# 4,4'-Methylene dianiline

| CAS number: | 101-77-9 |
| --- | --- |
| Synonyms: | DADPM, DDM, p,p'-Diaminodiphenylmethane, MDA |
| Chemical formula: | C13H14N2 |
| Structural formula: | — |

Workplace exposure standard (retained)

| TWA: | **0.1 ppm (0.81 mg/m3)** |
| --- | --- |
| STEL: | **—** |
| Peak limitation: | **—** |
| Notations: | **Carc. 1B, Sk., DSEN** |
| IDLH: | **—** |
| **Sampling and analysis:** The recommended value is quantifiable through available sampling and analysis techniques. | |

## Recommendation and basis for workplace exposure standard

A TWA of 0.1 ppm (0.81 mg/m3) is recommended to protect for hepatic effects including jaundice, hepatitis and cirrhosis in exposed workers.

## Discussion and conclusions

4,4-Methylenedianiline (MDA) has primarily been used in closed system preparation of isocyanates and polyisocyanates.

Critical effects of exposure include jaundice, hepatitis, cirrhosis, myocardial and renal damage. Twelve workers whose hands were in contact with MDA containing epoxy resin for several hours a day experienced acute febrile illness associated with jaundice. In this study air concentrations of 0.1 ppm were reported. However, workers nearby who did not directly handle the resin were not affected. Dermal contact with MDA and subsequent percutaneous absorption is main route of occupational exposure, with several cases of hepatic effects reported following contact with skin. There were no reports of increased mortality or morbidity among employees of a chemical company with TWA exposures at 0.03 to 0.4 ppm (ACGIH, 2001). As such, the ACGIH recommended a TLV-TWA of 0.1 ppm for occupational exposure.

Evidence in animals suggest carcinogenicity. However, the cancers reported in animals are not considered relevant for humans and there are inadequate data available to support carcinogenicity in humans.

A TWA of 0.1 ppm is recommended to protect for hepatic effects based on the information provided by ACGIH (2001) and supported by evidence from ECHA (2006).

## Recommendation for notations

Classified as a category 1B carcinogen according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS).

Classified as a skin sensitiser and not a respiratory sensitiser according to the GHS.

A skin notation is warranted based on systemic effects resulting from skin absorption in humans.

# Appendix

### Primary sources with reports

| Source Year set Standard |
| --- |
| SWA 1991 TWA: 0.1 ppm (0.81 mg/m3) | |
|  |
| ACGIH 2001 TLV-TWA: 0.1 ppm (0.81 mg/m3) |
| TLV-TWA recommended to minimise the potential for adverse liver effects including jaundice, hepatitis, cirrhosis and tumourgenicity in exposed workers. TLV-TWA derived based on no adverse effects in workers exposed at 0.1 ppm or chemical company employees exposed at 0.03–0.4 ppm.  Summary of data:  Human data:   * Accidental consumption of MDA from contaminated flour caused jaundice in 84 people * 12/100 workers whose hands were in contact with MDA containing epoxy resin several h/d experienced acute febrile illness associated with jaundice. Workers who did not directly handle MDA but worked nearby were not affected. Air concentrations of 0.1 ppm recorded * Acute hepatitis reported in 6/300 workers coating walls with MDA containing epoxy mixtures. No air concentrations provided but ample opportunity for skin absorption * Case of worker developing transient hepatic and myocardial damage following accidental exposure via inhalation and skin; concentrations not reported * Some reports of allergic sensitivity only in exposure to mixtures, including isocyanates, confound causation * Chemical company over a period of 26 yr did not report increased mortality or morbidity among employees with TWA exposures at 0.03–0.4 ppm * No reports of cancer associated with accidental, intentional or occupational exposure in humans * No cytogenetic changes in human leukocytes *in vitro*.   Animal data:   * LD50: 597–830 mg/kg (rat, oral) * Marked interspecies differences with respect to acute toxicity; symptoms included hepatic and renal damage and blindness * Hepatic degeneration in rabbits following oral and dermal treatment suggesting absorption through skin; concentration not determined * NTP concluded MDA was carcinogenic to both sexes of F344/N rats and B6C3F1 mice: * lifetime oral carcinogenicity bioassay of both species produced reduced survival in mice (dose of 57 mg/kg/d), reduced body weight in all groups at 300 ppm, increased incidence of liver and thyroid adenomas and carcinomas in rats and increased incidence of alveolar/bronchial adenomas and malignant lymphomas in mice * dose required for carcinogenic response far greater than recommended TLV * Feeding study in dogs, 70 mg 3 times/wk for 7 y and 2 mo produced liver damage but no cancer * Mutagenic in *S. typhimurium* strains TA100 and TA98 only following metabolic activation * Slight increase in sister-chromatid exchanges in bone marrow cells of mice administered single intraperitoneal injection of 9 or 18 mg/kg.   Skin notation assigned due to systemic toxicity following dermal contact and subsequent percutaneous absorption. Insufficient data to recommend SEN notation or TLV-STEL. |
| DFG 1987 Not assigned |
| Summary of additional data:   * Can cause photosensitisation in humans * No effects in male albino rats administered 3.2 mg/kg/d, 5 d/wk for 16 wk * Positive in mutagenic test *in vivo* causing DNA strand breaks in rat liver. |
| SCOEL 2012 Not assigned |
| Chemical is grouped as non-threshold genotoxic carcinogen based on oral studies in rats, mice and dogs, and thus not possible to derive health-based OEL. Inadequate epidemiological data to support carcinogenicity in humans. |
| OARS/AIHA NA NA |
| No report. |
| HCOTN 2000 Not assigned |
| Summary of additional data:   * Estimated additional lifetime cancer risk of 4x10-3 in humans for 40 yr occupational exposure to 0.9 mg/m3. |

