m-xylen-α,α'-ylenediamine

(CAS No: 1477-55-0)

Health-based Reassessment of Administrative Occupational Exposure Limits

Committee on Updating of Occupational Exposure Limits,
a committee of the Health Council of the Netherlands

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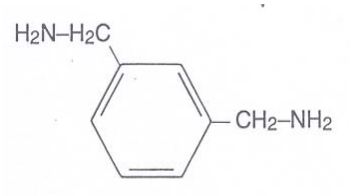
1 Introduction

The present document contains the assessment of the health hazard of *m*-xylen-α,α'-ylenediamine (MXDA) by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by AAE Wibowo, Ph.D. (Coronel Institute, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands).

The evaluation of the toxicity of MXDA has been based on the review by the American Conference of Governmental Industrial Hygienists (ACGIH) (ACG98). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, in November 1998, literature was searched in the on-line databases Medline, Embase, and Chemical Abstracts (starting from 1966, 1988, and 1970, respectively) as well as from CD-ROM versions of the databases HSELINE, CISDOC, MHIDAS, and NIOSHTIC (covering the period 1985/87 until 1998) and of Poltox (Toxline, Cambridge Scient Abstracts, FSTA, covering the period 1990 until 1995), and using the following key words: m-xylene-α,α'-diamine, xylenediamine, MXDA, and 1477-55-0. The final search was carried out in Toxline and Medline in January 2003.

In April 2003, the President of the Health Council released a draft of the document for public review. The committee received no comments.

2 Identity

name	:	*m*-xylene-α,α'-ylenediamine
synonym	:	*m*-xylene-α,α'-diamine; α,α'-diamino-*m*-xylene; 1,3-benzenedimethanamine; 1,3-bis(aminomethyl)benzene; *m*-phenylenebis(methylamine); *m*-xylenediamine
molecular formula	:	$C_8H_{12}N_2$
structural formula	:	
CAS number	:	1477-55–0

3 Physical and chemical properties

molecular weight	:	136.20
boiling point	:	200ºC (decomposes above 250ºC)
melting point	:	14.7ºC
flash point	:	>112ºC (closed cup)
vapour pressure	:	at 25ºC: 4 Pa
solubility in water	:	miscible
log $P_{octanol/water}$	:	0.15 (estimated)
conversion factors	:	at 20ºC, 101.3 kPa: 1 ppm = 5.68 mg/m^3 1 mg/m^3 = 0.18 ppm

Data from ACG98, NLM02, http://esc.syrres.com.

MXDA is a colourless liquid. Heating above 250ºC produces ammonia and secondary amines.

4 Uses

MXDA is used as a source for the production of polyamide fibres and resins. MXDA is also used as a starting chemical for the synthesis of *m*-xylene diisocyanate and as a curing agent for epoxy resins.

5 Biotransformation and kinetics

There is no data available on the biotransformation and kinetics of MXDA. However, analogous with other aromatic amines, e.g., methylenedianiline (MDA), it is expected that the compound absorbs through the skin in significant amounts. Following absorption, it is expected that at least part of MXDA will be metabolised into monoacetyl-MXDA and diacetyl-MXDA, which are rapidly excreted in the urine. It is also expected that MXDA will be activated by *N*-oxidation, to yield *N*-hydroxyl-MXDA. This metabolite can be further oxidised into nitroso-MXDA in erythrocytes in a co-oxidation reaction with oxyhaemoglobin. This yields methaemoglobin. Nitroso-MXDA can react with cysteine in haemoglobin to form a stable adduct (ECE89, Neu84). Measurement of the concentration of acetylated metabolites in urine or of haemoglobin adducts

in blood can be used for biological monitoring of workers occupationally exposed to MXDA.

6 Effects and mechanism of action

Human data

The incidence of contact dermatitis was studied in 135 male construction workers, who reported skin contact to epoxy resins and amines, the latter used as curing agents. Patch testing in 23 workers with a work history of eczema showed that 2 subjects had a positive reaction with MXDA (8.7%), while in 112 workers without eczema, 2 (1.8%) were positive (Put84). Patch testing in a 37-year-old worker, fitting industrial flooring, with a 6-month history of eczema on the forearm and hands that was linked with the introduction of a new tile adhesive caused a positive reaction with MXDA (0.1% pet.), a component of the new adhesive (Som01). MXDA was also reported as a potent skin sensitiser of workers in polyurethane silk production. Four workers with allergic contact dermatitis were examined with patch tests using various chemicals. It was found that all 4 patients had strong positive reactions to MXDA. Cross reactivity was also found for benzylamine and ethylenediamine (Ric90).

Animal data

Irritation and sensitisation

Instillation of one drop of MXDA (concentration not reported) into the eyes of rabbits (n=3) caused extensive lachrymation and severe conjunctivitis. The eyes returned to normal by the third day in 2 rabbits and by the fifth day in the third rabbit (Che53).

