Social Europe

Recommendation from the Scientific Committee on Occupational Exposure Limits for glyceryl trinitrate

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Table of content

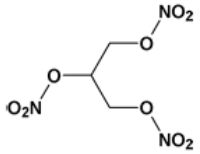
1. Occurrence/use and occupational exposure 4
2. Health significance 4
2.1. Toxicokinetics 4
2.1.1. Human data 4
2.1.2. Animal data 4
2.1.3. Biological monitoring 4
2.2. Acute toxicity 5
2.2.1. Human data 5
2.2.2. Animal data 5
2.3. Irritation and corrosivity 5
2.3.1. Human data 5
2.3.2. Animal data 6
2.4. Sensitisation 6
2.4.1. Human data 6
2.4.2. Animal data 6
2.5. Repeated dose toxicity 6
2.5.1. Human data 6
2.5.2. Animal data 7
2.6. Genotoxicity 8
2.6.1. In vitro 8
2.6.2. In vivo - Human data 8
2.6.3. In vivo - Animal data 8
2.7. Carcinogenicity 8
2.7.1. Human data 8
2.7.2. Animal data 9
2.8. Reproductive toxicity 9
2.8.1. Human data 9
2.8.2. Animal data 9
Developmental toxicity 10
Recommendations 10
References 12

Recommendation from the Scientific Committee on Occupational Exposure Limits for glycerol trinitrate (nitroglycerin)

Eight-hour TWA:	0.01 ppm (0.095 mg/m^3)
STEL (15 minutes):	0.02 ppm (0.19 mg/m^3)
Additional classification:	'skin' notation
SCOEL carcinogenicity group:	C (carcinogen with a practical threshold)
[Biological Limit Value (BLV):	not assigned – see Recommendation section]

Substance identification

Glycerol trinitrate:



Synonyms: nitroglycerin; glyceryl trinitrate; 1,2,3-propanetriol trinitrate

EC No.: 200-240-8

Annex 1 Index No.: 603-034-00-X

Classification: E; R3 - T+; R26/27/28 - R33 - N; R51-53

CAS No.: 55-63-0

MWt: 227.09

Conversion factor (20 °C, 101 kPa): 1 ppm = 9.45 mg/m^3; 1 mg/m^3 = 0.106 ppm

This evaluation is based an ACGIH (2001), ECB (2000), Greim (2006), Greim and Lehnert (1996), HCN (2005), Rosenblatt et al. (1991) and the references cited in these reviews.

Physico-chemical properties

Glycerol trinitrate (GTN) is a colourless to pale yellow, viscous liquid. The boiling point of the substance is 218 °C (explodes, decomposition starts at 50 - 60 °C) and the vapour pressure is 0.00035 - 0.002 hPa at 20 °C. The water solubility of GTN is 1.25 - 1.95 g/l at 20 °C and the log Pow is 1.62 - 1.77. The substance has a density of 1.5931 g/cm^3 (ACGIH, 2001; ECB, 2000; HCN, 2005; Rosenblatt et al., 1991).

1. Occurrence/use and occupational exposure

GTN is used in the production of dynamite and other explosives. It is used in medicine for the treatment of angina pectoris and hypertension (ACGIH, 2001; HCN, 2005).

2. Health significance

2.1. Toxicokinetics

2.1.1. Human data

Quantitative data on absorption by inhalation exposure are not available. In a study on workers exposed to GTN, dermal absorption was considered to be more important than the absorption by inhalation. Following oral application, the bioavailability was <1% (only very low plasma concentrations could be detected). After sublingual application it was 36%. The actual rate of oral absorption is presumed to be higher due to a rapid metabolism of GTN. Skin absorption in GTN-exposed workers was demonstrated by elevated concentrations of glycerol dinitrates (GDNs) in urine. In clinical studies, the dermal absorption rate of GTN from patches was 0.5 mg/cm^2 • d and the bioavailability has been estimated to be 68 - 76%. GTN was rapidly metabolised (within a few minutes) to 1,2- and 1,3-GDN. In addition to hepatic metabolism, there is relevant extrahepatic metabolism (intestine, kidney, vascular endothelial and muscle cells as well as skin). The metabolites of GTN were excreted in urine (Greim and Lehnert, 1996; HCN, 2005).

