

## N-NITROSODIMETHYLAMINE

**CAS number:** 62-75-9

**Synonyms:** N-methyl-N-nitrosomethanamine, N-nitrosodimethylamine, DMN, DMNA, dimethylnitrosoamine, nitrosodimethylamine, methanamine,N-methyl-N-nitroso-, dimethylamine,N-nitroso-

**Chemical formula:** C<sub>2</sub>H<sub>6</sub>N<sub>2</sub>O

**Structural formula:** —

### Workplace exposure standard (interim)

**TWA:** —

**STEL:** —

**Peak limitation:** —

**Notations:** Carc. 1B, Sk.

**IDLH:** —

**Sampling and analysis:** The recommended value is likely to be below the current limit of detection for standard sampling and analysis techniques.

### Recommendation and basis for workplace exposure standard

A TWA is not recommended as the available data is considered insufficient to support a health-based recommendation.

Uncertainties exist regarding carcinogenicity in humans. Therefore, it is recommended that a review of additional sources be conducted at the next scheduled review.

### Discussion and conclusions

N-nitrosodimethylamine (DMNA) is used primarily as a research chemical. However, it has also been used as an antioxidant, lubricant's additive and in the production of rocket fuels. DMNA may be formed as a by-product in the manufacture of cured meats, tobacco, rubber, dyes and in tanneries.

No quantitative human inhalation exposure data are available. No robust evidence of carcinogenicity in humans is available in the primary sources. It is carcinogenic in animals through multiple routes of exposure and it is assumed to have carcinogenic potential in humans by some sources. ACGIH (2018) classify its carcinogenicity as non-classifiable to humans. However, DFG (2004) and HCOTN (1999) cite the critical effects to humans as carcinogenicity and genotoxicity. It is structurally related to known carcinogens and similarities in metabolism between human and rodent tissues have been demonstrated. Studies indicate mutagenicity and carcinogenicity *via* reactive metabolites (ACGIH, 2018; DFG, 2004). Mutagenicity is demonstrated in *in vitro* assays. The mechanism of action for carcinogenicity is likely to act *via* a mutagenic mode of action (DFG, 2004). However, given the evidence of carcinogenicity in humans is lacking, it is unclear if cancer is a critical effect in recommending a TWA.



No occupational exposure limits are established by any of the primary sources. There is insufficient evidence to support a health-based recommendation. Given this, the status quo is recommended to be kept and no TWA is recommended. A review of additional data sources is recommended at the next scheduled review to investigate the carcinogenic potential and genotoxicity in humans.

### **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 systemic effects following dermal exposure in humans.

DRAFT

## APPENDIX

### Primary sources with reports

| Source  | Year set    | Standard            |
|---|-------------|---------------------|
| <b>SWA</b>  | <b>1991</b> | <b>Not assigned</b> |
| <b>ACGIH</b>  | <b>2001</b> | <b>Not assigned</b> |
| <p>No OEL recommended due to extreme carcinogenic potential in animals and absence of data supporting a threshold for neoplasia.</p> <p>Summary of data:</p> <p>Human data:</p> <ul style="list-style-type: none"> <li>1 death and several cases of hepatic dysfunction in workers handling DMNA; warrants skin notation</li> <li>Metabolic studies indicate carcinogenic potential <i>via</i> mutagenic and carcinogenic metabolite.</li> </ul> <p>Animal data:</p> <ul style="list-style-type: none"> <li>Oral LD<sub>50</sub> 27–41 mg/kg in male rats; hepatotoxicity</li> <li>4 h LC<sub>50</sub> 78 ppm in the rat; 57 ppm mouse</li> <li>Induced tumours via all routes of administration in all animal species tested</li> <li>Hepatic, renal and nasal carcinogen in rodents</li> <li>Synergistic relationship with other genotoxic chemicals.</li> </ul> <p>Significant mutagenicity demonstrated in mouse liver microsomes.</p> <p>Change in base sequence and deletion of 1 or more base pair changes <i>via</i> alkylation of DNA by reactive metabolites indicate genotoxic mechanism in carcinogenesis.</p> <p>Insufficient data to recommend a sensitiser notation.</p> |             |                     |
| <b>DFG</b>  | <b>2004</b> | <b>Not assigned</b> |
| <p>No MAK recommended due to carcinogenic potential.</p> <p>Summary of additional data:</p> <ul style="list-style-type: none"> <li>Reviewed as part of N-nitrosamines</li> <li>Principal target organs established in animals: liver, kidney, lung, blood vessels</li> <li>Carcinogenic effect may be demonstrated in rodents from total dose of 1 mg/kg</li> <li>87 rats continuously exposed at 0.005 mg/m<sup>3</sup> for 25 mo; no carcinogenic effects</li> <li>61 rats continuously exposed at 0.2 mg/m<sup>3</sup> for 25 mo: <ul style="list-style-type: none"> <li>12/61 lung tumours (control 5/77)</li> <li>12/61 liver tumours (control 3/77)</li> <li>32/61 kidney tumours (control 2/77).</li> </ul> </li> </ul>  |             |                     |
| <b>SCOEL</b>  | <b>NA</b>   | <b>NA</b>           |
| No report.  |             |                     |
| <b>OARS/AIHA</b>  | <b>NA</b>   | <b>NA</b>           |
| No report.  |             |                     |