Fifteen-minute contact of the shaved skin of rabbits (n=3) with swatches thoroughly impregnated with MXDA (concentration not reported) caused erythema but no blisters or vehicles. The skin returned to normal after one day in one rabbit and by the third day in the 2 other rabbits (Che53). In a range-finding exposure, 6-hour covered application of concentrations of MXDA of 10, 25, 50, or 100% to the clipped back skin of guinea pigs (n=2/group) produced severe irritation and erythema while no such effects were seen following application of a 5% solution. In the subsequent sensitisation study, guinea pigs were initially treated with 5% MXDA solutions and challenged with 2% or 5% MXDA. Only

challenge at the high dose caused sensitisation in one out of 10 animals (Upm73).

Acute toxicity

Referring to unpublished information, a 1-hour LC_{50} of 3750 mg/m^3 has been determined in rats following 1-hour exposures to aerosol concentrations ranging from 1740 to 6040 mg/m^3. During exposure, frank ocular irritation, lachrymation, and dyspnoea were observed. Mortality occurred between 1 and 48 hours after exposure, with some delays for up to 14 days (the observation period). Of the surviving animals, females showed reduced weight gain. Macroscopic examination showed changes primarily in the lungs, but also in the kidneys and the liver (ACG98).

The dermal LD_{50} rabbit was 2000 mg/kg bw (ACG98).

Oral LD_{50} values were 930 and 660 mg/kg bw for rats (Moo73) and mice (Che53), respectively. Upon post-mortem examination, only irritation of the gastrointestinal tract was seen in both rats and mice (Che53, Moo73).

Repeated-dose toxicity

In guinea pigs exposed to approximately 280 mg/m^3 of MXDA, 2 hours/day, for 3 days, clinical signs of toxicity observed were impaired appetite, reduced reaction to stimuli, reduced alertness, and dyspnoea. Mortality was observed in several animals after the second exposure. No data were reported on macroscopic or microscopic examination of organs (Sha57).

The committee did not find other data from repeated-dose toxicity studies, including carcinogenicity and reproduction toxicity, with MXDA.

Mutagenicity and genotoxicity

In vitro, MXDA did not induce chromosome aberrations in cultured Chinese hamster ovary (CHO) cells, when tested in the presence or absence of a S9 metabolic activation system at concentrations up to 600 µg/mL (Enn89a).

In vivo, MXDA did not produce an inceased frequency of micronuclei in polychromatic erythrocytes sampled from the bone marrow of mice (n=5/sex/group) 24, 48, or 72 hours after a single oral dose of 750 mg/kg bw (Enn89b).

7 Existing guidelines

The current administrative occupational exposure limit (MAC) of MXDA in the Netherlands is 0.1 mg/m^3, as a ceiling value.

Existing occupational exposure limits for MXDA in various countries are summarised in the annex.

8 Assessment of health hazard

In workers, the most likely route of exposure to MXDA is through skin contact. No qualitative or quantitative data is available of the dermal absorption of the compound. However, analogous with other aromatic amines, e.g., methylene dianiline, it can be expected that MXDA will penetrate the skin. No data is available on the metabolism and elimination of MXDA. It may be assumed that by *N*-acetylation, mono- and diacetyl-MXDA will be formed as major metabolites, which are excreted in the urine. In addition, by oxidation, *N*-hydroxyl-MXDA will be formed, eventually leading to haemoglobin adducts.

Case studies in humans showed that MXDA is a skin sensitiser.

In experimental animals, the compound was irritating to the eyes and the skin of rabbits, and induced sensitisation in guinea pigs. Inhalation to high concentrations showed irritation of the lungs. Acute lethal toxicity data in test animals included a 1-hour LC_{50} of 3750 mg/m^3 in rats, a dermal LD_{50} of 2000 mg/kg bw in rabbits, and oral LD_{50} values of 930 and 660 mg/kg bw in rats and mice, respectively.

The compound did not induce an increased incidence of chromosome aberrations *in vitro* in cultured CHO cells or of micronuclei *in vivo* in polychromatic erythrocytes from bone marrow of orally treated mice.

No relevant data are available on repeated-dose toxicity, including carcinogenicity or reproduction toxicity.

The committee concludes that the toxicological data base on *m*-xylene-α,α'-ylenediamine too poor to justify recommendation of a health-based occupational exposure limit.

The committee concludes that there is insufficient information to comment on the level of the present MAC-value.

References

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ACG03a American Conference of Governmental Industrial Hygienists (ACGIH). Guide to occupational exposure values - 2003. Cincinnati OH, USA: ACGIH®, Inc, 2003: 141.

ACG03b American Conference of Governmental Industrial Hygienists (ACGIH). 2003 TLVs® and BEIs® based on the documentation of the Threshold Limit Values for chemical substances and physical agents & Biological Exposure Indices. Cincinnati OH, USA: ACGIH®, Inc, 2003: 60.