Most authors state that hydrolysis releases NO, which stimulates the guanylyl cyclase of the smooth muscle of the blood vessels, leading to increased concentrations of cyclic GMP and vascular dilation. GDNs were excreted in urine of GTN-exposed workers or patients (e.g. Greim and Lehnert, 1996; Greim, 2006; HCN, 2005). However, Kleschyov et al. (2003) proposes a vasodilatory mechanism without direct involvement of free NO, because the vascular effect at pharmacological concentrations occurred without a relevant increase of NO concentrations in blood vessels.

2.1.2. Animal data

Quantitative data on absorption by inhalation exposure are not available. Absorption by the oral route (in rodents, rabbits, dogs and monkeys) was almost complete within 24 h. The dermal absorption rates in rats were 0.6 - 0.9 mg/cm^2 • h (HCN, 2005).

GTN is rapidly metabolised to 1,2- and 1,3-GDN, glycerol mononitrate (GMN), glycerol and NO, the latter possessing vasodilatory properties. After oral GTN exposure of rats, GDNs and GMN as well as glycerol were eliminated in urine (40 - 50% of the administered dose, partially as glucuronide conjugates), and 17 - 33% were exhaled as CO2 within 24 h. Dogs and rabbits excreted up to 70% of an administered oral dose in urine (Greim and Lehnert, 1996; HCN, 2005).

2.1.3. Biological monitoring

GTN itself is metabolised within a few minutes and is not an adequate parameter of internal exposure. Gjesdal et al. (1985) reported blood concentrations of GTN within a range of 0.4 - 519 nmol/l GTN (5117ng/ml) on two consecutive days at mean exposures to 2.3 - 2.7 mg/m^3 (range 1.0 - 4 mg/m^3). However, biological monitoring can be performed by using the internal burden of GTN metabolites based on a threshold value for vasodilatation in human studies. Gumbleton and Benet (1991) demonstrated that no vasodilatory effect was present 250 minutes after oral application of 1,2-GDN to three healthy volunteers. 1,2-GDN plasma concentration was 0.5 ng/ml at this point of time and was therefore regarded as threshold concentration. Similarly, no vasodilatory effect was present 200 minutes after oral

application of 1,3-GDN to three healthy volunteers. 1,3-GDN plasma concentration was 0.4 ng/ml at this point of time and was therefore regarded as threshold concentration. However, no dose response relationship was established and the determined (rough) thresholds only were based on limited data. A preliminary threshold value for biological monitoring (BAT-value) in plasma for 1,2- and 1,3-GDN was recommended by DFG (2006) and Greim and Lehnert (1996) (to be measured at the end of a work shift), based an the reported data by Gumbleton and Benet (1991). Although numerous studies examined effects of occupational GTN exposure, no more precise dose-response relationship is established between inhalation exposure concentrations and internal exposure (Greim and Lehnert, 1996).

A biological monitoring guidance value has been proposed in the U.K. of 15 µg total nitroglycols per mol ceratinine in urine, which although not being health-based, is intended serve as a starting point for controlling occupational exposure.

2.2. Acute toxicity

2.2.1. Human data

The most common effect of acute GTN exposure is the occurrence of throbbing headache, accompanied by a decrease in blood pressure. This action is due to a vasodilatory effect on vascular muscles. Higher doses produced depression, confusion, methaemoglobinaemia and cyanosis (HCN, 2005).

Acute exposure of workers (on Monday morning) to 0.5 mg/m^3 of a mixture of GTN and ethylene glycol dinitrate (EGDN) produced headaches and a decrease in blood pressure within 25 min (Trainor and Jones, 1966). EGDN may have been contributed to the observed effects (HCN, 2005). The occurrence of headache was also observed in workers exposed to 0.3 - 1.0 mg/m^3 GTN two or three times a week. When the exposure concentrations were reduced to 0.09 mg/m^3, the symptoms disappeared (Hanlon and Fredrick, 1966). In a field study, Gjesdal et al. (1985) reported the occurrence of increasing headache during the working day in gun powder workers at mean exposures to 2.3 (at 9:00 a.m.) and 2.7 mg/m^3 (at 1:00 p.m.) [total range: 1.0 - 4 mg/m^3]. Dermal absorption seemed to be of importance, since there was no clear relationship between airborne exposure and internal burden in the available studies (HCN, 2005).

Sublingual exposure to 0.3 mg GTN or oral exposure (in capsules) to 6.5 mg produced an increase in heart beat and a decrease in blood pressure in one volunteer (Blumenthal et al., 1977).

