		iii			iii		iii			iiib	iiib	
mixing curing formulations (max. 60 % MDA) with resins for epoxies (dust)		iii			iii		iii			iiib	iiib	
mixing (vapour)		iii			iii		iii				iiib	
handling of formulations containing MDA and epoxid resins (4.5 - 30 %)		iii			iii		iii				iiib	
mixing curing formulations (max. 5 % MDA) with resin for polyurethanes (dust)		iii			iii		iii			iiib	iiib	
handling of formulations containing MDA and polyurethane (2 - 3 %) (vapour)		iii			iii		iii				iiib	
handling of formulations containing MDA (0.1-10 %) and imid resins												
- dust		iii			iii	iii	iii			iiib	iiib	
- vapour		iii			iii		iii				iiib	

Table 4.14 continued overleaf

Table 4.14 continued

Exposure scenario	Acute toxicity (inhalation)	Acute toxicity (dermal)	Irritation/ Corrosivity	Sensitization (inhalation)	Sensitization (dermal)	Repeated dose toxicity (systemic, inhalation)	Repeated dose toxicity (systemic, dermal)	Repeated dose toxicity (local, inhalation and dermal)	Mutagenicity	Carcinogenicity (inhalation)	Carcinogenicity (dermal)	Reproductive toxicity
Skilled trade												
mixing formulations containing MDA (9 - 60 %) with epoxid resins (dust)		iii			iii		iii			iiib	iiib	
handling of formulations containing MDA and epoxid resins (4.5 - 30 %) (vapour)		iii			iii		iii				iiib	

Blanc fields = Conclusion ii or iiia (negligible risk for carcinogenicity) is applied
iii(b) = There is a need for limiting the risk; risk reduction measures which are already being applied shall be taken into account (the risk for carcinogenicity is considered substantial)

4.1.2.12 Consumers

Exposure of the general population is not assumed to exist.

In case of using products, colored with the recently notified azodye Cartasol Yellow an exposure of consumers cannot be excluded due to the possibility of liberation of MDA.

Free MDA might be released by irradiation sterilization of polyurethanes which are used in medical devices as potting materials used in plasma separators and artificial dialyzers. However, no quantitative data can be derived from the report because of limited information regarding experimental conditions (cf. 4.1.1.3). Therefore, there is a potential risk of exposure to MDA for uremic patients or patients who receive blood transfusions frequently.

Acute Toxicity**,** Irritation/Corrosivity

Conclusion

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.

Sensitization

There is evidence from a large number of well-conducted studies in humans, that MDA can cause skin sensitization.

Conclusion

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.

Repeated dose toxicity

After repeated exposure by several administration routes of MDA to animals relevant toxic effects were induced mainly in liver and thyroid; furthermore lesions occurred in stomach, kidneys, pituitary gland, erythropoietic system and the retina**.** In man re-exposure to MDA inducing an acute hepatic illness results in an prolonged reconvalescence period.

A NOAEL is not established. The LOAEL of 9 mg/kg bw/d for the non-neoplastic effects from the 2-year study on rats was considered to be the most appropriate one (cf. 4.1.2.6).

Conclusion

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.

Mutagenicity

MDA causes concern for man owing to possible mutagenic effects. There is evidence from an in vivo micronucleus test (although only weakly positive) which is supported by the induction of DNA fragmentation in vivo and chromosomal aberrations in vitro.

Conclusion

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

Carcinogenicity

MDA is carcinogenic in experimental animals. A genotoxic mechanism cannot be excluded. There are no adequate data on the carcinogenicity in humans.

Conclusion

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

Reproductive toxicity

Risk characterization with respect to a possible impairment of reproduction cannot be performed due to the lack of data for hazard assessment of both of the two endpoints. However, MDA is classified as Category 2 carcinogen.

Conclusion

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.

4.1.2.13 Man exposed indirectly via the environment

Indirect exposure via the environment is calculated using data for oral intake via drinking water and food. Following worst case scenario (both local and regional exposure) the main contribution to the intake are the $DOSE_{drw}$ and the $DOSE_{fish}$ with fractions of 55% and 45%, respectively, to the total daily dose.

