Ethylene dinitrate

(CAS No: 628-96-6)

Health-based Reassessment of Administrative Occupational Exposure Limits

Committee on Updating of Occupational Exposure Limits,
a committee of the Health Council of the Netherlands

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1 Introduction

The present document contains the assessment of the health hazard of ethylene dinitrate (EGDN) by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by AAE Wibowo, Ph.D. and MM Verberk, Ph.D. (Coronel Institute, Academic Medical Centre, Amsterdam, the Netherlands).

In September 1998, literature was searched in the databases Medline (from 1966 onwards), EMBASE (from 1988 onwards), and Chemical Abstracts starting from 1966, 1988, and 1970, respectively, and using the following key words: ethylene glycol dinitrate, EGDN, dinitroglycol or 628-96-6. HSELINE, CISDOC, MHIDAS, and NIOSHTIC (covering the period 1985/1987 until 1998) as well as POLTOX (Toxline, Cambridge Scientific Abstracts, FSTA; covering the period 1990 until 1995), databases available from CD-ROM, were consulted as well. The final literature search was performed in Medline and Toxline in October 2004.

In December 2004, the President of the Health Council released a draft of he document for public review. No comments were received.

2 Identity

name	: ethylene dinitrate
synonyms	: ethylene glycol dinitrate; dinitroglycol; ethanediol dinitrate; nitroglycol; glycol dinitrate
molecular formula	: $C_2H_4N_2O_6$
structural formula	: NO_2-O-CH_2-CH_2-O-NO_2
CAS number	: 628-96-6

3 Physical and chemical properties

molecular weight	: 152.06
boiling point	: 197-200°C
melting point	: -22.3°C
flash point	: 215°C (closed cup)
vapour pressure	: at 20°C: 7 Pa
solubility in water	: poorly soluble (at 25°C: 0.5 g/100 mL)
log $P_{octanol/water}$	: 1.16 (experimental); 1.17 (estimated)
conversion factors	: at 20°C, 101.3 kPa: 1 mg/m^3 = 0.16 ppm 1 ppm = 6.34 mg/m^3

Data from ACG99, NLM04, http://www.syrres.com/esc/est_kowdemo.htm.

EGDN is an odourless, yellowish, oily, explosive liquid (ACG99, NLM04).

4 Uses

The main use of EGDN is as an explosive. When mixed with glycerol trinitrate, EGDN lowers the melting point of the glycerol trinitrate, and reduces the hazard associated with the use of frozen dynamite. EGDN is a good explosive in its own right and it has gradually become the major component of dynamite mixtures. The EGDN:glycerol trinitrate ratio varies between 60-80% EGDN and 20-40% glycerol trinitrate (ACG99).

5 Biotransformation and kinetics

Human data

In a dermal absorption study, 100 mg of a mixture, comprising 22% EGDN, 6% dinitrotoluene, 5% trinitritoluene, and 65% NaCl, was applied under occlusion to 1 cm^2 of the underarm of 6 human volunteers, for 7 hours. The amount of absorption, determined indirectly by the measurement of the residual amount of EGDN on the skin and in the cover, was on average 13.7 % of the applied EGDN dose (Gro60). In another study, 1.5 g of dynamite was applied on rubber gloves worn by a human volunteer for 2 hours. At the end of the experiment, EGDN blood concentrations measured in the right and left arm were 2.2 and 1.9 mg/L, respectively, and signs of intoxication developed (see Chapter 6). In another experiment, the bare hands of a volunteer were exposed to the vapours from 0.1 g of dynamite in an isolated box, for 1.5 hours. The EGDN air concentration in the box varied from 4.1 mg/m^3 at the beginning to 2.3 mg/m^3 at the end of the experiment. EGDN blood levels in the arms were on average 26 µg/L. When the volunteer wore rubber and inner cotton gloves, 2-hour exposures to EGDN air concentrations, varying from 22.4 mg/m^3 at the beginning to 3.6 mg/m^3 at the end of the experiment, resulted in a mean EGDN blood level in the arms of 43 g/L. The authors conclude that skin absorption is a major route of entry for EGDN into the body, both in the solid and vapour phase, and that EGDN is also absorbed through rubber and cotton gloves (Hog80).

