# N-Vinyl-2-pyrrolidone

| CAS number: | 88-12-0 |
| --- | --- |
| Synonyms: | 1-Ethenyl-2-pyrrolidinone, vinylbutyrlactam, vinylpyrrolidinone, 1-vinylpyrrolidinone,  N-vinylpyrrolidinone, vinylpyrrolidone |
| Chemical formula: | C6H9NO |

Workplace exposure standard (new)

| TWA: | **0.01 ppm (0.046 mg/m3)** |
| --- | --- |
| STEL: | **—** |
| Peak limitation: | **—** |
| Notations: | **Carc. 2., 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 0.01 ppm (0.046 mg/m3) is recommended to protect for liver damage, upper respiratory tract (URT) irritation and carcinogenicity in exposed workers.

## Discussion and conclusions

N-vinyl-2-pyrrolidone is used in polymer and pharmaceutical production.

The critical effects of exposure are liver damage, URT irritation and carcinogenicity as observed in animals.

No quantitative human exposure data are available. A NOAEC of 0.2 ppm and LOAEC of 0.5 ppm for dose-dependent hyperplasia of the nasal epithelium and liver cell proliferation and degeneration are reported in a sub-chronic inhalation study in rats (DFG, 2017). These endpoints are consistent with the results of other less detailed sub-chronic inhalation studies in mice and rats with a LOAEC of 5 ppm for nasal irritation and 45 ppm for liver cell degeneration (ACGIH, 2018). Although chronic inhalation at 5 to 20 ppm does not affect the survival of exposed rats, but dose-dependent incidences of liver cell carcinomas and other adverse effects are consistent with those observed in sub-chronic inhalation studies (ACGIH, 2018; DFG, 2017; HCOTN, 2007). Although a NOAEC for carcinogenic activity is not determined experimentally in the available chronic exposure studies, the carcinogenic mechanism of action is non-genotoxic based on *in vitro* and *in vivo* mutagenicity data (ACGIH, 2018; DFG, 2017). Carcinogenic action likely depends on the generation of acidic metabolites, which cause cytotoxicity and chronic irritation in the liver (ACGIH, 2018; HCOTN, 2007). Prevention of these effects is likely to protect for carcinogenicity. Therefore, the NOAEC 0.2 ppm for liver cell proliferation and nasal irritation in rats may be regarded as a NOAEC for liver cancer (DFG, 2017).

ACGIH (2018) recommends a TLV-TWA of 0.05 ppm based on the LOAEC of 5 ppm and associated dose-response relationship for nasal epithelial damage in mice. DFG (2018) recommends a MAK of 0.01 ppm based on the more recently reported NOAEC of 0.2 ppm for nasal irritation and liver toxicity in rats. Carcinogenicity is likely due to chronic cell proliferation and liver degeneration caused by acidic metabolites and protection for these effects is considered preventative of cancer. In view of the more recently reported NOAEC of 0.2 ppm in rats, the TWA of 0.01 ppm by DFG (2017) is recommended to be adopted and expected to be protective of local irritation, liver damage and potential carcinogenicity.

## Recommendation for notations

Classified as a category 2 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 due to evidence of dermal absorption and contribution to adverse systemic effects in animals.

