# Ethylene glycol dinitrate

| CAS number: | 628-96-6 |
| --- | --- |
| Synonyms: | Ethylene dinitrate, glycol dinitrate, nitroglycol, EGDN |
| Chemical formula: | C2H6O2 |
| Structural formula: | — |

Workplace exposure standard (amended)

| TWA: | **0.01 ppm (0.063 mg/m3)** |
| --- | --- |
| STEL: | **—** |
| Peak limitation: | **—** |
| Notations: | **Sk.** |
| IDLH: | **75 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 0.01 ppm (0.063 mg/m3) is recommended to protect for adverse cardiovascular effects in exposed workers.

## Discussion and conclusions

Ethylene glycol dinitrate is used in explosives and may be present in dynamite formulations up 80%. Critical effects are to the cardiovascular system, which cause increased heart-rate, reduced blood pressure and headaches at 0.066 ppm (ACGIH, 2018).

Worker case studies and volunteer experiments indicate prolonged occupational exposure above 0.04 ppm causes adverse cardiovascular effects and brief exposures at 0.06 ppm induce headaches (HCOTN, 2005). Occupational exposures to the substance are frequently mixed with nitroglycerin, which exhibits a comparable toxic mechanism of action (DFG, 2017). A NOAEC of 0.01 ppm for the onset of headaches with a corresponding LOAEC of 0.03 ppm are reported for workers exposed to nitroglycerin (DFG, 2017).

Adverse effects in human dermal exposure studies are noted and formulations containing the substance may penetrate rubber gloves causing adverse effects within two to four hours (HCOTN, 2005).

No substance-specific carcinogenicity studies are currently available, but the compound is expected to be non-genotoxic by analogy to the structurally related nitroglycerin, which has similar toxic endpoints (ECHA, 2019).

A TWA of 0.01 ppm is recommended based on a weight of evidence from these data, which indicate adverse cardiovascular effects are not expected below this concentration. This approach is adopted from the evaluation of DFG (2017) and the proposed health-based recommendation reported by HCOTN (2005).

## 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.

A skin notation is recommended based on evidence for dermal absorption and adverse systemic effects in humans and animals.

