

NITROETHANE

CAS number: 79-24-3

Synonyms: Ethane, nitro-

Chemical formula: $C_2H_5NO_2$

Workplace exposure standard (retained)

TWA: 100 ppm (307 mg/m³)

STEL: —

Peak limitation: —

Notations: —

IDLH: 1,000 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 100 ppm (307 mg/m³) is recommended to protect for irritant effects in exposed workers and potential for methaemoglobinaemia.

Given the limited data available in the primary sources to determine if there is a threshold for MetHb formation in humans, it is recommended that a review of additional sources be conducted at the next scheduled review.

Discussion and conclusions

Nitroethane is used as a solvent and propellant.

Critical effects of exposure are local irritation at higher concentrations and potential methaemoglobinaemia as observed in animals.

Human inhalational toxicity information is limited to a poorly documented irritation threshold at 100 ppm; no further details are available about this (DFG, 2017; SCOEL, 2012).

Methaemoglobinaemia is unequivocally regarded as the most sensitive toxic endpoint in the available source material based on a LOAEC of 100 ppm in rats (DFG, 2017; SCOEL, 2012; HCOTN, 2004). A LOAEC of 100 to 350 ppm for evidence of transient local irritation in rats reported in a sub-chronic inhalation study is disputed in the sources (DFG, 2017; SCOEL 2012). A threshold for methaemoglobinaemia in humans is not available. In the absence of further information, DFG (2017) and SCOEL (2012) consider 100 ppm as the LOAEC due to slight methaemoglobinaemia observed at this dose.

The recommendation by ACGIH (2018) is preliminarily based on a maximal tolerated dose of 500 ppm for systemic toxicity in acute and sub-chronic inhalation studies with several animal model species. However, no further justification for this limit value is provided (ACGIH, 2018). The evaluations by DFG (2017), SCOEL (2012) and HCOTN (2004) uniformly use the LOAEC of 100 ppm for methaemoglobinaemia as a point of departure. SCOEL (2012) applies an uncertainty factor of four to account for experimentally determined NOAEC and inter- and intraspecies differences. HCOTN

(2004) applies a factor of 18 to account for these uncertainties and considers the current administrative OEL of 20 ppm potentially unprotective. Neither source provides further justification for the selection of these factors. DFG (2017) applies uncertainty factors of three and two respectively to account for the absence of a NOAEC and potential increase in severity of methaemoglobinaemia from chronic exposure to extrapolate a human NOAEC of 20 ppm. This is halved to a MAK of 10 ppm to account for increased respiratory volume in the workplace.

Overall, the available evaluations indicate that the LOAEC of 100 ppm for methaemoglobinaemia in rats is the most relevant point of departure for the derivation of a TWA. However, the derivations reported in the primary source evaluations are inconsistent and the available secondary source information favours neither of these approaches.

Due to the uncertainty in the database, the current SWA TWA of 100 ppm by ACGIH (2001) is recommended to be retained to protect for potential adverse effects in exposed workers. No suitable data are available to amend the current TWA.

Methaemoglobinaemia is reported to be the more sensitive endpoint based on slight methaemoglobinaemia observed in animals and a threshold for this endpoint is not available in humans. An assessment of additional source material is recommended during subsequent reviews to determine a threshold for methaemoglobinaemia in humans.

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 sensitiser or respiratory sensitiser according to the GHS.

There are insufficient data to recommend a skin notation. However, it is noted that, based on modelled skin permeation data and analogy to nitroalkanes, the DFG (2017) and SCOEL (2012) currently assign skin notations. As such, a further literature review is recommended.

APPENDIX

Primary sources with reports

Source	Year set	Standard
SWA	1991	TWA: 100 ppm (307 mg/m³)
ACGIH	2001	TLV-TWA: 100 ppm (307 mg/m³)
<p>TLV-TWA intended to protect for irritation of mucous membranes, skin and upper respiratory tract and potential liver damage and narcosis at higher concentrations.</p> <p>Summary of data:</p> <p>Human and animal exposure database is very limited. TLV-TWA based on toleration at 500 ppm in animals without observable adverse effects at brief or prolonged exposures; it appears this refers to acute and sub-chronic inhalation study with rabbits, guinea pigs and monkeys. In the absence of further information, TLV-TWA is recommended cautiously, and it is noted that the TLV-TWA values of related compounds (e.g. 1 and 2-nitropropane and nitromethane) are lower and assigned with an A3 carcinogenicity notation.</p> <p>Human data:</p> <ul style="list-style-type: none"> • Odour threshold 2.1 ppm. <p>Animal data:</p> <ul style="list-style-type: none"> • Mortality at 13,000 ppm in acute inhalation study (rats, 6–7 h); no overt signs of toxicity at 2,200 ppm (rats, 6 h): <ul style="list-style-type: none"> ◦ respiratory irritation, narcosis and liver damage observed at high concentrations (no further information provided) • Mortality at 1,000–30,000 ppm and no toxic effects reported at 500 ppm in acute inhalation study (rabbits, guinea pigs, monkeys, 0.5–140 total h, no further details): <ul style="list-style-type: none"> ◦ liver damage observed in all dead animals ◦ no evidence of dose-related methaemoglobinaemia • Rapidly metabolised and eliminated within 30 h; excreted <i>via</i> lungs (no further details) • No sub-chronic or chronic exposure data reported • No mutagenicity data. <p>Insufficient data to assign a TLV-STEL or notations for carcinogenicity, skin absorption or sensitisation.</p>		
DFG	2017	MAK: 10 ppm (31 mg/m³)
<p>Summary of additional information:</p> <p>Inadequate human exposure data available to derive a MAK. Therefore, MAK derived from a LOAEC of 100 ppm for methaemoglobin formation and adverse spleen effects from a sub-chronic inhalation study in rats. Previous MAK of 100 ppm withdrawn.</p> <p>Derivation of MAK:</p> <ul style="list-style-type: none"> • A NOAEC of ≈20 ppm calculated using the LOAEC by dividing by UF of 3 and 2 to account for the absence of an experimentally determined NOAEC and increasing severity of effects with chronic exposure, respectively • A MAK of 10 ppm derived by dividing the NOAEC to account for increased respiratory volume at the workplace 		