# Appendix

### Primary sources with reports

| Source Year set Standard |
| --- |
| SWA NA NA | |
| No report. |
| ACGIH 2003 TLV-TWA: 0.05 ppm (0.23 mg/m3) |
| TLV-TWA intended to protect for liver toxicity and nasal tissue damage.  Summary of information:  TLV-TWA based on LOAEC of 5 ppm for slight liver toxicity and nasal tissue damage in mice. Effects at the LOAEC minimal and a dose-response relationship established with results from higher doses; TLV-TWA of 0.05 ppm therefore considered protective of critical effects.  Human data:   * No adverse effects in exposed workers (n=94) compared with controls (n=95) with average employment duration of 12.7 yr (no details on exposure provided).   Animal data:   * Lethal at 2,250 mg/kg in single oral dose study (rats): * kidney and liver damage (not specified) observed at necropsy * no such effects in survivors dosed at 1,000 and 1,500 mg/kg * Laboured breathing and no mortality at 45,000 mg/m3 (rats, 8 h) * Non-sensitising to guinea pigs (no further details provided) * Increased liver weights and minimal incidence of foci of cellular alteration at 40 mg/kg/d in repeat gavage dose (rats, 13 wk); increased incidence of liver foci at 60 and 100 mg/kg/d * Series of sub-chronic inhalation studies with exposure groups of 0, 1, 5, 15 and 45 ppm are summarised (mice, rats, 6 h/d, 5 d/wk, 7 wk–3 mo):   + changes in serum protein levels, increased liver function and haematological changes reported at 15 and 45 ppm   + hepatocyte enlargement, single-cell necrosis and degeneration at 45 ppm   + atrophy of nasal epithelium at 5–45 ppm (mice) and 15–45 ppm (rats)   + slight proliferation of bronchial epithelium (mice) after 1 wk at 45 ppm, 3 wk at 15 ppm and 7 wk at 5 ppm * NOAEC of 10 ppm for signs of toxicity reported in separate sub-chronic inhalation study (rats, mice, 6 h/d, 5 d/wk, 6 mo, no further details provided) * Dose-dependent haematological and clinical chemistry changes, increased liver weight, liver cell necrosis and hyperplasia of nasal epithelium at 0, 5, 10 and 20 ppm in chronic inhalation study (rats, 6 h/d, 5 d/wk, 2 yr, animals per group not specified):   + survival unaffected by cancer incidence   + dose-dependent incidence of liver cell carcinomas reported as 1, 6, 5 and 17 (males) and 1, 3, 6, 26 (females) for exposure groups 0, 5, 10 and 20 ppm * Non-genotoxic in 4 *in vitro* assays with bacteria and mammalian cells with or without metabolic activation * Non-mutagenic *in vivo* in micronucleus assay at oral doses of 150–600 mg/kg (mice).   Insufficient data to recommend a TLV-STEL.  Classified as a confirmed animal carcinogen with unknown relevance to humans (A3) based on results of chronic inhalation study with rats.  Skin and sensitiser notations not recommended based on human exposure data. |
| DFG 2017 MAK: 0.01 ppm (0.046 mg/m3) |
| Summary of additional information:  Critical effects are liver toxicity and hyperplasia of nasal epithelia as observed in rats. MAK based on NOAEC of 0.2 ppm and LOAEC of 0.5 ppm for these effects reported in a sub-chronic inhalation study with rats. DFG’s publication on “List of MAK and BAT values 2018” describes that the NOAEC for sensory irritation in humans may be estimated from the NOAEC for irritation of the olfactory epithelium from a suitable short-term sub-chronic inhalation study with rats applying conversion factors according to DFG methodology. Accordingly, a factor of 6 is applied to estimate the NOAEC of 0.03 ppm in humans, this value is halved to account for increased respiratory volume in the workplace and rounded down to produce the MAK of 0.01 ppm.  Classified as a category 4 carcinogen based on absence of evidence for genotoxicity and evidence proliferative effects at 0.5 ppm reported in a sub-chronic inhalation study in rats are the likely cause of dose-dependent carcinogenicity observed in a chronic inhalation study (also reported in ACGIH, 2018). Therefore, if the MAK is protective of liver toxicity, it is protective of carcinogenicity.  Amount absorbed through skin is far above amount absorbed daily by inhalation at the MAK, as such is designated with a skin notation (2014).  Human data:   * None presented.   Animal data:   * NOAEC: 0.2 ppm for liver cell proliferation and degeneration and hyperplasia of nasal epithelium reported in OECD 412-compliant sub-chronic inhalation study with exposure of 0, 0.2, 0.5, 5 and 10 ppm (rats, 6 h/d, 28 d, exposure frequency not specified):   + LOAEC of 0.5 ppm for adverse dose dependent effects in liver and nose. |
| SCOEL NA NA |
| No report. |
| OARS/AIHA NA NA |
| No report. |
| HCOTN 2007 Not assigned |
| Summary of additional information:  Available report assesses carcinogenic potential only, no existing administrative OEL or health-based recommended OEL (HBROEL) discussed or presented. No mechanistic studies available in the toxicological database. However, all available genotoxicity data indicate substance is non-genotoxic; HCOTN therefore assumes carcinogenicity observed in animals not due to genotoxic mechanism. Possible cause for carcinogenicity could be generation of acidic metabolites, with cytotoxicity and irritation, further assessment is required.  Human data:   * No data available to evaluate carcinogenicity in humans.   Animal data:   * No haematotoxicity or hepatotoxicity observed in chronic inhalation study with exposure groups 0, 5, 10 and 20 ppm (rats, 6 h/d, 5 d/wk, 2 yr, also cited by ACGIH, 2018). |

