# 1,4-Dioxane

| CAS number: | 123-91-1 |
| --- | --- |
| Synonyms: | Diethylene dioxide, diethylene dioxide,  diethylene ether, *p*-Dioxane, glycol ethylene ether |
| Chemical formula: | C4H8O2 |

Workplace exposure standard (amended)

| TWA: | **5 ppm (18 mg/m3)** |
| --- | --- |
| STEL: | — |
| Peak limitation: | — |
| Notations: | **Carc. 2, Sk.** |
| IDLH: | **500 ppm** |
| **Sampling and analysis:** The recommended value is quantifiable through available sampling and analysis techniques. | |

## Recommendation and basis for workplace exposure standard

A TWA of 5 ppm (18 mg/m3) is recommended to protect for irritation of the eye, effects in the upper respiratory tract and cancer in exposed workers.

## Discussion and conclusions

1,4-Dioxane is used in paints, as a solvent in organic products, as a stabiliser in chlorinated solvents, varnish and paint strippers, dyes and lacquers, in certain fumigants, deodorants and preservatives. It is produced by commercial dehydrogenation of ethylene glycol.

Critical effects include eye and respiratory tract irritation in exposed workers. Evidence in animals suggests that 1,4-dioxane is a carcinogen. The carcinogenicity mechanism is non-genotoxic, involving metabolic pathway saturation and the production of a cytotoxic metabolite. No unusual incidence of cancer was identified in three factories with average vapour concentrations less than 6.5 ppm with worker exposure of between 15 to 50 years (ACGIH, 2018).

Eye irritation is reported in human volunteers exposed at 50 ppm. A LOAEC of 180 mg/m3 (50 ppm) for nasal lesions is reported in a study in rats exposed by inhalation for two years (HCOTN, 2015). The TWA is derived from the LOAEC of 180 mg/m3 in rats with an application factor of 10 to account for no NOAEL and interspecies variation (same as HCOTN, 2015, except for rounding up). This is considered sufficient as the effect is local. A TWA of 18 mg/m3 is considered to protect for the local effects on eyes and respiratory tract and systemic effects for non-genotoxic 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 based on evidence in humans.

# Appendix

### Primary sources with reports

| Source Year set Standard |
| --- |
| SWA 1991 TWA: 10 ppm (36 mg/m3) | |
|  |
| ACGIH 2001 TLV-TWA: 20 ppm (72 mg/m3) |
| TLV-TWA recommended to minimise the potential for liver and kidney toxicity and at high concentrations, eye and respiratory tract irritation.  TLV-TWA is based on data on hepatotoxic and nephrotoxic effects in workers ≈1/10 the exposure required to produce carcinogenic response in animals.  Carcinogenic mechanisms consider to be non-genotoxic.  Summary of data:  Human data:   * Case report of 5 workers who died following heavy exposure for 2 mo * severe haemorrhagic nephritis and central hepatic necrosis with no jaundice * surviving workers suffered nausea, vomiting and irritation of eyes and respiratory passages * no exposure information presented * Case report of worker who died following 1 wk exposure to an average of 470 ppm * skin absorption possible route * autopsy revealed damage to kidneys, liver and brain * other workers not affected * Inhalation at 5,000 ppm for 1 min resulted in slight vertigo * No unusual incidence of cancer in 3 factories with average vapour concentrations of 1.07 ppm, 0.9 ppm and 6.5 ppm; worker exposure 15 to 50 yr; abnormal liver and kidney function in workers at 1 factory * >200 ppm is required to elicit eye, nose and throat irritation.   Animal data:   * IV lethal dose in rabbits: 1.5 g/kg; acute renal and hepatic failure * LC50:14,250 ppm (rats, 4 h) * Repeated inhalation of 800 ppm (rabbits) for 30 d resulted in fatal kidney damage * Nasal and liver tumours developed in rats ingesting 7,000–18,000 ppm in drinking water for 14–23 mo * Liver tumours (12 of 66 vs 2 of 106 in control), nasal tumours (3 of 66 vs 0 in control), and liver and kidney pathology produced in rats (both sexes) drinking water containing 1.0% 1,4-Dioxane for 2 yr * no adverse effects males and female rats receiving 0.01% (9.6 and 19 mg/kg/d respectively) * No adverse effects in: * rats, rabbits and dogs, 130–136 7 h inhalation exposures at 50 ppm over 180–195 d * guinea pigs, 82 exposures at 50 ppm in 188 d * No adverse effects observed in groups of 288 male and 288 female rats exposed to average of 111 ppm for 7 h/d, 5 d/wk for 2 yr.   No evidence of mutagenicity or genotoxicity.  Insufficient evidence to recommend sensitisation notations or STEL. |
| DFG 1996 MAK: 20 ppm (73 mg/m3) |
| Summary of additional data:   * Human volunteers exposed once at 50 ppm reported eye irritation * Carcinogenic potential when administered at high levels to experimental animals * Long-term experiment with mice; hepatocellular adenomas and carcinomas developed at the lowest dose tested of 0.05% (≈50 mg/kg/d) * NOAEL 10 mg/kg/d in drinking water in rats; 102 wk * LOAEL 100 mg/kg/d: liver and kidney toxicity; slight increase in the incidence of hepatocellular adenomas or carcinomas * 2 yr inhalation study in rats; no carcinogenic effects detected at 111 ppm 7 h/d,  5 d/wk (≡100 mg/kg/d). |
| SCOEL 2004 8-hour TWA: 20 ppm (73 mg/m3) |
| Summary of additional data:   * Studies in human volunteers exposed at 50 ppm (180 mg/m3) indicated almost total excretion of the inhaled dose with no indication of saturation of metabolism * Carcinogenicity mechanism non-genotoxic, involves metabolic pathway saturation/disruption producing a reactive, cytotoxic metabolite * TWA based on no effects in rats with lifetime exposure to 400 mg/m3 (111 ppm) and the need to avoid eye irritation (seen in human volunteers at 50 ppm; 180 mg/m3). |
| OARS/AIHA NA NA |
| No report. |
| HCOTN 2015 TWA 8 hours 6 ppm (20 mg/m3) |
| Summary of additional data:   * LOAEL of 50 ppm (180 mg/m3) in male rats; 6 h/d, 5 d/wk for 2 yr; nasal lesions * TWA based on LOAEL of 180 mg/m3 local critical effect; applying a factor of 3 extrapolate to NAEL and an interspecies factor of 3 derives 20 mg/m3; critical effect is local. |

