# nicotine

| CAS number: | 54-11-5 |
| --- | --- |
| Synonyms: | 1-Methyl-2-(3-pyridyl)pyrrolidine,  (S)-3-(1-methylpyrrolidin-2-yl)pyridine,  (S)-3-(1-methyl-2-pyrrolidinyl)pyridine,  β-pyridyl-α-N-methylpyrrolidine |
| Chemical formula: | C10H14N2 |
| Structural formula: | — |

Workplace exposure standard (interim)

| TWA: | **0.5 mg/m3** |
| --- | --- |
| STEL: | **—** |
| Peak limitation: | **—** |
| Notations: | **Sk.** |
| IDLH: | **5 mg/m3** |
| **Sampling and analysis:** The recommended value is quantifiable through available sampling and analysis techniques. | |

## Recommendation and basis for workplace exposure standard

A TWA of 0.5 mg/m3 is recommended to protect for headache and nausea in exposed workers.

Given the limited data available from the primary sources, it is recommended that a review of additional sources be conducted at the next scheduled review.

## Discussion and conclusions

Nicotine is used as an insecticide, tranquilising agent and therapeutic medicine.

Critical effects of exposure are headache and nausea.

Adverse central nervous system (CNS) effects were associated with air concentrations of 1.18 mg/m3 at the workplace (HCOTN, 2005). Slight to moderate increases in respiration, heart rate and blood pressure were reported for intravenous doses at 0.6 mg in a volunteer study with some complaints of nausea and headache at 3 mg (ACGIH, 2018). Impaired foetal brain development was suggested in studies of women exposed to cigarette smoke containing nicotine (HCOTN, 2005), which is supported by evidence for developmental toxicity in rats administered subcutaneous doses at 0.1 mg/kg (DFG, 2003). A LOAEC of 10 mg/m3 for adverse liver, thymus, adrenal and uterine effects was reported in a sub-chronic combined inhalation and reproductive study in rats (ECHA, 2019).

DFG (2003) did not recommend a MAK because of absence of suitable chronic exposure data. While ACGIH (2018) recommend a TLV-TWA of 0.5 mg/m3 based on an intravenous dose study in volunteers. The current administrative occupational exposure limit (OEL) by HCOTN (2005) is presumably adopted from the TLV-TWA. Despite the present recommendations of ACGIH (2018) and HCOTN (2005), it is unclear if an air concentration of 0.5 mg/m3 is sufficiently low to protect for headaches and nausea observed at 3 mg in the intravenous dose study of volunteers. Although, it should be noted that the adaptive nature of these effects from intravenous route is unclear in the absence of chronic exposure data. Furthermore, suitable inhalational studies are not available to derive an OEL. Due to these uncertainties, the current TWA of 0.5 mg/m3 is recommended to be retained in the interim. Further assessment of additional source material is recommended during subsequent reviews to identify inhalation and chronic exposure studies.

## Recommendation for notations

Not classified as a carcinogen according to the Globally Harmonized System of Classification and Labelling on Chemicals (GHS).

Not classified as a skin or respiratory sensitiser according to the GHS. A dermal sensitiser notation is recommended by US NIOSH (2015) in addition to a dermal absorption notation based on cases of sensitisation in therapeutic patch studies with humans. These reports are also cited in the evaluations of ACGIH (2018) and DFG (2003) but are considered insufficient to assign a notation. A review of the sensitisation classification is recommended.

A skin notation is recommended based on evidence for rapid absorption through the skin and reports of acute poisonings in the workplace.

