

NITROGLYCERINE (NG)

CAS number: 55-63-0

Synonyms: Glycerol trinitrate, glyceryl trinitrate, nitroglycerol, 1,2,3-propanetriol trinitrate

Chemical formula: $C_3H_5N_3O_9$

Structural formula: —

Workplace exposure standard (amended)

TWA: 0.01 ppm (0.1 mg/m³)

STEL: 0.02 ppm (0.19 mg/m³)

Peak limitation: —

Notations: Sk., DSEN

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 (0.1 mg/m³) is recommended to protect for adverse cardiovascular changes in exposed workers.

A STEL of 0.02 ppm (0.19 mg/m³) is recommended to protect for acute headaches and irritation in exposed workers.

Discussion and conclusions

Nitroglycerine (NG) is used as an explosive and in the treatment of heart disorders.

Critical effects of exposure are cardiovascular changes that lead to headaches and reduced blood pressure. Workplace studies suggest that an air concentration of 0.01 ppm is protective of headaches and reduced blood pressure, which is consistent with a LOAEC of 0.05 ppm for moderate headaches reported in a volunteer inhalation study (ACGIH, 2018; DFG, 2011; SCOEL, 2011). Cardiovascular effects and irritation are associated with average exposures above 0.03 ppm (ACGIH, 2018). Carcinogenesis in the liver and testes (associated with the metabolic formation of nitric oxide) is reported at 30 mg/kg/day with a corresponding NOAEL of 3 mg/kg/day in a chronic feeding study in rats (DFG, 2011; SCOEL, 2011). An air concentration that would deliver an effective dose at the NOAEL for carcinogenicity is approximately 0.53 ppm (DFG, 2011).

Several workplace studies indicate a tolerance may be acquired from prolonged exposure. Re-exposure following a cessation period of approximately two days resulted in acute cardiovascular symptoms including heart failure. Additionally, the effects of exposure to NG are additive with those of structurally related nitrate esters, which may be present in common mixtures or workplace environments associated with NG handling and production (ACGIH, 2018). These factors should be considered when assessing workplace exposure conditions.

ACGIH (2018) based the TLV-TWA of 0.05 ppm on human exposure data and by analogy to propylene glycol dinitrate; no specific derivation was provided. HCOTN (2005) reported adverse effects related with vasodilation (headache and decreased blood pressure) as critical effects and considered it more sensitive endpoint than carcinogenicity reported in rats. While DFG (2011) and SCOEL (2011) based occupational limits on worker study with a NOAEL of 0.01 ppm for headaches, which is also cited by ACGIH (2018).

The available workplace and volunteer data indicate that cardiovascular effects are associated with air concentrations above 0.03 to 0.05 ppm and no adverse effects related to vasodilation are observed in workers at 0.01 ppm. Based on this, a TWA of 0.01 ppm by DFG (2011) and SCOEL (2011) is recommended. The recommended TWA is expected to protect for headaches caused by cardiovascular changes and potential carcinogenicity observed in animals at higher concentrations. A STEL of 0.02 ppm is recommended to protect for acute headaches and irritation that can result from peak exposures, as recommended by the SCOEL (2011).

Recommendation for notations

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

Classified as a skin sensitiser but not a respiratory sensitiser according to the GHS.

A skin notation is warranted as evidence indicates rapid absorption through the skin and reports of acute poisonings and contact dermatitis in the workplace.

APPENDIX

Primary sources with reports

Source	Year set	Standard
SWA	1991	TWA: 0.05 ppm (0.46 mg/m³)
ACGIH	2001	TLV-TWA: 0.05 ppm (0.46 mg/m³)
<p>TLV-TWA intended to protect for headache and decreased blood pressure. Skin notation warranted based on reports of vasodilation from dermal absorption in humans.</p> <p>Summary of data:</p> <p>Exposures to ethylene glycol dinitrate (EGDN) and NG are frequently mixed due to their use in explosives manufacture; their effects are considered additive. Available toxicological data are frequently of mixed exposures to EGDN and NG. TLV-TWA based on weight of evidence of human exposure data and by analogy to propylene glycol dinitrate (PGDN); TLV-TWA derivation and its deviation from the ceiling OEL recommended by a cited review of workplace studies, are not discussed.</p> <p>Human data:</p> <ul style="list-style-type: none"> • Severe headaches reported at 0.5 ppm in exposed workers • Single report of headaches occurring at 0.04 ppm in production plant • Sublingual dose of 0.3 mg relaxes vascular smooth muscle • Lethal dose estimated at 200 mg; however, non-lethal exposures to 1,200 mg are reported • Immediate hypotension and headaches at 0.1–0.2 ppm of NG/EGDN mixture in volunteer inhalation study (no further information provided) • Workplace study with exclusive NG exposure reported headaches and irritation at intermittent exposures of 0.03–0.11 ppm; headaches subsided at <0.01 ppm • Several reports of angina pectoris and sudden fatality reported in workers at dynamite and rocket propellant factories: <ul style="list-style-type: none"> ○ 2 of these reports suggest sudden death occurred in workers exposed at average of 0.18–0.24 ppm ○ case study reported greater incidence of heart disease in dynamite factory workers than regional average; in some cases, exposure was maintained ≤0.02 ppm. • Review of workplace studies concluded that exposure should be controlled to protect for vasodilation (indicated by throbbing headaches and reduced blood pressure); recommended 20 min ceiling concentration of 0.01 ppm for both EGDN and NG or NG alone and is considered protective if skin contact is prevented. <p>Animal data:</p> <ul style="list-style-type: none"> • None presented. <p>Insufficient data to recommend a TLV-STEL or notations for carcinogenicity or sensitisation.</p>		
DFG	2011	MAK: 0.01 ppm (0.1 mg/m³)
<p>Summary of additional data:</p> <p>Development of headaches considered the most sensitive endpoint and are likely caused by cerebral vasodilation. MAK derived from an acute inhalation study (pure NG exposure) in volunteers with a reported LOAEL of 0.05 ppm for mild to moderate headaches. This is supported by a workplace study that showed headaches were reported in workers at 0.03–0.11 ppm, but not</p>		