### Secondary source reports relied upon

| Source |  | Year | Additional information |
| --- | --- | --- | --- |
| NICNAS |  | 2014 | * LD50: 335 mg/kg; lowest reported in rats * Evidence of skin sensitisation in humans. |
| IARC |  | 1986 | * No additional data. |
| ECHA |  | 2006 | * NOEL of 3 mg/kg/d for skin lesions * NOEL of 90 mg/kg/d for systemic toxicity. |

### Carcinogenicity — non-threshold based genotoxic carcinogens

| Is the chemical mutagenic? | Insufficient data |
| --- | --- |
| Is the chemical carcinogenic with a mutagenic mechanism of action? | Insufficient data |
| **Insufficient data are available to determine if the chemical is a non-threshold based genotoxic carcinogen.** |  |

## Notations

| Source | Notations |
| --- | --- |
| SWA | Carc. 1B, Skin:Sen |
| HCIS | Carcinogenicity – category 1B, Skin sensitisation – category 1 |
| NICNAS | Carc. Cat 2, Skin sensitisation, Skin |
| EU Annex | Carcinogenicity – category 1B, Skin sensitisation – category 1 |
| ECHA | Carc. 1B, Skin Sens. 1 |
| ACGIH | Carcinogenicity – A3, Skin |
| DFG | Carcinogenicity – 2, H (skin), Sh (dermal sensitiser) |
| SCOEL | Carcinogenicity – A, Skin |
| HCOTN | NA |
| IARC | Carcinogenicity – Group 2B |
| US NIOSH | NA |

NA = not applicable (a recommendation has not been made by this Agency); — = the Agency has assessed available data for this chemical but has not recommended any notations

### Skin notation assessment

| Calculation |
| --- |
| |  |  |  |  | | --- | --- | --- | --- | | Adverse effects in human case study: | yes | 4.00 |  | | Dermal LD50 ≤1000 mg/kg: |  |  |  | | Dermal repeat-dose NOAEL ≤200 mg/kg: |  |  |  | | Dermal LD50/Inhalation LD50 <10: |  |  |  | | *In vivo* dermal absorption rate >10%: |  |  |  | | Estimated dermal exposure at WES >10%: |  |  |  | |  |  |  | **a skin notation is warranted** | |

### IDLH

| Is there a suitable IDLH value available? | No |
| --- | --- |

## Additional information

| Molecular weight: | 198.26 |
| --- | --- |
| Conversion factors at 25°C and 101.3 kPa: | 1 ppm = 8.10 mg/m3; 1 mg/m3 = 0.124 ppm |
| This chemical is used as a pesticide: |  |
| This chemical is a biological product: |  |
| This chemical is a by-product of a process: |  |
| A biological exposure index has been recommended by these agencies: | ACGIH  DFG  SCOEL |

## Workplace exposure standard history

| Year | Standard |
| --- | --- |
| Click here to enter year |  |

## References

American Conference of Industrial Hygienists (ACGIH®) (2018) TLVs® and BEIs® with 7th Edition Documentation, CD-ROM, Single User Version. Copyright 2018. Reprinted with permission. See the [*TLVs® and BEIs® Guidelines section*](http://www.acgih.org/tlv-bei-guidelines/policies-procedures-presentations) on the ACGIH website.

Deutsche Forschungsgemeinschaft (DFG) (2013) 4,40 -Diaminodiphenylmethan – MAK value documentation.

European Chemicals Agency Regulation (ECHA) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)..

EU Scientific Committee on Occupational Exposure Limits (SCOEL) (2012) Recommendation from the Scientific Committee on Occupational Exposure Limits for 4,4’-Diaminodiphenylmethane [MDA]. SCOEL/SUM/107.

International Agency for Research on Cancer (IARC) Some chemicals used in plastics and elastomers. IARC Monographs – 39.

Health Council of the Netherlands (HCOTN) (2000): Dutch Expert Committee on Occupational Standards: 4,4’-Methylene dianiline; Health-based calculated occupational cancer risk values. The Hague: Health Council of the Netherlands, 2000; publication no. 2000/11OSH.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2014) Benzenamine, 4,4'-methylenebis: Human health tier II assessment – IMAP report.

Tenth Adaptation to Technical Progress Commission Regulation (EU) No 2017/776 amending, for the purposes of its adaptation to technical and scientific progress, Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures (the CLP Regulation).