# nitrous oxide

| CAS number: | 10024-97-2 |
| --- | --- |
| Synonyms: | Dinitrogen monoxide, hyponitrous acid anhydride, laughing gas, nitrogen oxide |
| Chemical formula: | N2O |
| Structural formula: | — |

Workplace exposure standard (amended)

| TWA: | **50 ppm (90 mg/m3)** |
| --- | --- |
| STEL: | **—** |
| Peak limitation: | **—** |
| Notations: | **—** |
| IDLH: | **—** |
| **Sampling and analysis:** The recommended value is quantifiable through available sampling and analysis techniques. | |

## Recommendation and basis for workplace exposure standard

A TWA of 50 ppm (90 mg/m3) is recommended to protect for liver damage in exposed workers.

## Discussion and conclusions

Nitrous oxide is used as an anaesthetic in medical, dental and veterinary practices. It is also used as a propellant, foaming agent and an oxidant in rocket fuels.

Critical effects of exposure are hepatic, neurological, haematological and reproductive toxicity, which result from vitamin B12 inactivation and subsequent inhibition of methionine synthesis as observed in both humans and animals (ACGIH, 2018; DFG, 1998).

Neurological effects were investigated in several volunteer inhalation studies (ACGIH, 2018; DFG, 1998). The weight of evidence indicates that reaction times are unchanged at exposures between 50 and 500 ppm and short-memory impairment occurs at 500 ppm (DFG, 1998). Higher rates of liver disease are reported in chronically exposed dentists (ACGIH, 2018). Liver function impairment was observed in anaesthetists co-exposed at 200 ppm with halothane at 5 ppm, however exposure at 50 to 75 ppm produced no such effects (DFG, 1998). Increased rates of spontaneous abortions in female dentists at inferred concentrations above 1,000 ppm are reported in epidemiological studies and supported by reproductive studies with animals (ACGIH, 2018; DFG, 2007). In view of the available data, potential liver toxicity is considered to occur at occupational exposures of 200 ppm and may be expected to occur before neurological, haematological and reproductive endpoints (DFG, 1998, 2007).

The previous TWA of 25 ppm appears inconsistent with the remaining body of evidence provided by similar studies investigating comparable endpoints (ACGIH, 2018; DFG, 1998). Therefore, a TWA of 50 ppm by ACGIH (2018) is considered adequate to protect for liver damage in exposed workers and is recommended to be adopted.

## Recommendation for notations

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

Not classified as a skin or respiratory sensitiser according to the GHS.

There are insufficient data to recommend a skin notation.