Dermal exposure of volunteers to GTN patches (16, 31 and 47 mg, 24 h) produced headache and nausea. The patches were designed to deliver 5, 10 and 15 mg during the exposure period, respectively (Santoro et al., 2000).

2.2.2. Animal data

No Inhalation LC_{50} is available. The oral LD_{50} values were 105 - 884 mg/kg in rats and 115 - 1188 mg/kg in mice. Signs of toxicity included cyanosis, ataxia and depressed respiration. Dermal LD_{50} values were greater than 29, 35 and 280 mg/kg in rats, mice and rabbits, respectively (HCN, 2005).

2.3. Irritation and corrosivity

2.3.1. Human data

Irritation (not further specified) was reported in persons occupationally exposed to 0.3 - 1.0 mg/m^3 GTN (Hanlon and Fredrick, 1966). Dermal exposure of volunteers to 31 - 80 mg GTN in patches for 24 h produced erythema, which was attributed to a vasodilatory response in blood vessels of the skin. Similar effects were observed after

repeated (12 h/d, 14 days) dermal exposure (HCN, 2005).

2.3.2. Animal data

Skin

A 7.3% GTN paste (peanut oil/lactose) was very slightly irritating to the intact or abraded skin of rabbits. Minimal irritation was also observed in rabbits exposed once to patches with 2.5 - 4 mg/cm^2 GTN or occlusively to 0.5 ml undiluted GTN. Repeated patch application of 2.5 mg/cm^2 GTN (21 h/d, 28 days) produced very slight erythema (Greim, 2006; HCN, 2005).

Erythema, oedema, scales, papules and dermal thickening was observed in rabbits treated for 26 weeks with daily ointments of 10% GTN at doses of 15, 60 and 240 mg/kg • d. The effects were reversible after the end of exposure. These results of a Japanese study are available only as an English abstract (Imoto et al., 1986a).

Eyes

GTN was reported to be moderately irritating to the eyes of rabbits (ECB, 2000, no further details). Slight eye irritation was observed in a Draize test in rabbits (0.1 ml undiluted, 1 min of exposure and subsequent removal by washing; Greim, 2006). A 7.3% GTN paste (peanut oil/lactose) was not irritating (HCN, 2005).

2.4. Sensitisation

2.4.1. Human data

Four dynamite workers with allergic contact dermatitis reacted positively to GTN. Several case reports of sensitisation to GTN from topical treatment with patches or plasters have been published. In view of the great number of exposed persons, the rate of sensitisation is considered low (Greim, 2006; HCN, 2005). A controlled study with repeated exposure of 28 volunteers to patches containing 31 mg GTN (12 h/d, 14 days) reported slight erythema (due to local vasodilatation) in less than 30% of the subjects, but no sensitisation (Santoro et al., 2001).

2.4.2. Animal data

A Magnusson-Kligman maximisation test in guinea pigs with 3.4% GTN paste (peanut oil/lactose) yielded a 40% positive response. No sensitisation was observed following dermal exposure *of rabbits to 2.5 mg/cm^2* GTN *in* patches *using a* modified Buehler Test (Greim, 2006; HCN, 2005). These experiments were criticised due to conceptional flaws (Greim, 2006).

2.5. Repeated dose toxicity

2.5.1. Human data

The acute symptoms after repeated inhalation exposure (headache, decrease in blood pressure) and the effect concentrations are similar to those observed after single occupational exposure. The NOAEL was about 0.1 mg/m^3 (0.01 ppm) with concentrations 0.3 mg/m^3 (0.03 ppm) causing headache (Hanlon and Fredrick, 1966; Gjesdal et al.,1985; see "acute toxicity"). Repeated exposure led to tolerance, which disappeared after a 2- to 3-day exposure free period (HCN, 2005). This GTN tolerance is presumably a cause of a nitrate-induced stimulation of vascular superoxide and/or peroxynitrite production, possibly by activation of protein kinase C. This oxidative stress may promote uncoupling of the NO synthase and inhibition of the guanylyl cyclase and prostacyclin synthase. GTN, superoxide and peroxynitrite can also inhibit

mitochondrial aldehyde dehydrogenase (responsible for bioactivation of GTN). Both mechanisms lead to a decrease of the vasodilatory action of GTN. Radical scavengers reduce the tolerance phenomenon and this confirms the relevance of the reactive oxygen species. An older hypothesis for the development of tolerance (thiol-oxidation-induced inhibition of the enzymes, which are responsible for the biotransformation of GTN) was refuted recently (Münzel et al., 2005; for details, see Greim, 2006).