An intake of a total daily dose of $2.1 \cdot 10^{-5}$ mg/kg bw and of $5.4 \cdot 10^{-7}$ mg/kg bw is calculated (local resp. regional scenario).

A NOAEL has not been established; the LOAEL for systemic non-neoplastic toxic effects of 9 mg/kg bw was derived from a long term oral toxicity study (NTP, 1983).

In the following text the data base on repeated dose toxicity of MDA is considered to explain the conclusion about the appropriateness of the MOS for this endpoint.

Repeated dose oral studies

Rat

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 the Ciba-Geigy study (1982) which was accepted as valid. This LOAEL is corresponding to the LOAEL from the 2-year study on rats on nonneoplastic effects (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 the long term study was considered to be the most appropriate value for quantitative risk assessment. From these studies no NOAEL could be derived for the rat.

Mouse

The database of MDA-related toxic effects on mice was less than that in rat, because only few drinking water studies existed. A NOAEL can be derived from the 90-day study (NTP, 1983), which was 11.4 mg/kg bw/d in male mice and 14.4 mg/kg in female mice.

For the decision on the appropriateness of MOS, the following aspects have been considered and taken into account:

- overall confidence in the database

The data taken into account for performing the risk characterisation have been evaluated with regard to their reliability, relevance and completeness according to section 3.2 of the TGD. The data were published in peer reviewed journals or submitted to the Competent Authority in private reports being adequately detailed and in accordance with internationally recognized guidelines and to GLP.

The findings of all studies are not contradictory so that the judgment can be based on the database (cf. section 4.1.2.6 Summary on nonneoplastic lesions).

There are no reasons to assume limited confidence.

- uncertainty arising from the variability in the experimental data

The studies cited above allow to conclude on the LOAEL of severe toxicity (non neoplastic effects and anemia) from five studies on rats and mice. The LOAEL for nonneoplastic effects has been derived from two oral studies on rats which resulted in LOAELs ranging from 7.5 mg/kg bw/d (male rats) to 10 mg/kg bw/d (female rats). No NOAEL could be derived from all rat studies. Although the NTP-studies had not examined parameters of hematology, bioclinical chemistry and urinalysis, the LOAEL of 9 mg/kg bw/d from the long term study was considered to be the most appropriate value for risk assessment.

The results of this study were in conformity with the findings of the other studies. From the 90-day study on mice a NOAEL of 11.4 mg/kg bw/d (male mice) and 14.4 mg/kg bw/d (female mice) was derived. Comparing the effect levels rats seem to be more sensitive than mice without any clear sex preference.

There are no reasons to assume a special extent of uncertainty which have to be taken into account.

- intra- and interspecies variation

Data on kinetics of the substance do not allow to calculate the intraspecies and interspecies variability by applying modern approaches. However, the available data give no hint on a particular high variability in kinetics. The variability of the data on the toxicodynamics has been described above and has been considered to justify an increased MOS.

- the nature and severity of the effect

The carcinogenic activity of MDA in animals is proven. The effects described as „low observed adverse effect“ are liver and thyroid lesions as well as anemia, these effects are considered to be severe health effects.

There are no reasons to assume that the effects shown in the animal experiments are limited to the species tested, thus being not of relevance for humans. Therefore there is concern, which has to be expressed in the magnitude of the MOS.

- differences in exposure (route, duration, frequency and pattern)

The estimated total chronic body burden with an assumed absorption of 100% is compared with an oral LOAEL from a 2-year study.

There are no reasons to assume that special concern can be derived from this procedure.

- the human population to which the quantitative and/or qualitative information on exposure applies

Following the indirect exposure scenario there is no reason to assume a special risk for elderly, children or other people suffering from liver or thyroid diseases or anemia.

- other factors

There are no other factors known requiring a peculiar margin of safety.

MOS for the local exposure scenario

Man exposed indirectly via the environment

The total calculated internal dose at local exposure is $2.1 \cdot 10^{-5}$ mg/kg bw/d. The margin of safety between the

local exposure level of $2.1 \cdot 10^{-5}$ mg/kg bw/d

and the

oral LOAEL of 9.0 mg/kg bw/d

is judged to be sufficient regarding the non-neoplastic effects, even if special considerations on intra- and interspecies variation, nature and severity of the effect and possible human population at risk have been taken into consideration and being aware that the exposure assessment is based on worst case model calculations. However, there remains concern because MDA is to be considered as a non-threshold carcinogen.