# Appendix

### Primary sources with reports

| Source Year set Standard |
| --- |
| SWA 1991 TWA: 0.5 mg/m3 | |
|  |
| ACGIH 2001 TLV-TWA: 0.5 mg/m3 |
| TLV-TWA intended to protect for nausea, vomiting, diarrhoea, gastritis, increased blood pressure and heart rate and adverse CNS effects.  Skin notation warranted based on systemic uptake from dermal exposure in workers.  Summary of data:  Toxicological data for nicotine and its sulfate and hydrochloride salts are considered in the evaluation. TLV-TWA based on human and animal IV and ingestion data in the absence of suitable inhalational data. Effective dose at 0.5 mg/m3 over an 8 h shift calculated as 0.07 mg/kg/d; based on reported endpoints in volunteer study and LOAEL of 1.14 mg/kg/d for changes in blood biochemistry in chronically exposed rats, TLV-TWA is sufficiently low to be protective of these effects.  Human data:   * Several cases of poisoning reported from ingestion and dermal absorption, often from application as insecticide:   + 30–100 ppm in blood associated with fatalities; lethal dose estimated at 50–60 mg   + autopsy in fatal cases showed dilation of right side of heart, pulmonary and brain oedema, haemorrhagic gastritis, organ congestion and kidney hyperaemia * Slight/moderate increase in respiration, heart rate and blood pressure at 0.6 mg as IV dose in volunteer study (n=46); 3 volunteers experienced nausea:   + 3 mg produced increased blood pressure and heart rate in 8/46 volunteers, initial slowed heart rate, nausea and euphoria reported in 4/46 volunteers at this dose * Diarrhoea, vomiting, nausea, headache, dizziness and neurologic stimulation reported in exposed workers * Dermal exposure produced the same symptoms as ingested doses; free base penetrates skin at higher rate than corresponding acid salts.   Animal data:   * Threshold concentration for poisoning: 0.2 mg/m3 (no further details provided) * Oral LD50: 3.3 mg/kg (mice); 53 mg/kg (rats) * Reduced feeding and growth inhibition at 60 ppm of diet in chronic feeding study (young rats, 300 d); 500 ppm in diet was lethal * Slight blood biochemistry changes at 4.56 mg/kg/d when administered in drinking water in chronic feeding study (rats, 34 wk):   + LOAEL of 1.14 mg/kg/d * Reduced gestation period at 2.7 mg/kg/d as subcutaneous injection (mice) * Reduced body weight and brain development in offspring at 6 mg/kg/d as subcutaneous injection (rats, GD 4–20) * Concentration-dependent elimination of IV doses; 4–12% excreted unchanged in urine following <48 mg/kg (dogs), 30% following 48 mg/kg dose * Following absorption, substance localises in brain (8%), kidney (14%), stomach, adrenals, nasal mucosa and salivary glands (other proportions not specified) * Mutagenicity and carcinogenicity not discussed, but carcinogenicity associated with tobacco smoking not related to nicotine exposure.   Insufficient data to recommend TLV-STEL or notations for carcinogenicity and sensitisation. |
| DFG 2003 Not assigned |
| Summary of additional data:  Available data unsuitable to derive MAK for chronic inhalational exposure in humans. Not considered carcinogenic based on 2 yr inhalation study with female rats.  Skin notation warranted based on low dermal LD50­ in animals and evidence for systemic effects in dermally exposed humans. Available data do not indicate dermal sensitisation. Reproductive toxicity not ruled out from available animal data, for which a NOAEL is not determined.  Human data:   * Absorption of 14 mg over 24 h from dermal dose of 78 mg in volunteer patch test (n=12):   + reported systemic effects were increased heart rate and blood pressure after 4 h   + erythema observed in 2 volunteers after 6 h * Cardiovascular effects also caused by acute inhalation up to 20 mg/m3 (5 min) in volunteer study * Itching and burning sensation reported in 50% of 183 or 664 volunteers in patch studies; erythema observed in 39% (n=183) or 14% (n=664):   + available dermal sensitisation studies are equivocal or inadequate to classify substance as dermal sensitiser * Addiction not expected below daily exposure (from cigarettes) of 5 mg ≈0.07 mg/kg; nicotine addiction is not reported in occupationally exposed workers * 60–80% inhalational absorption at 40–200 µg/m3 in volunteer study (n=17, duration not specified) * Urine t1/2: 8.4 h in exposed non-smoking workers.   Animal data:   * Dermal LD50: 140 mg/kg (rats), 50 mg/kg (rabbits) * No evidence for increased atherosclerosis or tumour incidence at 0.5 mg/m3 in chronic exposure study (rats, n=68, 20 h/d, 5 d/wk, 2 yr) * Decreased litter size and increased stillbirths at 0.1 mg/kg/d in developmental subcutaneous injection study (rats, GD 5–12) * Non-mutagenic *in vitro* with or without metabolic activation, equivocal clastogenicity (as induction of sister chromatid exchange, SCE) reported in Chinese hamster ovarian cells; unaffirmed induction of SCE *in vivo* at oral dose of 0.77 or 1.1 mg/kg (mice)   Insufficient data to assign respiratory sensitiser notation. |
| SCOEL NA NA |
| No report. |
| OARS/AIHA NA NA |
| No report. |
| HCOTN 2005 8-hour TWA: 0.07 ppm (0.5 mg/m3) |
| Summary of additional data:  Existing administrative OEL TWA of 0.5 mg/m3 with a skin notation; toxicological database considered insufficient to make health-based recommendation. No reliable occupational exposure data present in the available database.  Human data:   * 18% average dermal absorption rate over 24 h in volunteer patch test study * Occupational dermatitis reported in tobacco workers * Workplace study of workers exposed by inhalation (n=100) reported either nausea, vomiting, giddiness, headache, weakness or loss of appetite in 69 workers at mean air concentrations of 1.18 mg/m3; no deficits in pulmonary function noted * Agency considers available case studies of multiple myeloma and leukaemia too limited to draw conclusions on carcinogenicity:   + no association found between spraying nicotine as pesticide and incidence of multiple myeloma in farmers (n=111) compared with non-farmer controls (n=378)   + statistically significant increase in leukaemia reported in farmers spraying nicotine (n=30) compared with controls (n=47) * Possible developmental toxicity resulting from reduction in uteroplacental blood flow and decreased foetal brain development   Animal data:   * Increased locomotor activity and decreased exploratory efficiency and body weight at 1.5 and 3.8 mg/kg/d in chronic drinking water study (female rats, 131 d) * Non-mutagenic *in vitro*, but clear evidence for clastogenicity *in vitro* and *in vivo.* |

