# 4,4’-Methylene bis(2-chloroaniline)

| CAS number: | 101-14-4 |
| --- | --- |
| Synonyms: | DACPM, 4,4’-methylenebis(2-chlorobenzamine), MBOCA, MOCA |
| Chemical formula: | C13H12Cl2N2 |
| Structural formula: | — |

Workplace exposure standard (interim)

| TWA: | **0.02 ppm (0.22 mg/m3)** |
| --- | --- |
| STEL: | **—** |
| Peak limitation: | **—** |
| Notations: | **Carc.1B, Sk.** |
| IDLH: | — |
| **Sampling and analysis:** There is uncertainty regarding quantification of the recommended value with available sampling and/or analysis techniques. | |

## Recommendation and basis for workplace exposure standard

A TWA of 0.02 ppm (0.22 mg/m3) is recommended to minimise the risk of cancer in exposed workers.

A priority review of the data for the chemical in the next scheduled review of the workplace exposure standards is recommended.

## Discussion and conclusions

4,4’-methylene bis(2-chloroaniline) (MOCA) is used a curing agent in polyurethane production.

Based on evidence in animals, it is considered to have carcinogenic potential in humans, particularly in the bladder and liver. Mutagenicity has been demonstrated in both *in vitro* and *in vivo* studies. Carcinogenicity is likely to act *via* a mutagenic mode of action. MOCA, is considered to be a genotoxic carcinogen (ACGIH, 2018; DFG, 1975; IARC, 2012; SCOEL 2013).

An Inhalation Unit Risk or Oral Slope Factors could not be identified to derive a risk-based TWA.

The current TWA of 0.02 ppm (0.22 mg/m3) by SWA is recommended in the interim. This recommended TWA is within one order of magnitude of the concentration of 0.02 mg/m3 calculated by the HCOTN (2000) as an additional lifetime cancer risk of four in 10,000. An evaluation of additional data sources is recommended as priority at the next scheduled review.

## Recommendation for notations

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

Not classified as a skin sensitiser or respiratory sensitiser according to the GHS.

A skin notation is recommended based on evidence of dermal uptake and the potential systemic carcinogenicity in humans.

# Appendix

### Primary sources with reports

| Source Year set Standard |
| --- |
| SWA 1991 TWA: 0.02 ppm (0.22 mg/m3) | |
|  |
| ACGIH 2001 TLV-TWA: 0.01 ppm (0.11 mg/m3) |
| TLV-TWA is recommended to minimise the significant risks of cyanosis, methemoglobinemia and adverse effects including cancer of the kidney and bladder.  Summary of data:   * Skin contact is considered a major route of exposure * Haematuria reported in a small group of workers exposed to MOCA with other chemicals; no concentrations provided * Study of 31 workers with exposure of 6 mo–16 yr: * no evidence of bladder cancer risk identified * authors of the study report considered the failure to identify excess cancer risk as not representative of a negative study because the exposure was <20 yr and the study had limited statistical power to detect an excess of cancer of the bladder * A screening study of 540 workers employed at a chemical plant producing MOCA provided the following information: * 2 cases of non-invasive papillary tumours of the bladder in non-smoking males (both <30 yr old) * no measurement of airborne concentrations within the plant were undertaken * urine samples obtained several months after production ceased had detectable MOCA levels that ranged up to 50,000 ppb * authors concluded detection of 2 tumours in young, non-smoking males is consistent with the hypothesis that MOCA induces bladder neoplasms in humans * A worker accidentally sprayed over upper body: * conjunctivitis in both eyes and complain of a sick stomach * no other symptoms of acute toxicity * MBOCA in urine indicated high dose uptake.   Animal data:   * LD50:>5,000 mg/kg (rabbits, dermal) * Exhibited toxicity characteristic of aromatic amines; cyanosis and methemoglobinemia; no further information * Clearly carcinogenic in rats, mice and dogs after oral administration * Oral study in rats for 560 d: * a higher incidence of primary lung tumours attributable to the ingestion of 1,000 ppm compared to controls * Oral study in 25 male and 25 female rats; 1,000 ppm for lifespan: * 23 male rats died with tumours (22 with multifocal hepatomas) and 20 females died with tumours (18 with multifocal hepatomas) * primary lung tumours, predominantly carcinomas in 13 rats, 10 of which also had hepatoma * 6 female beagle dogs receiving daily doses of 100 mg *via* capsule 5 d/wk for 9 yr; 6 female beagle dogs controls: * 1 dog died after 3.4 yr due to incidental disease * remaining 9 dogs survived but one dog was sacrificed because of papillary translational cell carcinoma of urinary bladder * remaining dogs were sacrificed at the end of the study; carcinomas of urinary bladder found in 3 dogs and combined transitional cell carcinoma and adenocarcinoma of urethra were observed in one dog * Formed DNA adducts in the lungs and liver of rats * Induced unscheduled DNA synthesis in rat, mouse and hamster primary hepatocytes * Mutagenic response in L5178Y mouse lymphoma cell forward mutation assay * Mutagenic in *S. typhimurium* strains TA100, TA98, TA1535, TA1537, and TA1538 and *E. coli* WP2 (uvrA)with activation system * Positive in DNA-damaging activity in *E. coli*.   Insufficient data to recommend a sensitiser notation or STEL. |
| DFG 1975 Not assigned |
| No MAK recommended based on genotoxic carcinogenic potential.  Summary of additional data:   * MOCA-DNA adduct found in urine samples taken 4–98 h following accidental dermal exposure of a worker (cited by ACGIH, 2018)   Metabolite *N-hydroxy-*MOCA mutagenic without metabolic activation in 2 *S. typhimurium* strains. |
| SCOEL 2013 Not assigned |
| No health-based OEL recommended. Considered a genotoxic carcinogen.  Summary of additional data:   * DNA adducts are formed by reaction with N-hydroxy-MOCA a metabolite produced by rats, dogs and humans by hepatic cytochromes P450 * An aromatic amine; based on similarity to benzidine expected to exert carcinogenic effects in urothelium in humans; supported limited data in humans and by the induction of urothelial carcinomas in dogs by MOCA * Readily absorbed by the skin. |
| OARS/AIHA NA NA |
| No report. |
| HCOTN 2000 Not assigned |
| Estimated additional lifetime risk of cancer.  Summary of additional data   * Reported a calculated cancer incidence of 3.7 x 10-2 per mg/kg/d based on an 18–24 mo oral diet study in rats; 0, 250, 500 and 1,000 ppm exposure groups; lung adenocarcinomas/dose 0/100, 14/100, 20/75, 31/50; statistically significant difference from controls * Calculated health-based occupational cancer risk value of 2 x 10-3 per mg/m3 based on starting point of 3.7 x 10-2 per mg/kg; assuming 75 yr life, exposed 8 h/d, 5 d/wk, 48 wk/yr, for 40 yr, inhaling 10 m3 air per 8 h * Calculated the following: * 4/10,000 (4 x 10-5) for 40 yr of exposure at 0.02 mg/m3 * 4/1,000 (4 x 10-3) for 40 yr of exposure at 2 mg/m3. |