Several case reports describe the occurrence of angina pectoris-like pains and sudden deaths due to heart failure, partially after co-exposure to GTN and EGDN. These cases were observed predominantly after 2 or 3 days without exposure ("nitrate withdrawal symptoms", "Monday morning angina", "Monday morning death"). No precise exposure data were stated. In two cases, it was suggested that the heart failure occurred following exposure to 1.8 - 2.4 mg/m3 (NIOSH, 1978; Fine 1983).

A case referent study on 169 cases and 184 referents in a Swedish region with a dynamite factory revealed a significantly increased mortality from cardio- or cerebrovascular disease due to a significant excess mortality from ischaemic heart diseases found in older workers with more than 20 years of exposure (standardised mortality risk: 3.6). The risk for cerebrovascular disease alone was not significantly elevated (Hogstedt and Axelson, 1977). A follow-up of this study confirmed the findings for cardiovascular heart disease. In contrast to the original study of 1977, a significant increase in mortality from cerebrovascular disease was reported (Hogstedt, 1984).

Stayner et al. (1992) examined about 5500 US ammunition workers (and about 5000 controls) for adverse effects due to GTN exposure. For the entire cohort, there was no increase in cardiovascular and cerebrovascular diseases. An excess mortality from ischaemic heart disease was observed in workers, who were younger than 45 years of age and highly exposed.

A cohort study examined about 4000 workers of a Swedish explosives factory (883 exposed, 3159 internal controls). The workers were exposed to GTN and EGDN simultaneously and the workers were divided into high and low exposure categories (not further quantified). There was a significant excess mortality for acute myocardial infarction in highly exposed younger workers among the blasting worker group compared to internal controls (Craig et al., 1985). Due to the higher volatility and dermal absorption rate of EGDN compared to GTN, these results were predominantly attributed to EGDN exposure. The same reason was assumed for similar observations in other studies on workers in the dynamite industries (HCN, 2005).

2.5.2. Animal data

Inhalation

No adequate studies on repeated inhalation exposure are available. An older study by Gross et al. (1942) observed the occurrence of lymphocytosis and anaemia, but not methaemoglobinaemia or Heinz bodies, in cats exposed to GTN-saturated air (about 5 mg/m3) for 31 to 156 days (one animal each).

Oral

CD rats (38 per sex and group) were fed GTN in doses of 0, 3 - 4, 32 - 38 and 363 - 434 mg/kg • d for 2 years (Ellis et al., 1984). The high-dose animals showed reduced feed consumption and decreased body weight gain as well as tan, rough and matted fur. Methaemoglobinaemia was restricted to the high dose group up to 12 months of exposure and was no Tonger detectable at the end of the study. Other haematological alterations were evident at 3 months, but not at 12 months of exposure or later. At the

end of the study, male high-dose animals showed increased levels of serum transaminases and of alkaline phosphatase. Interim sacrifices at 12 months revealed increased liver weights, an increase in preneoplastic hepatocellular alterations, cholangiofibrosis, proliferation of the bile ducts and fibrous liver tissue as well as spleen and kidney pigmentation in high-dose animals. Similar, but more marked lesions were seen at the end of exposure (for tumours see section "carcinogenicity").

Ellis et al. (1984) also exposed CD-1 mice (58 per sex and group) 2 years via feed to GTN in doses of 0, 10 - 111, 96 - 115 and 1022 - 1058 mg/kg • d. High-dose animals showed decreased feed consumption and body weight gain as well as a tan, matted fur. Observed effects in the high dose groups were compensated anaemia, methaemoglobinaemia (males only) and pigmentation of liver, spleen and kidney. The pigmentations occurred also in mid-dose animals.

Furthermore, Ellis et al. (1984) exposed beagle dogs (6 per sex and group) orally to 0, 1, 2, 5 and 25 mg/kg • d GTN in capsules for 12 months. The only effect was a transient, slight methaemoglobinaemia (< 3% MetHb) in all exposed animals. HCN (2005) considered the highest dose as a NOAEL. Doses of 100 mg/kg • d, given for 5 consecutive days in feed, caused more marked methaemoglobinaemia and cyanosis (Ellis et al., 1984).

