Recommendation from the Scientific Committee on Occupational Exposure Limits for 4,4'-methylenedianiline

8 hour TWA	:	not feasible to derive a health-based limit (see Recommendation)
STEL (15 mins)	:	not feasible to derive a health-based limit (see Recommendation)
Additional classification	:	"skin"

Substance:

4,4'-methylenedianiline

Identity and properties:

Synonyms:	bis (4-aminophenyl)methane 4,4-diaminodiphenylmethane 4,4'-diphenylmethane diamine 4,4'-methylene-bis(benzenamine), MDA
EINECS No:	202-974-4
EEC No:	
CAS No:	101-77-9
Empirical formula:	$C_{13}H_{14}N_2$
MWt:	198.3
Conversion factor:	1 ppm = 8.22 mg/m³ ; 1mg/m³ = 0.12 ppm

The following evaluation is based on the EU Risk Assessment Report 4,4'-methylenedianiline (draft 01.12.1999). Some further publications are available, confirming the evaluation of the Risk Assessment Report.

Occurrence and use

More than 98% of the total production volume of 4,4-methylenediamine (MDA), i.e. the technical-grade MDA, is used as an intermediate for the production of 4,4'-methylene diphenyl isocyanate (MDI). MDI is further processed to make polyurethanes.

Health significance

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

The evaluation of the available information from animal experiments and *in vitro* studies 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. The biological half-life of excretion of MDA metabolites in urine can be estimated to be between 9 and 14 hours. Much slower excretion has been observed in workers with relatively high exposure to MDA via skin, where half-lives of approximately 48 hours were seen.

MDA and its N-acetylated metabolites are mainly excreted in the urine. The N-acetylation apparently represents the detoxification pathway, whereas the N-hydroxylation indicated from *in vitro* studies can lead to potentially toxic intermediates.

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, myocardial effects and persistent retinal damage were reported in some cases. Acute intoxication in 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 1 000 mg/kg bw (vehicle dimethylsulfoxide) after dermal exposure; the inhalation LC_{50} for rats (>0.837 mg/l) is demonstrated to exceed the highest possible concentration in the air at room temperature. Damage to the liver and kidneys has been reported as the most prominent toxic effect in rats. Cats and dogs seem to be much more sensitive than rats. Liver and kidney damage and blindness due to retinal atrophy being the most severe effects. Fatalities were observed after oral application of 25-50 mg/kg bw.

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 sensitisation do not provide conclusive evidence of the skin sensitisation potential of MDA. However, based on the data on humans, there is convincing evidence that MDA is a skin sensitiser. MDA also demonstrates cross-reactivity to substances of the para-substituted compound group.

This conclusion is supported by a new study (Fortina *et al.* 2001). Patch testing of 6 809 patients with suspected dermatitis was positive for MDA in 132 patients (1.9%). There was a highly significant correlation between sensitivity to MDA and para-groups. The frequency of concomitant positive reactions to other allergens was high.

The main toxic effects in rats and mice after repeated oral exposure to MDA via food were degeneration and fibrosis in the liver, bile duct hyperplasia and hyperplastic lesions of the thyroid. Further treatment-related effects were anaemia, irritation of the

stomach, basophilic hypertrophy of the pituitary and kidney toxicity. From a subchronic study (Ciba-Geigy 1982) LOAELs for the most sensitive adverse (non-neoplastic) effect were 7.5 mg/kg bw/d for male rats and 8 mg/kg bw/d for female rats. These LOAELs correspond to the LOAELs on non-neoplastic effects from the 2-year study in rats with 9 and 10 mg/kg bw/d for male and female rats, respectively. Although the NTP studies had not examined parameters of haematology, bioclinical chemistry and urinanalysis, 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 in rats. The database of MDA-related toxic effects on mice is more limited than that in rats. NOAELs of 11.4 mg/kg bw/d for male mice and 14.4 mg/kg bw/d for female mice can be derived from a 90-day study (NTP 1983). No valid repeated dose studies with inhalation and dermal application route were available.