# Appendix

### Primary sources with reports

| Source Year set Standard |
| --- |
| SWA 1990 TWA: 25 ppm (45 mg/m3) | |
|  |
| ACGIH 2001 TLV-TWA: 50 ppm (90 mg/m3) |
| TLV-TWA intended to protect for adverse reproductive, haematological and nervous system effects. Not classified as a human carcinogen (A4) based on animal carcinogenicity studies.  Summary of data:  TLV-TWA based on animal studies, which are supported by weak epidemiological data in humans. Based on these data, TLV-TWA is expected to be protective of embryotoxicity and potential neurotoxicity; derivation not discussed.  Human data:   * Reversible bone marrow depression at 50% in air in narcotised patients (14–17 d) * Three epidemiological studies indicate increased rate of cancers in occupationally exposed females; tumour types and locations were inconsistent across these studies:   + 3-fold higher rate of malignant subcutaneous tumours in nurse-anaesthetists exposed for 1–31 yr, but only in 1971 (n=525); presumably 1971 is the end of study (no further explanation)   + 30–100% increase in cancer rate in exposed female operating room personnel compared to matched controls, but not in males (n=489, 585) * Four epidemiological studies showed negative correlation between exposure and cancer mortality in workers exposed to waste anaesthetic gas (no further details) * Increased unplanned abortions in exposed females reported in qualitative surveys * No changes to hepatic and haematological clinical parameters in exposed hospital workers, exposures were typically between 500–1,275 ppm * Higher rate of liver and kidney disease in heavily exposed dentists (no further details) * No task performance impairment reported in exposed volunteers at 50 ppm (n=24, 4 h); non-significant increasing trend in tiredness noted * Separate volunteer study reported task performance impairment at 50 ppm, which was used by NIOSH to recommend OEL of 25 ppm.   Animal data:   * No histopathological changes including to brain, liver, kidney, and reproductive organs or biochemical markers for inflammation at up to 50% in air (mice, 4 h/d, 5 d/wk, 14 wk) * No haematopoietic changes at 1% in air (rats, duration not specified, 1–6 mo); bone marrow toxicity reported at 80% in oxygen * No effect to methionine production at 450 ppm (rats, no further details) * No evidence for carcinogenic effects in 3 chronic inhalation studies (mice, rats, 2–7 h/d,  5–7 d/wk, 15–24 mo) * Equivocal data for foetal mortality and teratogenicity in rodents are reported:   + foetal mortality above 100 ppm in developmental inhalation study with exposure groups 0, 100, 1,000 15,000 ppm (rats, 8 or 24 h/d, 5–9 d, wk 2–3 of pregnancy)   + smaller litter sizes and congenital abnormalities only at 1,000 ppm in separate study with exposure groups 0, 250, 500 and 1,000 ppm (rats, 24 h/d, GD 1–19)   + no congenital abnormalities at 0.5, 5 or 50% in air (mice, 4 h/d, GD 5–15) * Non-mutagenic *in vitro* in bacteria and mammalian cells, and *in vivo* in *Drosophila.*   Insufficient data to recommend a TLV-STEL or notations for skin absorption or sensitisation. |
| DFG 1993 MAK: 100 ppm (180 mg/m3) |
| Summary of additional data:  Critical neurological, haematological and reproductive effects are caused by vitamin B12 inactivation and subsequent inhibition of methionine synthesis. Anaesthetists co-exposed at 200 ppm with 5 ppm halothane showed 10% decreased liver function. As decrease in liver function due to nitrous oxide exposure in these workers cannot be excluded, MAK of 100 ppm is expected to be protective of these and other critical effects. Agency notes that weight of evidence suggests adverse behavioural symptoms in humans do not occur at 50 ppm.  Human data:   * No neurological symptoms at 300–1,200 ppm in dentists (10 h/wk) * Chronic overexposure or abuse causes irreversible neuromyelopathy (no further details) * Dentists co-exposed to mercury for 3,000 h over 10 yr had 2% higher incidence of neurological disorders (concentrations not specified) * Weight of evidence from acute volunteer exposure studies indicate no adverse effects to reaction time at 50–500 ppm; short-term memory impairment suggested by some studies at 500 ppm * 10% decreased liver function (measured by antipyrine metabolism) in anaesthetists co-exposed at 200 ppm with halothane at 5 ppm; effect likely due to presence of halothane * No change in antipyrine metabolism in anaesthetists and technicians exposed to 2–7 ppm halothane and 50–75 ppm nitrous oxide compared to controls * Decreased haematopoiesis in dentists exposed to 1,800–2,500 ppm, 6–27 h/wk * Normal haematological parameters at 155–180 ppm in operating room workers (2–10 yr) * Significant increase in spontaneous abortions in female dentistry assistants reported in epidemiological studies (also cited in ACGIH, 2018) associated with workplace air concentrations of 1,000 ppm (concentration inferred from type of exhaust systems used in dental practices); no impairment in fertility in females at lower exposure durations and inferred concentrations of 100 ppm * No increase in sister chromatid exchanges (SCE) or chromosomal aberrations in peripheral lymphocytes of workers exposed at 25–900 ppm.   Animal data:   * Liver methionine synthase inhibition at 1,000–1,100 ppm shown in continuous inhalation study (rats, mice, 3–8 d); after 28 d effects were indistinguishable from controls, no effects reported at 500 ppm:   + no methionine synthase inhibition from intermittent exposure in separate inhalation study with dose groups 50, 500, and 5,000 ppm (mice, 6 h/d, 5 d/wk, 2–13 wk) * Reproductive/developmental studies with rats (also presented in ACGIH, 2018) not considered for MAK evaluation due to experimental inadequacies:   + NOAEL of 10,000 ppm for foetal toxicity indicated from several additional reproductive studies (rats, 6 h/d, 5–7 d/wk, GD 1–21) * Non-mutagenic *in vitro* in bacteria and mammalian V79 cells, and *in vivo* in *Drosophila* at 400,000–800,000 ppm (1 h) in a sex-linked recessive lethal mutation study:   + dose-dependent clastogenicity shown in rats exposed to mixture of halothane and nitrous oxide at 1–500 ppm (7 h/d, 5 d/wk, 12 wk with 3 wk cessation followed by 40 wk at same regimen).   78-wk carcinogenicity study with mice (also cited in ACGIH, 2018) does not indicate potential for carcinogenic activity, but other available carcinogenicity studies are inadequate to assign a notation. |
| SCOEL NA NA |
| No report. |
| OARS/AIHA NA NA |
| No report. |
| HCOTN NA NA |
| No report. |

### Secondary source reports relied upon

| Source |  | Year | Additional information |
| --- | --- | --- | --- |
| IARC |  | 1976 | * Limited to range of anaesthetic gases in operating theatres. |

### 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 | — |
| HCIS | NA |
| NICNAS | NA |
| EU Annex | NA |
| ECHA | NA |
| ACGIH | Carcinogenicity – A4 |
| DFG | — |
| SCOEL | NA |
| HCOTN | NA |
| IARC | NA |
| 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 |
| --- |
| Insufficient data to assign a skin notation |

### IDLH

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

## Additional information

| Molecular weight: | 44.02 |
| --- | --- |
| Conversion factors at 25°C and 101.3 kPa: | 1 ppm = 1.83 mg/m3; 1 mg/m3 = 0.55 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) (2007) Nitrous oxide – MAK value documentation.

Deutsche Forschungsgemeinschaft (DFG) (1998) Nitrous oxide – MAK value documentation.

Health Council of the Netherlands (HCOTN) (2000) Nitrous oxide. Evaluation of the effects on reproduction, recommendation for classification. The Hague: Health Council of the Netherlands; publication no. 2000/03OSH.

International Agency for Research on Cancer (IARC) (1976) Nitrous oxide. IARC Monographs on the evaluation of the carcinogenic risk to humans.