# Dimethyl sulphate

| CAS number: | 77-78-1 |
| --- | --- |
| Synonyms: | DMS, methyl sulfate, dimethyl sulphate |
| Chemical formula: | C2H6SO4 |
| Structural formula: | — |

Workplace exposure standard (interim)

| TWA: | **3 ppb (0.015 mg/m3)** |
| --- | --- |
| STEL: | **—** |
| Peak limitation: | **—** |
| Notations: | **Carc. 1B, Sk., DSEN** |
| 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

An interim TWA of 3 ppb (0.015 mg/m3) is recommended to protect for cancer in exposed workers.

A review of the available data sources is recommended as a priority at the next WES review.

## Discussion and conclusions

Dimethyl sulphate is used as a methylating agent in the manufacture of many organic chemicals including dyes, perfumes, pharmaceuticals, separation of mineral oils and analysis of automobile fluids (ACGIH, 2018; HCOTN, 2014).

Critical effects include severe skin and eye irritation and potential reproductive effects and bronchial and nasal cancers. Based on evidence in animals (HCOTN, 2014; NICNAS, 2013), it is characterised as a non-threshold based genotoxic carcinogen. Carcinogenicity is likely to act *via* a mutagenic mode of action. A statistically significant increase in tumours (mainly lung adenoma) was observed in mice exposed at concentrations at 3 ppm for 6 months (SCOEL, 2004).

At present, Inhalation Unit Risk or Oral Slope Factors could not be identified to derive a TWA. Using the concentration of 3 ppm, associated with tumour development, reported in mice as a starting point and applying an uncertainty factor of 1,000 (to account for interspecies variation, lack of chronic data and severity of effect), results in a recommended TWA of 3 ppb (0.015 mg/m3). The TWA of 3 ppb is recommended in the interim to protect for listed effects in exposed workers. A priority review of the available data sources is recommended.

## 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 recommended based on evidence suggesting dermal absorption and adverse systemic effects in humans and animals.

# Appendix

### Primary sources with reports

| Source Year set Standard |
| --- |
| SWA 1991 TWA: 0.1 ppm (0.52 mg/m3) | |
|  |
| ACGIH 2001 TLV-TWA: 0.1 ppm (0.5 mg/m3) |
| TLV-TWA recommended to protect against skin and eye irritation and potential reproductive effects reported in rodents.  TLV-TWA is derived from evidence of irritation in workers at 1 ppm; no further information  Summary of human data:  Human data   * Symptoms include headache and giddiness with burning of the eyes reaching maximal intensity between 2–10 h: * progressing to painful, reddened eyes, photophobia, irritation of nose and throat, cough and oppression in the chest * followed by difficulty breathing, swallowing, vomiting, diarrhoea and painful urination persisting 3–4 d * eye effects are caused by metabolism of dimethyl sulphate to methanol and sulfuric acid * death as a result of circulatory failure reported in some cases * Chronic symptoms include impairment of liver function and reduction in visual fields for various colours reported after 6 yr * A review of medical records of 25 workers with employment between 8 and 25 yr; irritation of the eyes and skin at ~1 ppm (averaged); no evidence of excess cancer deaths * Epidemiologic study covering a period of 15 yr showed no excess incidence of cancers of the respiratory tract among the dimethyl sulfate workers * Skin absorption caused blistering, ulceration, necrosis and systematic toxicity at multiple sites * Inadequate evidence for carcinogenicity in humans.   Animal data   * 4 h inhalation at 30 ppm resulted in death (rats), at 15 ppm rats survived: * at 26 ppm, cats died in 1.5 wk and monkeys lived only 3 d * Inhalation study in rats exposed for 1 h/d, 5 d/wk for 30 d at 10 or 3 ppm (calculated, not measured); intense irritation and suppuration of the rats' noses; some deaths; malignant tumours among the survivors 643 d post-exposure; no further information * Cancers in offspring (late life) after pregnant rats injected with 20 mg/kg on GD 15 * Noted IARC classification Group 2A, probably carcinogenic to humans.   Insufficient data to recommend a SEN notation or TLV-STEL. |
| DFG 1980 Not assigned |
| No further information. |
| SCOEL 2004 Not assigned |
| Summary of additional data:  Human data:   * Symptoms following inhalation are irritation of upper respiratory tract, fever, irritation of conjunctivae, glottis oedema and oedema of lung and brain and corrosion of respiratory tract * Erythema and oedema following dermal exposure * Increased chromosome and chromatid aberrations in lymphocytes reported at   0.2–20 mg/m3   * Bronchial cancer after 11 yr exposure following several acute poisoning incidents, choroidal melanoma reported after 6 yr exposure.   Animal data:   * LD50: 106–440 mg/kg (rats, oral); dyspnoea, convulsions and apathy reported * LC50: 335 mg/m3 for 1 h; 45 mg/m3 for 4 h; cyanosis of mucosa, hyperaemia of lung, haemorrhage and nasal discharge * Nasal epithelial cell proliferation, hypertrophy, hyperplasia and squamous metaplasia in respiratory epithelium in rats in 2 wk inhalation study (0.5–6.3 mg/m3, 6 h/d, 5 d/wk) * Changes in CNS function, kidney, respiratory organs and peripheral blood parameters reported in inhalation exposure in rats and guinea pigs (0.29 mg/m3 for 4 mo) * Inhalation study in mice 2 h/d, 5 d/wk for 6 mo; statistically significant increase in tumours (mainly lung adenoma) observed at concentrations ≥3 ppm (1.62 mg/m3) * Nasal induced tumours with rats more sensitive than other test species |
| OARS/AIHA NA NA |
| No report. |
| HCOTN NA NA |
| * Recommends classification in category 1B (substance presumed to be carcinogenic to humans) * Potent direct-acting genotoxic based on *in-vitro* test results for primary DNA damage, gene mutations and chromosome aberrations. |