### Secondary source reports relied upon

| Source |  | Year | Additional information |
| --- | --- | --- | --- |
| ECHA |  | 2019 | * LC50: 2,300 mg/m3 (rats, 20 min) ≡190 mg/m3 (rats, 4 h) * Sub-chronic inhalation and reproductive study with treatment range 10–20 mg/m3 (rats, 6 h/d, males for 5 wk, females for 10 wk) used as basis for DNEL:   + LOAEC: 10 mg/m3 for liver cell necrosis and signs of chronic stress in adrenals, thymus and uterus   + Overall factor of 225 applied to account for allometric conversion and inter- and intraspecies differences (12.5), differences in experimental conditions and the workplace (6) and dose-response relationship and absence of an experimentally determined NOAEL (3) to arrive at long-term DNEL of 0.031 mg/m3 |
| US NIOSH |  | 2015 | * Acute and chronic exposure data for humans and animals indicate systemic availability following dermal absorption with the potential to cause a variety of symptoms; critical effects include adverse CNS effects, chronic cerebrovascular disease and pregnancy loss * Several studies of therapeutic dermal patch use provide sufficient evidence for skin sensitisation in humans (also cited by ACGIH, 2018 and DFG, 2003):   + 5/183 (2.6%) cases of allergic contact dermatitis reported in smokers undergoing transdermal therapy with dermal doses of 7.2–21.6 mg/d (8 wk)   + 11/664 (1.6%) cases reported in another study of therapeutic transdermal patches * Composite skin notation of SK:SYS-DIR (IRR)-SEN assigned. |

### Carcinogenicity — non-threshold based genotoxic carcinogens

| Is the chemical mutagenic? | No |
| --- | --- |
| **The chemical is not a non-threshold based genotoxic carcinogen.** |  |

## Notations

| Source | Notations |
| --- | --- |
| SWA | Sk. |
| HCIS | — |
| NICNAS | NA |
| EU Annex | — |
| ECHA | — |
| ACGIH | Skin |
| DFG | H (skin) |
| SCOEL | NA |
| HCOTN | Skin |
| IARC | NA |
| US NIOSH | SK:SYS, SK:SEN |

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: | yes | 3.00 |  |  | |  | Dermal repeat-dose NOAEL ≤200 mg/kg: |  |  |  |  | |  | Dermal LD50/Inhalation LD50 <10: |  |  |  |  | |  | *In vivo* dermal absorption rate >10%: |  |  |  |  | |  | Estimated dermal exposure at WES >10%: |  |  |  |  | |  |  |  | 3  **a skin notation is warranted** | | | |

### IDLH

| Is there a suitable IDLH value available? | Yes |
| --- | --- |

## Additional information

| Molecular weight: | 162.23 |
| --- | --- |
| Conversion factors at 25°C and 101.3 kPa: | 1 ppm = 6.7 mg/m3; 1 mg/m3 = 0.15 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) (2003) Nicotine – MAK value documentation.

Health Council of the Netherlands (HCOTN) (2005) Nicotine. Health-based Reassessment of Administrative Occupational Exposure Limits. The Hague: Health Council of the Netherlands; publication no. 2000/15OSH/105(R).

European Chemicals Agency (ECHA) (2019) Nicotine – REACH assessment.

US National Institute for Occupational Safety and Health (NIOSH) (1994) Immediately dangerous to life or health concentrations – nicotine.

US National Institute for Occupational Safety and Health (NIOSH) (2015) Skin Notation Profiles: Nicotine.