Mean EGDN blood concentrations of 3 workers in a Japanese dynamite production facility, measured during 4 working days, ranged from 63 to123 µg/L and from 40 to 70 µg/L in samples collected at the end of the morning and at the end of the afternoon, respectively. EGDN concentrations in urine samples collected at those time points, varied from 4.3 to 37.7 g/L, and accumulated

during the working week. Air concentrations in the workplace, measured with static air monitoring, were from 0.13 to 0.63 mg/m^3. Each worker wore an airline mask or a gas mask during his work to avoid inhalation of vapour, indicating that EGDN concentrations measured in blood or urine were the result of absorption through the skin. No EGDN was found in the blood of 6 control workers (Fuk81).

Animal data

Rats (n=15) were exposed to ^{14}C-labelled EGDN air concentrations, ranging from 133 to 428 mg/m^3. The mean pulmonary absorption was about 20% of the inhaled dose (range: 10-31%). In one guinea pig, the pulmonary absorption was 27% (Fri60). In a dermal absorption study in rats, amounts of 100-600 mg of a mixture of 93% EGDN and 7% nitrocellulose were applied to 1 cm^2 of clipped, occluded back skin for 0.5 to 8 days. After 8 days, the amount of absorption of EGDN, determined indirectly by the measurement of the residual amount of EGDN on the skin and in the cover, varied from 100% to 80% of the dose, after application of 100 mg and 600 mg, respectively. The absorption rate was 10 mg/cm^2 /hour. When 100-400 mg of a mixture, comprising 22% EGDN, 6% dinitrotoluene, 5% trinitrotoluene, and 65% NaCl was applied, EGDN was completely absorbed through the skin at all doses after 8 days. The rate of absorption was 6.5 mg/cm^2/hour (Gro60).

Following a single subcutaneous injection of 65 mg/kg bw into rats, EGDN in blood reached a peak 30 minutes after injection and fell to zero 8 hours later. Inorganic nitrite was maximal at 1 to 2 hours, falling to zero at 12 hours, whereas nitrate rose more slowly to its maximum at 3 to 5 hours, reaching pre-injection levels again 12 hours after the injection. Ethylene glycol mononitrate (EGMN) concentrations in blood reached a maximum at about 3 hours and then fell to zero within 12 hours. In 24-hours urine, collected following the EGDN injection, EGDN, EGMN, inorganic nitrite, and inorganic nitrate were excreted in amounts of <0.1%, 1.5%, <0.1%, and 58.0% of the applied EGDN dose, respectively. Non-published data by the same authors suggest that approximately 10% of the EGDN dose was excreted as ethylene glycol (Cla67). In a later study, following administration of a single dose of approximately 200 mg EGDN/kg bw to rabbits (route of exposure not given), peak blood levels of EGDN (23 µg/L), and of its metabolite ethylene glycol (1.4 µg/L) were reached at 1 and 2 hour after application, respectively. Half-lives of elimination from the blood were approximately 1 hour for both EGDN and ethylene glycol. The concentration of inorganic nitrate in blood reached a plateau of about 100 µg/L at 2 hours after

administration, and declined gradually between 6 and 24 hours after dosing (Fur83). Following daily subcutaneous injections with 65 mg EGDN/kg bw/day, 5 days/week, for 10 weeks, peak blood levels were reached at 30 to 60 minutes after the last administration for EGDN (15 mg/L) and at 2 and 4 hours after the last administration for inorganic nitrite (8 mg/L) and inorganic nitrate (23 mg/L), respectively. The half-lives of elimination from the blood were approximately 2 hours for EGDN and organic nitrite and approximately 4 hours for inorganic nitrate. No differences were observed in the kinetics of EGDN and its metabolites following administration of single or repeated doses of EGDN. In the urine collected for 24 hours after the last EGDN injection, the excretion (in % of the applied dose) was <0.1% for EGDN, 0.6% for EGMN, <0.1 % for inorganic nitrite, and 57.5 % for inorganic nitrate. The total recovery was 58.2% of the administered dose. No results of excretion products in faeces or expired air were reported (Cla69).