# Appendix

### Primary sources with reports

| Source Year set Standard |
| --- |
| SWA 1991 TWA: 0.05 ppm (0.31 mg/m3) | |
|  |
| ACGIH 2001 TLV-TWA: 0.05 ppm (0.31 mg/m3) |
| TLV-TWA intended to minimise potential for headaches and changes in blood pressure.  Summary of data:  TLV-TWA based on weight of evidence from human case studies, primarily from workers in the explosives industry and by analogy to the similarly toxic propylene glycol dinitrate. Most available data are for mixed exposures with nitroglycerin, but reported symptoms are expected to be due to ethylene glycol dinitrate exposure because volatility is 160-fold higher. TLV-TWA expected to be protective of effects from vasodilation that occur above 0.066 ppm.  Human data:   * No serious adverse effects noted in industries that maintained a level of 0.16–0.32 ppm * Therapeutic doses of 0.3 mg used as coronary artery dilator, which causes headaches in some individuals * Reported fatalities may have resulted from withdrawal symptoms rather than exposure * Easily absorbed through skin (no further details) * Volunteer inhalation study with mixture of ethylene glycol dinitrate and nitroglycerin reported headaches and immediate blood pressure reduction at 0.32 ppm (2 mg/m3, duration not specified); slight headaches and lower blood pressure at 0.11 ppm (0.7 mg/m3) for 25 min * Case study of explosives production workers (n=1,271) reported heart-pulse abnormalities in 143 subjects and slight headaches during shift when exposed to 0.066 ppm with peak levels at 0.1 ppm   + 0.5 ppm: >100 reported cases of poisoning (no further information provided) * US NIOSH reported mixtures with nitroglycerin caused headaches and blood pressure changes between 0.016–2.3 ppm in exposed workers:   + changes in electrocardiogram, chest pain, palpitation and nausea were reported with concentrations between 0.2–2.3 ppm   + single fatality occurred between 0.05–0.23 ppm   + recommended NIOSH ceiling level of 0.02 ppm * Greater probability of death from heart disease in dynamite production workers than control group that never worked in industry * Tolerance to headaches acquired from repeated exposure (8 h) to propylene glycol dinitrate at 0.2 ppm (no further details).   Animal data:   * None presented * No ADME, mutagenicity or carcinogenicity data presented.   A skin notation is recommended based on evidence of facile dermal absorption that contributes to overall exposure. Insufficient data to recommend a TLV-STEL or notations for carcinogenicity and sensitisation. |
| DFG 2016 MAK: 0.01 ppm (0.063 mg/m3) |
| MAK based on analogy to nitroglycerin, which has the same mechanism of action and LOAEL of 0.05 ppm for slight headaches in volunteers exposed to mixtures of ethylene glycol dinitrate and nitroglycerin. NOAEL expected to be near 0.01 ppm due to mildness of effects at the LOAEL and is supported by a NOAEL of 0.01 ppm in workers exposed to nitroglycerin.  Summary of additional data:  A skin notation is recommended based on *in vivo* data that suggests dermal exposure contributes significantly to overall internal exposure. Sensitisation notation not warranted based on only a single case of allergic reaction and by analogy to nitroglycerin, which demonstrates sensitisation potential only under prolonged or occlusive conditions.  Human data:   * Dermal absorption rate: 0.4 mg/cm2/h * Blood half-life 0.4–1.4 h in exposed workers with 0.01–0.07 µg/mL in blood * Slight decrease in blood pressure at 0.05 ppm in volunteer inhalation study with mixed exposure to nitroglycerin (n=7, 25 min) * Metabolised primarily in the liver, probably via reduction by glutathione to nitrate, nitrite and ethylene glycol * Tolerance to nitrate ester-containing drugs may be acquired, which is resolved in 36–48 h * Workers in nitroglycerin tablet production developed headaches at 0.03–0.11 ppm, but not at 0.01 ppm * Quantification of effects from inhalational exposure complicated by significant dermal uptake of vapour * One case of contact dermatitis from occupational exposure; positive when challenged with 0.01–2% aqueous solutions.   Animal data:   * Oral LD50: 540 mg/kg (rats); 460–616 mg/kg (mice) * LD100: 100 mg/kg (rabbits, subcutaneous) * Subcutaneous dose of 65 mg/kg peaked at 0.5 h in blood no longer detectable in blood after 8 h (rats) * Lethal as occlusive patch (4 x 6 cm) after 4 h – 7 d (cats); severe methemoglobinemia noted * Repeat inhalation study with treatment range: 2–26 ppm (cats, 8 h/d, 5 d/wk, 97–1,000 d):   + NOAEL: 2 ppm   + fatty degeneration of heart, liver and kidneys, haemosiderosis in liver and spleen and methemoglobinemia at 26 ppm * Haemolysis, drowsiness and some convulsions at 47–79 ppm in repeat inhalation study (mice, rats, guinea pigs, 3 mo, exposure duration and frequency not specified) * No substance-specific reproductive toxicity studies; developmental with nitroglycerin in feed reported maternal NOAEL: 86 mg/kg for reduced bw gain and increased liver weight. * No mutagenicity or carcinogenicity data available for assessment. |
| SCOEL NA NA |
| No report. |
| OARS/AIHA NA NA |
| No report. |
| HCOTN 2005 TWA: 0.05 ppm (0.3 mg/m3) |
| Summary of additional data:  Current administrative OEL is an 8-h TWA of 0.05 ppm (0.3 mg/m3) with skin notation.  Health-based recommendation (HBR-OEL) is based on a NOAEL of 0.04 ppm (0.25 mg/m3) for changes in heart-rate and reduced blood pressure and a LOAEL of 0.04 ppm for headaches in the same study. An overall factor of 4 is applied to the NOAEL/LOAEL to account for uncertainties in the monitoring methods and absence of a NOAEL for the onset of headaches. Based on the relatively rapid onset of headaches at higher concentrations (1–3 min) and sampling time of 10‑20 min in the cited case study, a 15-min STEL value is proposed in favour of an 8-h TWA. The proposed HBR-OEL is therefore a 15-min STEL of 0.008 ppm (0.05 mg/m3) and is considered protective of prolonged headaches and changes in blood pressure and heart-rate.  Human data:   * Cardiovascular system is target organ * 13.7% of substance in explosive formulation (22%) absorbed through skin * Substance, as component of dynamite, can penetrate rubber gloves; 1.5 g dynamite applied to rubber gloves for 2 h, substance present in blood samples of arms at  2.2 and 1.9 mg/L and signs of intoxication developed * Mean blood concentrations in dynamite factory workers 40–123 µg/L; measured over 4 d:   + corresponding concentrations in urine: 4.3–37.7 µg/L * Volunteer chamber study with dynamite workers reported 18% of subjects had headaches at 0.06–0.12 ppm (0.4–0.74 mg/m3) and 83% at 0.32 ppm (2 mg/m3) within 1–3 min * Case study (n=19) of combined skin and air exposure in explosives factory reported increased incidence of headaches, pulse rates and drop in blood pressure:   + workers were exposed to 0.005–0.7 ppm ≡0.03–4.35 mg/m3 (sampled over 10–20 min) and potential skin exposures of <0.1–1.0 mg over 2–4 h   + workers exposed to 0.04 ppm (0.25 mg/m3) in air and no- or minimal skin exposure only reported onset of headaches   + NOAEL: 0.04 ppm (0.25 mg/mg3) for heart rate and blood pressure changes, but headaches were still reported at this level   + LOAEL: 0.04 ppm (0.25 mg/m3) for onset of headaches.   Animal data:   * LD50: 3,800 mg/kg (rats, dermal) * Inhibits monoamine oxidase function in heart muscle, which regulates catecholamine release; withdrawal symptoms may be related to sudden release of stored catecholamines upon cessation of inhibition/exposure * No substance-specific carcinogenicity, genotoxicity or reproductive toxicity data available for assessment. |