Source	Year set	Standard
<p>MAK is considered protective of excess methaemoglobin formation in humans by analogy to other methaemoglobinaemia producers e.g. nitromethane and aniline and due its distance from a NAEC derived from the LOAEC of 84 ppm for decreased bw gains in chronically fed rats.</p> <p>Not considered carcinogenic based on lack of tumorigenicity in chronic inhalation study in rats.</p> <p>A skin notation is warranted based on modelled dermal uptake from a saturated aqueous solution that contributes significantly to the overall burden relative to inhalational exposure at the MAK.</p> <p>No evidence for skin or respiratory sensitisation reported in humans and animals.</p> <p>Human data:</p> <ul style="list-style-type: none"> Accidental ingestion (<90 mL) in children led to vomiting, cyanosis, and hypoxia Sensory irritation threshold of 100 ppm (no further information provided) Modelled dermal flux from 3 studies: 39, 81 and 250 µg/cm²/h, respectively. <p>Animal data</p> <ul style="list-style-type: none"> Sub-chronic inhalation studies indicate histopathological changes to spleen and methaemoglobinaemia; agency considers these effects more sensitive endpoints than irritation of olfactory epithelia; treatment range of 100–1,000 ppm (mice, rats, 6 h/d, 5 d/wk, 4–13 wk): <ul style="list-style-type: none"> LOAEC: 100 ppm (rats) for methaemoglobinaemia NOAEC: 100 ppm (mice) for methaemoglobinaemia, LOAEC: 350 ppm (mice) NOAEC: 100 ppm (rats, mice) for irritation of olfactory epithelia; LOAEC: 350 ppm, but severity did not increase with exposure duration Considered non-carcinogenic based on chronic inhalation studies of the pure substance and mixtures; increased tumorigenicity from mixtures not caused by nitroethane exposure: <ul style="list-style-type: none"> no increased tumour incidence at 84 or 168 ppm (rats, 7 h/d, 5 d/wk, 2 yr) slight decreased bw gain (<10%) observed at 84 ppm; >10% decrease at 168 ppm in females only methaemoglobin (MetHb) formation was not measured Non-sensitising when induced with 10% in saline intradermal injection and challenged with 1% solution after 2 wk (guinea pigs) Non-mutagenic <i>in vitro</i> in bacterial or mammalian cells or <i>in vivo</i> in mice. 		
SCOEL	2012	TWA: 20 ppm (62 mg/m³); STEL: 100 ppm (312 mg/m³)
<p>Summary of additional data:</p> <p>TWA derived from LOAEC of 84 ppm for bw gain delay in a chronic inhalation study in rats and supported by a LOAEC for transient, slightly elevated MetHb levels and signs of nasal irritation/inflammation at 100 ppm in rats (non-significant at terminal necropsy, only significant at interim necropsy), which SCOEL presumes to be close to the NOAEC. An OEL of 20 ppm recommended by dividing the LOAEC by overall UF of 4 to account for the absence of a NOAEC and uncertainty in the database.</p> <p>STEL derived from a reported sensory irritation threshold of 100 ppm in humans, which is presumably treated as a LOAEC for this endpoint and supported by the calculated median respiratory depression (RD₅₀).</p> <p>Not considered carcinogenic based on chronic inhalational studies in animals.</p> <p>Skin notation recommended based on modelled data and by analogy to other nitroalkanes, which suggest dermal uptake contributes to overall burden relative to inhalational exposure.</p> <p>Human data:</p> <ul style="list-style-type: none"> Sensory irritation threshold of 100 ppm (also cited in DFG, 2017); no further details on this study are provided: 		