Source	Year set	Standard
		<p>at 0.01 ppm (also cited in ACGIH, 2018). MAK of 0.01 ppm is therefore considered protective of headaches but is additive with exposures to EGDN and PGDN.</p> <p>Carcinogenic activity, as observed in chronically fed rats with NOAEL of 3 mg/kg, is not considered likely if the MAK is observed; equivalent inhalational dose at the NOAEL would be 0.53 ppm.</p> <p>Assigned with 3B notation.</p> <p>Skin notation recommended based on established transdermal medicinal use.</p> <p>No evidence for contact dermatitis under conditions relevant to the workplace, therefore not classified as a dermal sensitiser.</p> <p>Human data:</p> <ul style="list-style-type: none"> • LOAEC: 0.05 ppm for mild–moderate headaches in 3/7 volunteers in acute inhalation study (25 min, pure NG also cited in ACGIH, 2018): <ul style="list-style-type: none"> ◦ severity of headaches increased at 0.07 ppm • Study of explosives industry workers reported headaches at 0.01–0.05 ppm and chest pains, dizziness and blood pressure changes above 0.03 ppm in workers exposed to NG and EGDN/NG mixtures • Patch tests with 0.1, 0.5 and 1% were positive, but reactions were less pronounced at 72 h compared to 48 h. <p>Animal data:</p> <ul style="list-style-type: none"> • Hepatocellular carcinomas and interstitial cell tumours in testes reported in chronic feeding study with treatment groups 0, 3, 30 and 363–434 mg/kg/d (rats, 2 yr): <ul style="list-style-type: none"> ◦ NOAEL: 3 mg/kg/d for increased tumour incidence ◦ tumour formation in higher dose groups may relate to exposure to nitric oxide (NO) metabolite, mechanism is however unclear • Negative, weakly positive genotoxicity <i>in vitro</i> in bacteria; negative results <i>in vivo</i> in dominant lethal test (rats, 13 wk) and no chromosomal aberrations in chronic feeding study at 363–434 mg/kg (rats, 2 yr).
SCOEL	2011	TWA: 0.01 ppm (0.095 mg/m³); STEL: 0.02 ppm (0.19 mg/m³)
		<p>Summary of additional data:</p> <p>Metabolic release of NO associated with adverse cardiovascular and chronic carcinogenic effects; avoidance of cardiovascular effects therefore considered to be protective of potential carcinogenicity. Dermal dose of 5 mg over 24 h in humans associated with same effect level as 0.5 mg/m³ inhalational exposure under workplace conditions. TWA derived from workplace study (also cited in ACGIH, 2018), which reported NOAEL of 0.01 ppm for these effects.</p> <p>STEL based on reported irritation (from same workplace study) that occurred at 0.03 ppm.</p> <p>Group C notation recommended based on tumorigenicity in chronic feeding study with rats (also cited in DFG, 2011).</p> <p>Skin notation recommended based on reported cardiovascular effects following dermal absorption.</p> <p>Rate of sensitisation summarised from several studies not considered sufficient to warrant sensitiser notation.</p> <p>Human data:</p> <ul style="list-style-type: none"> • Volunteer oral dose studies showed threshold limits for vasodilation, measured by metabolites 1,2-glycerol dinitrate (GDN) and 1,3-GDN, are 0.5 ng/mL and 0.4 ng/mL in blood, respectively • Dermal absorption reported to be major contributing factor in producing headaches in exposed workers at gunpowder factory at air concentrations of 1–4 mg/m³; no dependence of air concentrations on resulting symptoms noted • Headache and nausea in volunteer dermal patch study; patches delivered 5–15 mg in 24 h • Several sensitisation studies show low rate of sensitisation:



Source	Year set	Standard
		<ul style="list-style-type: none"> dynamite workers (n=4) with allergic dermatitis had positive reactions to NG no sensitisation in volunteer patch test (n=28, 12 h/d, 14 d) Epidemiological studies indicate association between NG/EGDN exposure and cardiovascular disease and excess acute myocardial infarction; unclear, but unlikely that NG alone is associated with these effects No excess mortality due to cancers in cohort studies of explosives factory (n=900) and ammunition (n=5,500) workers; non-significant increase in lung cancers noted in workers co-exposed to NG and EGDN.
OARS/AIHA	NA	NA
No report.		
HCOTN	2005	TWA: 0.05 ppm (0.5 mg/m³)
<p>Summary of additional data:</p> <p>Vasodilation causing headache and decreased blood pressure considered critical effect; is more sensitive than carcinogenic endpoint reported in rats at higher concentrations (also cited in DFG, 2011; and SCOEL, 2011).</p> <p>Current administrative OEL considered too high to protect for adverse cardiovascular effects; health-based recommended OEL (HBROEL) derived from NOAEL of 0.1 mg/m³ (0.01 ppm) for headaches and irritation in exposed workers with a corresponding LOAEL of 0.3 mg/m³ (0.03 ppm). A factor of 2 is applied to the NOAEL to account for the small difference between the NOAEL and LOAEL to arrive at the proposed HBROEL of 0.05 mg/m³ (0.006 ppm). Due to the rapid onset of headaches at peak exposures, the proposed HBROEL is a 15 min STEL.</p> <p>A skin notation is recommended based on evidence for significantly increased body burden resulting from dermal exposure.</p> <p>Human data:</p> <ul style="list-style-type: none"> Bioavailability of dermal doses from medical transdermal patches is 68–76%: <ul style="list-style-type: none"> blood t_{1/2}: 5–30 min. <p>Animal data:</p> <ul style="list-style-type: none"> Dermal absorption rate: 0.6–0.9 mg/cm²/h (rats) Available genotoxicity data are insufficient for conclusive assessment; mutagenic mechanism of action for carcinogenicity in chronically fed rats therefore not dismissed. 		

Secondary source reports relied upon

Source	Year	Additional information
NICNAS	✓ 2017	<ul style="list-style-type: none"> Allergic contact dermatitis reported in humans following application as ointment or transdermal patch: <ul style="list-style-type: none"> sensitising in humans at 0.01% (no further details) 4/10 guinea pigs exposed to 3.41 % in peanut oil, for the induction and challenge test phases developed signs consistent with sensitisation LD₅₀: >9,560 mg/kg (rats, dermal): <ul style="list-style-type: none"> available data support an amendment to the 'fatal in contact with skin' classification in the HCIS database Isolated positive <i>in vitro</i> genotoxicity test result not affirmed in a standardised <i>in vivo</i> test at 59 or 229 mg/kg/d in repeat feeding chromosomal aberration study (rats, 4–13 wk).



Source	Year	Additional information
US NIOSH	✓ 2011	<ul style="list-style-type: none"> Evidence for systemic availability following dermal absorption in animals and humans; systemic uptake causes cardiovascular changes, which can be fatal: <ul style="list-style-type: none"> tolerance gained from chronic exposure and abrupt cessation can cause lethal cardiovascular symptoms upon re-exposure in workers Human patch tests and one guinea pig maximisation test provide limited evidence that prolonged and repeated exposure causes allergic contact dermatitis Composite notation SK: SYS (FATAL)-DIR (IRR)-SEN assigned.

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	Sk.
HCIS	—
NICNAS	Carc. 2, Skin sensitisation – category 1
EU Annex	—
ECHA	—
ACGIH	Skin
DFG	Carcinogenicity – 3B, H (skin)
SCOEL	Carcinogenicity – C, Skin
HCOTN	Skin
IARC	NA
US NIOSH	SK: SYS, SK: SEN

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
Dermal LD ₅₀ ≤ 1000 mg/kg:	no
Dermal repeat-dose NOAEL ≤ 200 mg/kg:	
Dermal LD ₅₀ /Inhalation LD ₅₀ < 10:	
<i>In vivo</i> dermal absorption rate > 10%:	yes
Estimated dermal exposure at WES > 10%:	yes
a skin notation is warranted	

IDLH

Is there a suitable IDLH value available? Yes

Additional information

Molecular weight:	227.09
Conversion factors at 25°C and 101.3 kPa:	1 ppm = Number mg/m ³ ; 1 mg/m ³ = Number 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 checked="" type="checkbox"/> DFG <input type="checkbox"/> 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](#) on the ACGIH website.

Deutsche Forschungsgemeinschaft (DFG) (2018) Nitroglycerin – MAK value documentation.

Deutsche Forschungsgemeinschaft (DFG) (2011) Glycerintrinitrat – MAK value documentation, German language edition.

EU Scientific Committee on Occupational Exposure Limits (SCOEL) (2011) Recommendation from the Scientific Committee on Occupational Exposure Limits for glyceryl trinitrate. SCOEL/SUM/147.

Health Council of the Netherlands (HCOTN) (2005) Glycerol trinitrate. Health-based Reassessment of Administrative Occupational Exposure Limits. The Hague: Health Council of the Netherlands; publication no. 2000/15OSH/150.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2017) 1,2,3-Propanetriol, trinitrate: Human health tier II assessment – IMAP report.

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

US National Institute for Occupational Safety and Health (NIOSH) (2011) Skin Notation Profiles: Nitroglycerin