| Source   | Year set    | Standard            |
|--|-------------|---------------------|
| <b>HCOTN</b>   | <b>1999</b> | <b>Not assigned</b> |
| No OEL recommended.  |             |                     |
| Summary of additional data:  |             |                     |
| <ul style="list-style-type: none"> <li>• Similarities in metabolism between human and rodent tissues have been demonstrated</li> <li>• Estimated the additional lifetime risk of cancer in humans under workplace exposure conditions, assuming: <ul style="list-style-type: none"> <li>○ lifetime of 75 yr</li> <li>○ exposure for 8 h/d, 5 d/wk for 40 yr</li> <li>○ inhales 10 m<sup>3</sup> over 8 h workday</li> </ul> </li> <li>• 4 x 10<sup>-5</sup> for 40 yr exposure at 0.002 µg/m<sup>3</sup></li> <li>• 4 x 10<sup>-3</sup> for 40 yr exposure at 0.2 µg/m<sup>3</sup>.</li> </ul> |             |                     |

## Secondary source reports relied upon

| Source | Year   | Additional information   |
|--------|--------|--|
| IARC   | ✓ 1978 | <ul style="list-style-type: none"> <li>• Carcinogenic in all animal species tested: mice, rats, hamsters, guinea pigs, rabbits and other animals</li> <li>• It induces benign and malignant tumours following administration by various routes, including ingestion and inhalation, in various organs in various species</li> <li>• Considered sufficient evidence of carcinogenicity in the animal species tested</li> <li>• No human case report or epidemiological studies were available at time of review</li> <li>• Similarities in metabolism by human and rodent tissues have been demonstrated</li> <li>• Agency considered that for practical purposes it should be regarded as carcinogenic in humans.</li> </ul> |
| NTP    | 2016   | <ul style="list-style-type: none"> <li>• Ecological studies also suggested an association between high dietary intake and high rates of oesophageal cancer in populations</li> <li>• Reasonably anticipated to be a human carcinogen based on enough evidence of carcinogenicity from studies in experimental animals; based primarily on IARC, 1978.</li> </ul>   |
| US EPA | ✓ 1987 | <ul style="list-style-type: none"> <li>• Probable human carcinogen; induction of tumours at multiple sites in both rodents and non-rodent mammals exposed by various routes</li> <li>• Mutagenic for <i>E. coli</i> and <i>S. typhimurium</i>; dependent upon the addition of a mammalian metabolism system</li> <li>• Structurally related to known carcinogens</li> <li>• A one in one hundred thousand inhalational risk of 0.0007 µg/m<sup>3</sup>.</li> </ul>   |



## Carcinogenicity — non-threshold based genotoxic carcinogens

Is the chemical mutagenic? Yes

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      | —                             |
| HCIS     | Carcinogenicity – category 1B |
| NICNAS   | NA                            |
| EU Annex | Carcinogenicity – category 1B |
| ECHA     | Carcinogenicity – category 1B |
| ACGIH    | Carcinogenicity – A3, Skin    |
| DFG      | Carcinogenicity – 2, H (skin) |
| SCOEL    | NA                            |
| HCOTN    | —                             |
| IARC     | Carcinogenicity – Group 2A    |
| 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

Dermal LD<sub>50</sub> ≤ 1000 mg/kg:

Dermal repeat-dose NOAEL ≤ 200 mg/kg:

Dermal LD<sub>50</sub>/Inhalation LD<sub>50</sub> < 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:   | 74.08  |
| Conversion factors at 25°C and 101.3 kPa:                           | 1 ppm = Number mg/m <sup>3</sup> ; 1 mg/m <sup>3</sup> = Number ppm                        |
| This chemical is used as a pesticide:                               | <input type="checkbox"/>   |
| This chemical is a biological product:                              | <input type="checkbox"/>   |
| This chemical is a by-product of a process:                         | ✓  |
| A biological exposure index has been recommended by these agencies: | <input type="checkbox"/> ACGIH <input type="checkbox"/> DFG <input type="checkbox"/> SCOEL |

## Workplace exposure standard history

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

## References

American Conference of Industrial Hygienists (ACGIH®) (2018) TLVs® and BEIs® with 7<sup>th</sup> Edition Documentation, CD-ROM, Single User Version. Copyright 2018. Reprinted with permission. See the [TLVs® and BEIs® Guidelines section](#) on the ACGIH website.

Deutsche Forschungsgemeinschaft (DFG) (2004) N-Nitrosodimethylamin – 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).

Health Council of the Netherlands (HCOTN) (1999) N-Nitrosodimethylamine (NDMA). Health based calculated occupational cancer risk values. The Hague: Health Council of the Netherlands; publication no. 1999/12OSH.

International Agency for Research on Cancer (IARC) (1978) Volume 17, Some N-Nitroso compounds. IARC Monographs on the evaluation of the carcinogenic risk to humans.

National Toxicology Program (NTP) (2016) 14th Report on Carcinogens.

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).

US Environmental Protection Authority (US EPA) (1987) Integrated Risk Information System (IRIS) Chemical Assessment Summary – N-Nitrosodimethylamine.