MOS for the regional exposure scenario

Man exposed indirectly via the environment

The total calculated internal dose at regional exposure is $5.4 \cdot 10^{-7}$ mg/kg bw/d.

The margin of safety between the

estimated regional exposure level of $5.4 \cdot 10^{-7}$ mg/kg bw/d

and the

oral LOAEL of 9.0 mg/kg bw/d

is judged to be sufficient regarding the non-neoplastic effects, even if special considerations on intra- and interspecies variation, nature and severity of the effect and possible human population at risk have been taken into consideration and being aware that the exposure assessment is based on worst case model calculations. However, there remains concern because MDA is to be considered as a non-threshold carcinogen.

Conclusion

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

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

With regard to the physico-chemical properties and with regard to the occupational and consumer exposure described in chapter 4.1.1.2 and 4.1.1.3 MDA is not expected to cause specific concern relevant to human health.

There is no need for further information and/or testing with regard to physico-chemical properties (**conclusion II**).

5 RESULTS

Environment

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

Complexes of MDA with humic substances accumulate in sediments. There are indications that also the bound MDA is bioavailable. For a risk assessment of this sub-compartment, a test on sediment organisms with pre-incubated MDA is necessary. A test with sediment organisms (Lumbriculus variegatus) is proposed.

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.

Workers

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

With regard to occupational risk assessment 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. Further data on biological monitoring (industry, skilled trade, urinary MDA content, haemoglobin adducts) might be useful to assess different exposure situations.

Consumers

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

Uremic patients or patients receiving blood transfusions frequently are identified to be at risk if polyurethanes used in medical devices as potty materials are sterilized by gamma irradiation. Other treatments for sterilization must be used.

Azodyes which can release MDA are recommended to be restricted for the use as dyes for paper, writing inks, leather and textiles.

Man exposed via the environment

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

The risk assessment shows that the margin of safety can be assumed to be sufficient, but that risks cannot be excluded at any exposure, as the substance is identified as non-threshold carcinogen.

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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)
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[5]
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
w	gram weight
GLP	good laboratory practice
h	hour(s)
ha	Hectares / *h*
HPLC	high pressure liquid chromatography
IARC	International Agency for Research on Cancer
C_{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)
log	logarithm to the basis 10
$L(E)C_{50}$	lethal concentration, median
m	Meter
µg	microgram(s)
mg	milligram(s)

[5] Commission of the European Communities, 1996. Technical Guidance Documents 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]

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

European Commission

EUR 19727 – European Union Risk Assessment Report
4,4'-methylenedianiline, Volume 9

Editors: B.G. Hansen, S.J. Munn, S. Pakalin, C.J.A. Heidorn, R. Allanou, S. Scheer, G. Pellegrini, S. Vegro, M. Luotamo, J. De Bruijn, F. Berthault, H. Loonen, K. Vormann, A. Naughton, V. Anfossi, L. Praderio

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The report provides the comprehensive risk assessment of the substance 4,4'-Methylenedianiline. It has been prepared by Germany in the frame of Council Regulation (EEC) No. 793/93 on the evaluation and control of the risks of existing substances, following the principles for assessment of the risks to man and the environment, laid down in Commission Regulation (EC) No. 1488/94.

The evaluation considers the emissions and the resulting exposure to the environment and the human populations in all life cycle steps. Following the exposure assessment, the environmental risk characterisation for each protection goal in the aquatic, terrestrial and atmospheric compartment has been determined. For human health the scenarios for occupational exposure, consumer exposure and humans exposed via the environment have been examined and the possible risks have been identified.

The human health risk assessment for 4,4'-Methylenedianiline concludes that there is at present concern for workers and consumers. For humans exposed via the environment the risk assessment concludes that a risk can not be excluded, though the risk is not of a magnitude that additional risk reduction measures are necessary. The environmental risk assessment for 4,4'-Methylenedianiline concludes that there is at present a need for further information in order to characterise the risks for the aquatic ecosystem, while no concern for the atmosphere, terrestrial ecosystem and for micro-organisms in the sewage treatment plant was concluded.

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