In vitro experiments showed that in whole blood or erythrocytes taken from rats or dogs, EGDN was metabolised into inorganic nitrite and nitrate (Cla69). The denitration of EGDN into EGMN involves glutathione in a reaction catalysed by 'nitrate or nitrate-forming enzymes', such as organic nitrate reductases (Tsu70a, Tsu70b).

In summary, EGDN is rapidly metabolised to EGMN by a glutathione-dependent reaction. EGMN is further degraded to ethylene glycol by hydrolysis. These steps occur under liberation of inorganic nitrite, which is subsequently oxidised to inorganic nitrate. Part of the ethylene glycol may be further degraded to CO_2, which is excreted in expired air (Lit73).

6 Effects and mechanism of action

Human data

A dynamite worker with occupational allergic contact dermatitis was positive in a patch test with EGDN. However, the worker also showed positive reactions to glycerol trinitrate and dinitrotoluene, suggesting cross-reactivity between these compounds (Kan91).

The target organ of exposure to EGDN is the cardiovascular system. Exposure to EGDN has been found to result in a fall in systolic blood pressure because of vasodilation, increased pulse rate, headache, dizziness, nausea, vomiting, tachycardia, peripheral paraesthesia, and chest pain. These cardiovascular effects usually appear during the first few days of employment. Tolerance then develops and the rest of the week is usually free from effects. On

returning to work after an exposure-free weekend, however, exposure to EGDN often leads to the above-mentioned effects again. These effects are known in the dynamite industry as 'Monday headache', or 'Monday morning angina' (Bar67, For58, Kri89, McG61). Exposure to EGDN has also lead to sudden death among workers (Bar67, Bil63, For58, Pre65, Vig68). Fatalities apparently occur as a result of withdrawal symptoms after an exposure-free period (Bar67, Car63). However, in another study, it is reported that the health of workers is threatened only during exposure, and that upon termination, symptoms of vasomotor disorders subsided and cases of sudden death no longer occurred (Pre76).

In a human volunteer study (number of subjects not given), 18% of the volunteers (dynamite workers) complained of headache when exposed in a chamber to EGDN air concentrations of 0.40-0.74 mg/m^3, and 83% when exposed to 2.0 mg/m^3 (duration of exposure was not reported) (Lam93). The effects of dynamite vapours were examined in 6 to10 volunteers, exposed to average total air concentrations of EGDN and glycerol trinitrate of 0.5 or 0.7 mg/m^3 (range: 0.40-0.67 or 0.65-0.74 mg/m^3, respectively) for 25 minutes, or 2.0 mg/m^3 (range and duration of exposure not specified). Air concentrations were expressed as mg glycerol trinitrate/m^3. Skin contact with the dynamite was avoided. At the highest level, headache developed within 1-3 minutes in 5/6 subjects, and decreases in systolic and diastolic blood pressure were measured in 5/6 and 4/6 subjects, respectively. One subject did not have a headache or effects on blood pressure. All 10 volunteers exposed to 0.7 mg/m^3 developed headache or pulsating feelings or dullness in the head, and decreases in systolic and diastolic blood pressure were seen in 8/10 and 7/10 subjects, respectively. Out of the 7 subjects exposed to 0.5 mg/m^3, 6 had (slight or transitory) headache or a feeling of dullness in the head, while there were decreases in systolic and diastolic blood pressure in 6 and 4 persons, respectively (Tra66). Since the vapour pressure of EGDN is much higher than that of glycerol trinitrate, EGDN completely predominates the vapour phase from a mixture of them in dynamite production, irrespective of the ratios used (Hog84). Therefore, the committee considers that the effects observed are attributable to EGDN. The LOAEL for the induction of headache and a fall in blood pressure was 0.5 mg/m^3 (expressed as glycerol trinitrate) or 0.35 mg/m^3 (expressed as EGDN).