### Secondary source reports relied upon

| Source |  | Year | Additional information |
| --- | --- | --- | --- |
| IARC |  | 2012 | * Acts similarly to other aromatic amines that are known to cause cancer of the urinary bladder in humans * Genotoxicity evidence: high micronucleus frequencies measured in exfoliated bladder epithelial cells and in peripheral lymphocytes of exposed workers * Genotoxic mechanism of action; metabolic activation, formation of DNA adducts and induction of mutagenic effects in humans. |

### Carcinogenicity — non-threshold based genotoxic carcinogens

| Is the chemical mutagenic? | Yes |
| --- | --- |
| Is the chemical carcinogenic with a mutagenic mechanism of action? | Yes |
| **The chemical is a non-threshold based genotoxic carcinogen.** |  |
| Is a cancer slope factor or inhalation unit risk value available? | No |

## Notations

| Source | Notations |
| --- | --- |
| SWA | Carc. 1B, Skin |
| HCIS | Carcinogenicity – category 1B |
| NICNAS | Carc. Cat 2 |
| EU Annex | Carcinogenicity – category 1B |
| ECHA | Carc. 1B |
| ACGIH | Carcinogenicity – A2, Skin |
| DFG | Carcinogenicity – 2, H (skin) |
| SCOEL | Skin |
| HCOTN | — |
| IARC | Carcinogenicity – Group 1 |
| 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, the chemical is a genotoxic carcinogen |
| --- | --- |

## Additional information

| Molecular weight: | 267.15 |
| --- | --- |
| Conversion factors at 25°C and 101.3 kPa: | 1 ppm = 10.92 mg/m3; 1 mg/m3 = 0.09 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) (1996) 4,4'-Methylenebis(2-chloroaniline) – MAK value documentation.

EU Scientific Committee on Occupational Exposure Limits (SCOEL) (2013) Recommendation from the Scientific Committee on Occupational Exposure Limits for 4,4’-Methylene-bis-(2-chloroaniline). SCOEL/SUM/174.

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).

Health Council of the Netherlands (HCOTN) (2000) 4,4’-Methylene bis (2-chloroaniline). Health-based calculated occupational cancer risk values. The Hague: Health Council of the Netherlands; publication no. 2000/09OSH.

International Agency for Research on Cancer (IARC) Chemical agents and related occupations. IARC Monographs – 100F.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2014) Benzenamine, 4,4'-methylenebis[2-chloro: 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).