A new publication from Dugas *et al.* (2001) showed that MDA is more toxic in female than in male rats and that gender has a significant effect on the disposition and biliary excretion of MDA metabolites.

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 at high doses. Furthermore, a high MDA dose led to DNA fragmentation in rat liver cells. Weak marginal effects were obtained for induction of SCE (mouse bone marrow) and DNA binding (rat liver). *In vivo* DNA repair (UDS) tests were negative for livers of rats and mice.

Zhong *et al.* (2001) showed that micronuclei formation *in vitro* (V79 cells) was due to interaction between MDA and DNA, resulting in chromosome breakage. Robbiano *et al.* (1999) found that MDA, which does not induce kidney tumours, does not induce DNA damage in kidney cells *in vitro* or *in vivo*.

MDA is carcinogenic in experimental animals. Long-term studies on rats and mice indicated that oral MDA treatment was associated with tumours of the thyroid and the liver. For the MDA-dichloride (*Dybing et al.* (1997)) a T_{25}-value of 8.4 mg/kg per day has been calculated. For MDA a corrected value of 6.4 mg/kg per day is given. The results from the reports on human exposure did not show clearly the presence of carcinogenic activity in humans. Various reports of limited reliability which describe effects after repeated exposures of humans showed a coincidence of bladder cancer and work in areas with exposure to MDA.

The mechanism of MDA carcinogenicity is not yet known. On the basis of the results of carcinogenicity studies in animals and the results of genotoxicity studies, and also in the 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 ruled out.

There is insufficient information on a possible toxic potential of MDA with respect to reproduction.

Recommendation

There is sufficient evidence of carcinogenic potential of MDA in rats and mice. Indications for a "threshold" for the carcinogenic effects are not available. Furthermore, the long-term studies do not indicate a NOAEL. MDA is structurally related to benzidine, which is a strong human bladder carcinogen. Hence, carcinogenicity of MDA on the human urothelium cannot be ruled out. This provides a further argument that a quantitative assessment of the tumour risk for MDA in humans based on animal data is not possible. The Scientific Committee on Occupational Exposure Limits is not able to recommend a health-based 8 h TWA or STEL.

In view of the evidence for appreciable absorption of MDA through the skin, a "skin" notation is appropriate.

There is convincing evidence that MDA is a skin sensitiser.

Biological monitoring may be a useful aid in assessing exposure to MDA, particularly in the light of appreciable absorption through the skin. Analysis of MDA in the urine gives information on current exposure (Greim and Lehnert 1995), whereas analysis of MDA adducts in erythrocytes indicates cumulative exposures. These parameters are also used for monitoring exposure to 4,4'-methylene diphenyl isocyanate (MDI).

Key bibliography

EU Risk Assessment Report 4,4'-methylenedianiline. Draft of 01.12.1999

Further references

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Fortina AB, Piaserico S, Larese F, Recchia GP, Corradin MT, Gennaro F, Carrabba E, Peserico A (2001) Diaminodiphenylmethane (DDM): frequency of sensitisation, clinical relevance and concomitant positive reactions. Contact Dermatitis 44: 283-288

Greim H and Lehnert G (1995) Biological Exposure Values of Occupational Toxicants and Carcinogens

Robbiano L, Carrozzino R, Puglia CP, Corbu C, Brambilla G. (1999) Correlation between induction of DNA fragmentation and micronuclei formation in kidney cells from rats and humans and tissue-specific carcinogenic activity. Toxicol Appl Pharmacol 161: 153-159

Zhong BZ, Depree GJ, Siegel PD (2001) Differentiation of the mechanism of micronuclei induced by cysteine and glutathione conjugates of methylene-p-phenyl-diisocyanate from that of 4,4'methylenedinailine. Mutat Res 497: 29-