Dermal

Dermal application of 10% GTN in ointments to rabbits at doses of 15, 60 and 240 mg/kg • d for 26 weeks caused skin irritation (see section "irritation and corrosivity") and histopathological skin alterations in all exposed animals. Systemic effects were restricted to the high dose group, consisting of an increase in kidney and heart weight as well as an increase in leucocytes (neutrophiles) and gamma-globulins. These results of a Japanese study are available only as an English abstract (Imoto et al., 1986b).

2.6. Genotoxicity

2.6.1. In vitro

A saturated aqueous solution of GTN did not induce mutations in five strains of *Salmonella typhimurium*. Some studies reported a weak positive response in strains TA1535 and TA1537 with or without metabolic activation, but a negative response in most experiments with other strains of S. *typhimurium* as well as in yeast and CHO hamster cells (Greim, 2006; HCN, 2005).

2.6.2. In vivo - Human data

Human data an genotoxic effects in vivo are not available.

2.6.3. In vivo - Animal data

GTN was negative in a dominant lethal assay in rats exposed to 3 - 363 mg/kg • d in feed for 13 weeks (Ellis et al., 1978). No numerical or structural chromosomal aberrations were observed in peripheral lymphocytes or kidney cells of rats fed GTN in doses of 59 mg/kg • d for 5 weeks and 230 mg/kg • d for an additional 8 weeks (Lee et al., 1976), or in the bone marrow or kidneys of rats exposed to doses of about 400 mg/kg • d for 2 years (Ellis et al., 1978). All these *in vivo* data are unpublished.

2.7. Carcinogenicity

2.7.1. Human data

In cohort studies on about 900 exposed workers of a Swedish explosives factory and about 5500 exposed US ammunition workers, there was no excess mortality from all

cancers, lymphatic or haematopoietic neoplasms, compared to the controls (Craig et al., 1985; Stayner et al., 1992). Craig et al. (1985) observed a slight increase in lung cancers (co-exposure to GTN and EGDN), but statistical significance was not stated.

2.7.2. Animal data

In the chronic rat study by Ellis et al. (1984), described in more detail in the section "repeated dose toxicity", there was a marked increase in hepatocellular carcinomas and/or neoplastic nodules in the high dose groups (males: controls, low, mid and high dose groups: 1/24, 0/28, 4/26 and 15/21; females: 0/29, 1/32, 3/28 and 16/25, respectively). There were also non-neoplastic liver lesions at the highest dose. The incidences of interstitial tumours of the testes were also increased (2/24 in controls, 1/28, 3/26 and 11/21), accompanied by testicular atrophy and aspermatogenesis. No statistical evaluation was given. Hepatic tumours (adenocarcinomas and carcinomas) and preneoplastic lesions were also observed in rats after 70 weeks of exposure to 500 mg/kg • d GTN in feed (Tamano et al., 1996).

Suzuki et al. (1975) exposed C57BI/6Jms mice to 0, 1.5, 6.2 and 58.1 mg/kg • d via drinking water for 12 - 18 months. They reported an increased incidence of tumours, mainly pituitary gland adenomas, in high-dose females. These results could not be confirmed by Ellis et al. (1984). No treatment-related increases in tumours were noted in CD-1 mice exposed to GTN in doses up to 1058 mg/kg • d for 2 years.

No tumours were detected in dogs exposed orally up to 25 mg/kg • d for 12 months (Ellis et al., 1984), but the exposure duration was too short to draw firm conclusions (HCN, 2005).

2.8. Reproductive toxicity

2.8.1. Human data

Human data on reproductive or developmental effects are not available.

2.8.2. Animal data

Fertility

Oral exposure of rats to 1406 mg/kg • d GTN in feed for 13 weeks produced moderate to severe testicular degeneration and/or atrophy with inhibition of spermatogenesis (NOAEL 230 mg/kg • d). No effects were noted in the reproductive organs of females (Ellis et al., 1984).

In an unpublished 3-generation study by Ellis et al. (1978), male and female rats were fed GTN in doses of 0, 3 - 4, 32 - 38 and 363 - 434 mg/kg • d for 6 months prior to mating through to weaning of the Fib offspring. Animals were further exposed and held until the production of the F2 generation. From these animals, F3 litters were obtained and the exposure continued until weaning of the F3b offspring. The fertility of the F0 generation was not affected. Severe impaired fertility was observed in F1 and F2 males (aspermatogenesis). The litter size, live-born index, weight of offspring at birth and at weaning as well as the viability and lactation index were impaired in litters of the high dose groups. These effects were attributed to maternal toxicity. The maternal and reproductive NOAEL of this study was 32 - 38 mg/kg • d.