Arb02 Arbejdstilsynet. Grænseværdier for stoffer og materialer. Copenhagen, Denmark: Arbejdstilsynet, 2002: 51 (At-vejledning C.0.1).

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EC03 European Commission: Directorate General of Employment and Social Affairs. Occupational exposure limits (OELs). http://europe.eu.int/comm/employment_social/h&s/areas/oels_en.htm.

ECE89 European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC). DNA and protein adducts: evaluation of their use in exposure monitoring and risk assessment. Brussels, Belgium: ECETOC, 1989; ECETOC Monograph No 13.

Enn89a Enninga IC. Evaluation of the ability of metaxy-lenediamine to induce chromosome aberrations in cultured Chinese hamster ovary (CHO) cells (including multiple fixation times). ‘s-Hertogenbosch, the Netherlands: RCC Notox BV, 1989; RCC Notox proj no 017324 (available from NTIS, Springfield VA, USA; order no: NTIS/OTS0524014).

Enn89b Enninga IC. Micronucleus test in bone marrow cells of the mouse with metaxylenediamine. ‘s-Hertogenbosch, the Netherlands: RCC Notox BV, 1989; RCC Notox proj no 017313 (available from NTIS, Springfield VA, USA; order no: NTIS/OTS0524014).

HSE02 Health and Safety Executive (HSE). EH40/2002. Occupational Exposure Limits 2002. Sudbury (Suffolk), UK: HSE Books, 2002.

Moo73 Moore GE. Acute LD_{50} investigation in rats of m-xylenediamine (MXDA). Baltimore MD, USA: Huntington Research Center, 1973; rep no 7375.

Neu84 Neumann HG. Dosimetry and dose-response relationships. In: Monitoring human exposure to carcinogenic and mutagenic agents. Berlin A, Draper M, Hemminki K, et al, eds. IARC Scientific Publications No 59, pp115-126, 1984

NLM02 US National Library of Medicine (NLM), ed. 1,3-Benzenedimethanamide. In: Hazardous Substances Data Bank (HSDB) (last revision date MXDA file: 8 September 2001; last review date: not given); http://toxnet.nlm.nih.gov.

Put84 Van Putten PB, Coenraads PJ, Nater JP. Hand dermatitis and contact allergic reactions in construction workers exposed to epoxy resins. Contact Dermatitis 1984; 10: 146-50.

Ric90 Richter G, Kadner H. Allergische Kontaktekzeme durch m-Xylene-diamin in der Polyurethanseidenproduktion. Dermatosen 1990; 38: 117-20.

Sha57 Shahrok BK. Report on respiratory toxicity studies. Berkeley CA, USA: Bio-Research Laboratories, 1957 (available from NTIS, Springfield VA, USA; order no: NTIS/OTS 215309).

Som01 Sommer S, Wilkinson SM. Occupational contact dermatitis due to the epoxy hardener m-xylylenediamine. Contact Dermatitis 2001; 44: 374.

Swe00 Swedish National Board of Occupational Safety and Health. Occupational exposure limit values and measures against air contaminants. Solna, Sweden: National Board of Occupational Safety and Health, 2000; Ordinance AFS 2000:3.

SZW03 Ministerie van Sociale Zaken en Werkgelegenheid (SZW). Nationale MAC-lijst 2003. The Hague, the Netherlands: Sdu, Servicecentrum Uitgevers, 2003: 44.

TRG00 TRGS 900. Grenzwerte in der Luft am Arbeitsplatz; Technische Regeln für Gefahrstoffe. BArbBl 2000; 2.

Upm73 Upman PJ. Guinea pig skin sensitization of m-xylenediamine (MXDA). Baltimore MD, USA: Huntingdon Research Center, 1973; rep no 7212-334.

Annex

Occupational exposure limits for *m*-xylene-α,α'-ylenediamine in various countries.

country - organisation	occupational exposure limit		time-weighted average	type of exposure limit	note[a]	reference[b]
	ppm	mg/m^3				
the Netherlands						
- Ministry of Social Affairs and Employment	-	0.1	ceiling	administrative		SZW03
Germany						
- AGS	-	0.1	8 h			TRG00
- DFG MAK-Kommission	-	-				DFG02
Great Britain						
- HSE	-	-				HSE02
Sweden	-	-				Swe00
Denmark	-	0.02	ceiling		S	Arb02
USA						
- ACGIH	-	0.1	ceiling	TLV	S	ACG03b
- OSHA	-	-				ACG03a
- NIOSH	-	0.1	ceiling	REL	S	ACG03a
European Union						
- SCOEL	-	-				EC03

[a] S = skin notation, which means that skin absorption may contribute considerably to body burden; sens = substance can cause sensitisation.

[b] Reference to the most recent official publication of occupational exposure limits.