### Secondary source reports relied upon

| Source |  | Year | Additional information |
| --- | --- | --- | --- |
| NICNAS |  | 1998 | * LD50:7,600 mg/kg (rabbits, dermal). |
| US EPA |  | 2010 | * Chronic Rfc derived from same study LOAEL 50 ppm (male rats) as HCOTN (2015) * Absence of induced mesotheliomas in female rats in drinking water study; similar pattern of effects after oral exposure in other study on female rats justifies 50 ppm LOAEL for both sexes. |

### 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 | Carc. 2, Skin |
| HCIS | Carcinogenicity – category 2 |
| NICNAS | NA |
| EU Annex | NA |
| ECHA | Carc. 2 |
| ACGIH | Carcinogenicity – A3, Skin |
| DFG | Carcinogenicity – 4, H (skin) |
| SCOEL | — |
| HCOTN | Carcinogenicity – category 1B |
| IARC | Carcinogenicity – Group 2B |
| 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: | no |  |  | | 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? | Yes |
| --- | --- |

## Additional information

| Molecular weight: | 88.11 |
| --- | --- |
| Conversion factors at 25°C and 101.3 kPa: | 1 ppm = 3.60 mg/m3; 1 mg/m3 = 0.28 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) (2016) 1,4-Dioxane – MAK value documentation.

European Chemicals Agency (ECHA) (2019) 1,4-Dioxane – REACH assessment.

EU Scientific Committee on Occupational Exposure Limits (SCOEL) (2004) Recommendation from the Scientific Committee on Occupational Exposure Limits for 1,4-dioxane. SCOEL/SUM/112.

Health Council of the Netherlands (HCOTN) (2015) 1,4-Dioxane. Health-based calculated occupational cancer risk values. The Hague: Health Council of the Netherlands; publication no. 2015/26.

International Agency for Research on Cancer (IARC) (1999) 1,4-Dioxane. IARC Monographs on the evaluation of the carcinogenic risk to humans.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (1998) Priority Existing Chemical (PEC) Number 7.

US Environmental Protection Authority (US EPA) (2010) Integrated Risk Information System (IRIS) Chemical Assessment Summary – 1,4-Dioxane.

US National Institute for Occupational Safety and Health (NIOSH) (1994) Immediately dangerous to life or health concentrations – 1,4-dioxane.