### Secondary source reports relied upon

| Source |  | Year | Additional information |
| --- | --- | --- | --- |
| NICNAS |  | 2013 | * Restricted carcinogen in Australia, approval required to use * DNA damage and/or mutations in bacteria, yeast or human cell lines * in vivo rodent studies (with oral, inhalation or intraperitoneal administration) showing genotoxicity * Carcinogenic, mutagenic, corrosive and a skin sensitiser; very toxic by inhalation and toxic by ingestion. * Human data: * lowest published lethal concentration 97 ppm/10 min. * Animal data: * LLNA gave positive results for skin sensitisation (mouse). |
| US EPA |  | 1988, 1992 | * Inadequate data available for carcinogenicity classification; cases reported cancer-related deaths including respiratory tract and bronchial carcinomas * Quantitative estimate of oral CSF and inhalation IUR not available * Animal data: * B2 probable human carcinogen based on induction of local carcinomas following inhalation in test species (rats, mice and hamsters), subcutaneous exposures in rats, and prenatal exposures. |

### 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, Sen |
| HCIS | Carcinogenicity – category 1B, Skin sensitisation – category 1 |
| NICNAS | Carc. Cat 2 |
| EU Annex | Carcinogenicity – category 1B |
| ECHA | Carc. 1B |
| ACGIH | Carcinogenicity – A3, Skin |
| DFG | Carcinogenicity – 2 H, (skin) |
| SCOEL | Skin |
| HCOTN | NA |
| IARC | Carcinogenicity – Group 2A |
| US NIOSH | SK:SYS |

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 |
| --- |
| |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | | **Conclusion:** |  |  |  |  |  |  | |  |  | 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: | 126.13 |
| --- | --- |
| Conversion factors at 25°C and 101.3 kPa: | 1 ppm = 5.15 mg/m3; 1 mg/m3 = 0.194 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 |
| --- | --- |
| 1991 | 0.1 ppm (0.52 mg/m3) |

## 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) (1998) Dimethyl sulfate – MAK value documentation.

European Chemicals Agency (ECHA) (2019) Dimethyl sulphate – REACH assessment.

EU Scientific Committee on Occupational Exposure Limits (SCOEL) (2004) Recommendation from the Scientific Committee on Occupational Exposure Limits for Dimethyl sulphate. SCOEL/SUM/111.

Health Council of the Netherlands (HCOTN) (2014) Dimethyl sulphate. Health-based calculated occupational cancer risk values. The Hague: Health Council of the Netherlands, 2014; publication no. 204/27.

International Agency for Research on Cancer (IARC) (1999) Dimethyl sulfate. IARC Monographs on the evaluation of the carcinogenic risk to humans.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2013) Sulfuric acid, dimethyl ester: 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).

U.S. Environmental Protection Agency (US EPA). (1988, 1992). Chemical Assessment Summary – Dimethyl sulfate; CASRN 77-78-1. Integrated Risk Information System (IRIS).

US National Institute for Occupational Safety and Health (NIOSH) (2017) NIOSH Skin Notation Profiles: Dimethyl Sulfate (DMS).