Dermal application of ointments containing 10% GTN to female rabbits at doses of up to 240 mg/kg • d on gestation days 6 - 18 did not cause adverse effects on reproduction. These results of a Japanese study are available only as an English abstract (Imoto et al., 1986b).

Developmental toxicity

In an unpublished developmental study, female rats were fed GTN in doses of 0, 4, 38 and 434 mg/kg • d on gestation days 6 - 15. There was an increased incidence of incomplete or absent ossification of the hypoid bone in offspring of the high dose group. The dams used were not virgin but presumably mated for the third time after the performance of a 3- generation study (see above) (Ellis et al., 1978).

Dermal exposure of rats to 1000 - 4000 mg/kg • d on gestation days 7 - 17 did not produce developmental or reproductive effects in the F1 generation (according to a study by Skutt and Schardein, 1985, as reported by Greim, 2006).

Dermal application of 10% GTN in ointments to rabbits at doses of up to 240 mg/kg d on gestation days 6 - 18 did not cause adverse effects on offspring. These results of a Japanese study are available only as an English abstract (Imoto et al., 1986b).

Recommendations

Human data indicate that the critical health effect of GTN exposure is its vasodilatory action. This is also the primary pharmacological effect of GTN as a pharmaceutical.

Based on experimental animal studies there is a suspicion of carcinogenicity. This can reasonably be viewed in conjunction with its mode of pharmacological action as an NO liberator (for details, see Greim 2006). The available data on mutagenic effects have been considered inadequate to allow a conclusive evaluation, and are indicating at best a weak positive response. Observed mutations in bacteria are similar to those induced by nitric oxide (HCN, 2005), and standard genotoxicity tests with GTN were mostly negative. A slight increase in lung tumours in humans was observed after occupational co-exposure to GTN and EGDN (significance not stated; Craig et al., 1985). Other tumours were not increased in studies with occupational exposure. The experimentally observed carcinogenicity in rats (Ellis et al., 1984) at high doses was accompanied by concurrent organ toxicity, so that the tumour formation is likely induced by cell damage and subsequent cell proliferation and of questionable relevance with regard to presumably low occupational exposure (HCN, 2005). The mouse carcinogenicity data are conflicting. An increase in pituitary tumours was observed in the study of Suzuki et al. (1985), but negative results were noted at higher doses and longer exposure duration in the study of Ellis et al. (1984).

The experimental data are generally consistent with the view that the pharmacological NO-liberating effect of GTN (at high and sustained exposures) is causally connected with the carcinogenic effect. Therefore, it is plausible that an avoidance of pharmacological effects would coincide with the avoidance of possible carcinogenic effects. Accordingly, GTN is categorized as a carcinogen with a practical threshold in the SCOEL carcinogenicity group C.

As effect symptoms, in consequence of vasodilatation, GTN produces headache, decrease in blood pressure and nausea. Dermal absorption is important in addition to inhalation, and co-exposures to EGDN (with an almost identical mode of action) may occur under workplace conditions. The importance of dermal absorption is demonstrated by a study with dermal exposure (Santoro et al., 2000), in which 5 mg GTN (absorbed within 24 h) caused complaints similar to those observed after inhalation exposure. This dose corresponds to an air concentration of 0.5 mg/m^3 (10 m^3 respiratory volume per 8 h shift). Higher exposures may produce depression, methaemoglobinaemia and cyanosis (HCN, 2005).

There are no convincing data that neat GTN increases the risk of cardio- or cerebrovascular diseases, as the results of different studies are conflicting and EGDN was regarded as causative agent in some cohorts.

No adequate animal studies on repeated inhalation exposure are available. Systemic

effects in animal studies (methaemoglobinaemia, hepatic and testicular toxicity) were observed only at high oral doses. Studies in rats and dogs revealed NOAEL values in the range of 25 - 40 mg/kg • d for systemic effects including reproductive toxicity, corresponding to air concentrations far higher than human effect levels.