Source	Year set	Standard
<ul style="list-style-type: none"> ○ SCOEL acknowledges the ambiguity of this reported threshold but supports the derivation of STEL by the relation of $TLV \approx 0.03 \times RD_{50} \approx 153 \text{ ppm}$ (where RD_{50} is 5,085 ppm, which SCOEL calculated from physicochemical parameters) • Modelled dermal penetration rate based on QSAR: $0.6 \text{ mg/cm}^2/\text{h}$. <p>Animal data:</p> <ul style="list-style-type: none"> • Acute inhalation study (also cited in ACGIH, 2018) reported increased mortality in rabbits at 28,850 ppm (0.5 h), 4,800 ppm (3 h), 960 ppm (12 h) • Sub-chronic inhalation studies (also cited in DFG, 2017) reported LOAEC of 100 ppm for nasal irritation and inflammation of olfactory epithelium (mice, rats, 6 h/d, 5 d/wk, 13 wk) • Chronic inhalation study (rats, 7 h/d, 5 d/wk, 2 yr, also cited in DFG, 2017) reported LOAEC of 84 ppm for delayed body weight gain • Non-mutagenic <i>in vitro</i> or <i>in vivo</i>. <p>Insufficient data to assign a sensitiser notation.</p>		
OARS/AIHA	NA	NA
No report.		
HCOTN	2004	TWA: 60 mg/m³ (20 ppm)
<p>Summary of additional data:</p> <p>Current administrative OEL of 20 ppm considered too high to be protective of methaemoglobinaemia, which is considered the critical effect based on sub-chronic inhalation studies in rats and mice. LOAEC of 100 ppm for slight increase in MetHb levels from sub-chronic inhalation study with rats and mice (also cited in DFG, 2017 and SCOEL, 2012) chosen as starting point for HBROEL derivation. An overall factor of 18 is applied to account for the absence of a NOAEC and inter- and intraspecies differences to produce the proposed HBROEL of 6 ppm.</p> <p>Animal data:</p> <ul style="list-style-type: none"> • Slight transient increase in MetHb levels (statistical significance not specified) in nasal turbinates (females only) and salivary glands at 100 ppm in sub-chronic inhalation study (mice, 6 h/d, 5 d/wk, 90 d, also cited in DFG, 2017, and SCOEL, 2012); 100 ppm regarded as LOAEC by the HCOTN • Not considered carcinogenic based on chronic inhalational studies in animals. Non-mutagenic <i>in vitro</i> or <i>in vivo</i>. 		

Secondary source reports relied upon

Source	Year	Additional information
NICNAS	* 2018	<ul style="list-style-type: none"> • Tier I: not assessed (no further information provided).

Source	Year	Additional information
ECHA	✓ 2019	<ul style="list-style-type: none"> • LD₅₀ >2,000 mg/kg (rabbits, dermal) • Chronic systemic effects more sensitive than chronic local irritational effects • Long-term systemic DNEL based on LOAEC of 100 ppm for methaemoglobinaemia from 13 wk inhalation study in rats (also cited in DFG,2017; SCOEL, 2012; and HCOTN, 2004): <ul style="list-style-type: none"> ◦ factors of 8/6 and 10/6.7 applied to LOAEC to account for exposure duration and increased respiratory volume in workers, respectively ◦ overall assessment factor of 18 applied to adjusted LOAEC to account for absence of a NOAEL, translation from sub-chronic to chronic effects and intraspecies variation to produce the DNEL of ≈3 ppm (8.4 mg/m³).
OECD	✓ 2010	<ul style="list-style-type: none"> • Grouped with nitromethane and 1-nitropropane due to similarities in chemical structure and toxicological behaviour.
US NIOSH	✓ 1994	<ul style="list-style-type: none"> • IDLH based on acute inhalation toxicity data in animals.

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	—
NICNAS	NA
EU Annex	—
ECHA	NA
ACGIH	—
DFG	H (skin)
SCOEL	Skin
HCOTN	—
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

Adverse effects in human case study:
 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%: yes

insufficient data to assign a skin notation

IDLH

Is there a suitable IDLH value available? Yes

Additional information

Molecular weight:	75.07
Conversion factors at 25°C and 101.3 kPa:	1 ppm = 3.1 mg/m ³ ; 1 mg/m ³ = 0.32 ppm
This chemical is used as a pesticide:	<input type="checkbox"/>
This chemical is a biological product:	<input type="checkbox"/>
This chemical is a by-product of a process:	<input type="checkbox"/>
A biological exposure index has been recommended by these agencies:	<input type="checkbox"/> ACGIH <input type="checkbox"/> DFG <input type="checkbox"/> SCOEL

Workplace exposure standard history

Year	Standard
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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](#) on the ACGIH website.

Deutsche Forschungsgemeinschaft (DFG) (2017) Nitroethan – MAK value documentation, German language edition.

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EU Scientific Committee on Occupational Exposure Limits (SCOEL) (2012) Recommendation from the Scientific Committee on Occupational Exposure Limits for Nitroethane. SCOEL/SUM/183.

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

Health Council of the Netherlands (HCOTN) (2004) Nitroethane. Health-based Reassessment of Administrative Occupational Exposure Limits. The Hague: Health Council of the Netherlands; publication no. 2000/15OSH/124.

Organisation for Economic Cooperation and Development (OECD) (2010) SIDS initial assessment profile – Nitroethane.

Tenth Adaptation to Technical Progress Commission Regulation (EU Annex) 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).

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

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