### Secondary source reports relied upon

| Source |  | Year | Additional information |
| --- | --- | --- | --- |
| ECHA |  | 2019 | * No studies were available; conclusion based on available genotoxicity assays on nitroglycerin; not considered mutagenic based on negative results *in vitro* in bacteria and mammalian cells and *in vivo* assays in mammalian cells * No carcinogenicity studies available. |
| US NIOSH |  | 2011 | * SK:SYS assigned; capable of causing decreased blood pressure, vasodilation, headaches, dizziness, nausea, chest pains and palpitations following dermal exposures. |

### Carcinogenicity — non-threshold based genotoxic carcinogens

| Is the chemical mutagenic? | Insufficient data |
| --- | --- |
| Is the chemical carcinogenic with a mutagenic mechanism of action? | Insufficient data |
| **Insufficient data are available to determine if the chemical is a non-threshold based genotoxic carcinogen.** |  |

## Notations

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

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%: | yes | 2.00 |  | |  |  | 2 | **a skin notation is warranted** | |

### IDLH

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

## Additional information

| Molecular weight: | 152.10 |
| --- | --- |
| Conversion factors at 25°C and 101.3 kPa: | 1 ppm = 6.22 mg/m3; 1 mg/m3 = 0.161 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) (2018) Ethylene glycol dinitrate – MAK value documentation.

Health Council of the Netherlands (HCOTN) (2005) Ethylene dinitrate. Health-based calculated occupational cancer risk values. The Hague: Health Council of the Netherlands; publication no. 2000/15OSH/148.

European Chemicals Agency (ECHA) (2019) Ethylene dinitrate – REACH assessment.

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) (2011) NIOSH Skin Notation Profiles: Ethylene Glycol Dinitrate (EGDN).

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