As mentioned above (chapter 3.3.1), there are reports that GTN produced headache, a decrease in blood pressure and nausea at airborne concentrations at the following airborne concentrations: Gjesdal et al., 1985, at 1-4 mg/m³; Trainor and Jones, 1966, at 0.7 and 0.5 mg/m³ (headache); Hanlon and Fredrick, 1966, headache between 0.3 and 0.11 mg/m³). No effects were noted after reduction of workplace exposure concentrations to <0.1 mg/m³ [0.01 ppm] (Hanlon and Fredrick, 1966). Therefore, an OEL (8 h TWA) of 0.01 ppm can be recommended.

A STEL of 0.02 ppm is proposed (effect levels of >0.3 mg/m³ [0.03 ppm], as irritation, was also observed at or above exposure to 0.3 mg/m³ GTN (Hanlon and Fredrick, 1966). The use of a higher uncertainty factor was not considered necessary, because the assessment rests immediately on human data of occupationally exposed persons.

In the presence of EGDN, the sum of the exposure concentrations of EGDN plus GTN should not exceed the OEL for GTN, because the mode of action of both compounds (liberation of NO) is identical (see ACGIH, 2001).

A "skin" notation is proposed, as GTN is absorbed very efficiently via the skin and produces systemic effects by this route.

In view of the great number of exposed persons and that there are only few case reports of sensitisation, the rate of sensitisation is considered low (Greim, 2006) and no respective qualification is necessary.

Biological monitoring can be performed by using the internal burden of GTN metabolites based on a threshold value for vasodilatation in human studies. Gumbleton and Benet (1991) determined that no vasodilatatory effects should be expected at plasma concentrations of 0.5 pg 1,2-GDN/liter or at 0.5 pg 1,3-GDN/liter. However, direct correlations between GTN exposure and effects were not determined and the assessment is based in a small sample (three exposed volunteers). Thus, this guidance for biological monitoring has been regarded as being preliminary (Greim and Lehnert, 1996). Recently, a GC-MS based analytical method has been developed for GTN and its metabolite 1,2-GDN in human urine (Akrill and Cocker 2002). This method has been used in a limited number of GTN-exposed pharmaceutical and ammunition workers (Akrill et al. 2002). These data may serve as guidance for biological monitoring, but they do not yet allow the recommendation of a BLV (see 3.1.3).

At the recommended OEL, no analytical difficulties are expected (see Annex).

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ANNEX I. ANALYTICAL INFORMATION ON LIMIT OF DETECTION FOR GLYCEROL TRINITRATE

Table 1 summarises the methods examined and their estimated limit of detection (LOD) for glycerol trinitrate.

The analytical techniques used to determine this substance is gas chromatography with electron-capture detection (GC-ECD).

Following the "OSHA 43" method to determine glycerol trinitrate, samples are collected by drawing a known volume of air through large (100/50-mg sorbent beds) sampling tubes containing Tenax-GC resin. The samples are desorbed with methyl alcohol and analyzed by liquid chromatography with a Thermal Energy Analyzer or an ultraviolet HPLC detector.

Conclusion

The revised European Standard EN 482:2005 stipulates the requirements that measurements procedures should fulfil in order to perform a reliable and valid assessment of an exposure to a chemical agent.
In view of the proposal of 0.01 ppm (0.95 mg/m^3) and a STEL of 0.02 ppm (1.9 mg/m^3 and according to the mentioned standard, the measuring range of the method should cover at least the concentrations from 0.1 to 2 times the limit value (TWA) and from 0,5 to 2 times for the STEL value, and, in this range, overall uncertainty should be kept under certain values.

At workplaces with glycerol trinitrate no problems exist to measure the long and the short-term exposures at concentrations around the present proposal.

Table 1. GLYCEROL TRINITRATE

METHOD	YEAR OF PUBLICATION	ANALYTICAL DATA	LOD	REMARKS	COMPLIANCE WITH OEL
NIOSH 2507 Gas chromatography, ECD	1994	Working range: 0.6-3.2 mg/m^3 Recommended air volume:15 l Sampling time: 15 – 75	0,6 µg per sample	validated	**YES**
OSHA 43 Gas chromatography, ECD	1983	Recommended air volume: 15 l Sampling time: 15 min Flow rate: 1 l/min	19 µg/m^3	validated	**YES**
DFG HPLC	1998	Sampled air volume: 60 l Sampling time: 2h Flow rate: 0.5 l/min	0,03 mg/m^3	validated	**NO**