### Secondary source reports relied upon

| Source |  | Year | Additional information |
| --- | --- | --- | --- |
| NICNAS |  | 2000 | * Confusion and fatigue following single acute exposure in humans reported in poorly documented study (no further details provided) * LC50: 666 ppm (rats, 4 h) * No NOAEC for carcinogenicity determined in available chronic inhalation study (rats, 6 h/d, 5 d/wk, 2 yr, also cited by ACGIH, 2018):   + substance non-mutagenic, underlying carcinogenic mechanism not known * Dermal absorption <2% in dermal application study using 5 mg/kg on 25 cm2 of skin (dogs, 6 h):   + physicochemical properties indicate appreciable dermal absorption is anticipated, log KOW­: 0.4, water solubility ≥100,000 mg/L. |
| IARC |  | 1999 | * Insufficient evidence for carcinogenicity in humans * Limited evidence for carcinogenicity in animals * Overall: not classifiable as carcinogenic to humans (Group 3). |
| ECHA |  | 2020 | * LD50: 560 mg/kg (rabbits, dermal):   + mortality within 5 d of dosing at ≥375 mg/kg   + 100% mortality at ≥1000 mg/kg   + no mortality at 200 mg/kg * Long-term systemic DNEL of 0.022 ppm and local DNEL of 0.066 ppm derived from NOAEC of 0.2 ppm for liver cell proliferation/degeneration and nasal epithelial hyperplasia reported in sub-chronic inhalation study (rats, 6 h/d, 28 d, also presented in DFG, 2017). |

### 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 | NA |
| HCIS | Carcinogenicity – category 2 |
| NICNAS | NA |
| EU Annex | Carcinogenicity – category 2 |
| ECHA | Carc. 2 |
| ACGIH | Carcinogenicity – A3 |
| DFG | Carcinogenicity – 4, H (skin) |
| SCOEL | NA |
| HCOTN | Carcinogenicity – category 3 |
| IARC | Carcinogenicity – Group 3 |
| 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: |  |  |  | | Dermal LD50 ≤1000 mg/kg: | yes | 3.00 |  | | Dermal repeat-dose NOAEL ≤200 mg/kg: |  |  |  | | Dermal LD50/Inhalation LD50 <10: | yes | 3.00 |  | | *In vivo* dermal absorption rate >10%: | no | -3.00 |  | | Estimated dermal exposure at WES >10%: | yes | 2.00 |  | |  |  | 1.25 | **insufficient data to assign a skin notation** | |

### IDLH

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

## Additional information

| Molecular weight: | 111.14 |
| --- | --- |
| Conversion factors at 25°C and 101.3 kPa: | 1 ppm = 4.55 mg/m3; 1 mg/m3 = 0.22 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) (2014) N-Vinyl-2-pyrrolidone – MAK value documentation.

Deutsche Forschungsgemeinschaft (DFG) (2018) N-Vinyl-2-pyrrolidone – MAK value documentation.

Deutsche Forschungsgemeinschaft (DFG) (2018) List of MAK and BAT Values 2018, Section I.

European Chemicals Agency (ECHA) (2019) N-Vinyl-2-pyrrolidone – REACH assessment.

Health Council of the Netherlands (HCOTN) (2007) N-vinyl-2-pyrrolidone. Health-based calculated occupational cancer risk values. The Hague: Health Council of the Netherlands; publication no. 2007/11OSH.

International Agency for Research on Cancer (IARC) (1999) N-Vinyl-2-pyrrolidone. IARC Monographs on the evaluation of the carcinogenic risk to humans.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2000) 1-Vinyl-2-pyrrolidone – Priority Existing Chemical (PEC) Report No.11.

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).