When EGDN was applied to human skin as a 1% solution in alcohol, a dose of 18 to 35 mg was reported to cause headaches. When it was applied in fractional doses totalling 170 mg, tolerance developed in 24 to 36 hours and lasted for 10 to 13 days (Cra31). In another study, a human volunteer who wore rubber gloves smeared with 1.5 g of dynamite for 2 hours developed symptoms of intoxication 45 minutes after the start of the experiment. At the end of the

experiment, symptoms comprised severe headache, nausea, and dizziness. EGDN concentrations measured in the right and left arm were 2.2 and 1.9 mg/L, respectively (see Chapter 5). He recovered 80 minutes later (Hog80).

In a validation study to use the applicability of results from a human volunteer study (Lam93, see above), short-term EGDN air concentrations in the breathing zone of 72 workers were collected during a 3-month air-monitoring study (time of air sampling not given). A health questionnaire was administered before and after sampling. The concentrations of EGDN ranged from 0.06 to 1.64 mg/m^3. Workers (n=63), who indicated that they were headache-free at the start of the air sampling, were divided in 3 groups: group 1 comprised 35 workers exposed to <0.40 mg/m^3, group 2 comprised 17 workers exposed to 0.40-0.74 mg/m^3, and group 3 comprised 11 workers exposed to 0.75-1.64 mg/m^3. Only one subject, in exposure group 1, developed unrated headache. The incidence of 'no induced headaches' after EGDN exposures was lower than predicted by the chamber study (Lam93).

Combined measurements of air and skin exposures and medical examination of 37 workers were undertaken in an explosives-manufacturing plant in California. A control group comprised 19 workers without occupational exposure to nitro esters. Air concentrations of EGDN in the various workplaces of the plant, at the operator's breathing zone, varied from 0.03 to 4.35 mg/m^3 (time of air sampling not given, but probably ca. 10-20 minutes as calculated from the air sampling method described). Potential skin exposures (2-4 hours measurements) ranged from <0.1 to 1.0 mg (as total EGDN and glycerol trinitrate). Medical examinations revealed that after the work shift, workers had an exposure-related increased incidence of headache, rise in pulse rate, and drop in systolic blood pressure. No exposure-related changes in diastolic blood pressure were found. Workers, who had worked in areas of the plant where EGDN air levels were below 0.25 mg/m^3 without significant skin exposure, only showed an increased incidence of headache, compared to workers who had had no occupational exposure to nitro esters. No statistical evaluation of the data was undertaken (Ein63). Based on these data, the committee considers 0.25 mg/m^3 as a NOAEL for effects on pulse rate and systolic blood pressure and as a LOAEL for induction of headache.

In 3 workers in a Japanese dynamite-production facility (see Chapter 5), systolic blood pressure and pulse pressure were measured during 4 working days before the start of the work, at the end of the morning, and at the end of the afternoon. The mean systolic blood pressure of the workers decreased significantly at the end of the morning of each working day, compared to pre-work measurement, with a tendency of slight recovery in the afternoon. The

mean pulse pressure (the difference between systolic and diastolic blood pressure) was significantly narrower at the end of the morning and the afternoon when compared with pre-work measurement. A significant negative correlation was found between pulse pressure and EGDN concentration in blood (Fuk81).

Dynamite workers (n=8) exposed to total EGDN and glycerol trinitrate air levels in the range of 0.10 to 0.53 mg/m^3 (expressed as glycerol trinitrate), as measured by static monitoring, developed headache, but no effect on blood pressure was measured. The LOAEL for the induction of headache was 0.07 mg/m^3 (expressed as EGDN) (Tra66).

A health-survey was conducted on 276 workers (174 males and 102 females) employed in 3 dynamite-producing factories in Sweden. Exposure was to both EGDN and glycerol trinitrate. Air concentrations in the different workplaces, measured with static monitoring, were generally below 5 mg/m^3 total EGDN and glycerol trinitrate. Because of the much higher vapour pressure of EGDN compared with glycerol trinitrate, it was assumed that air exposures were mainly to EGDN. Major symptoms were throbbing headache, dizziness, nausea, and intolerance to alcohol. No differences were observed in the health status of workers who had been employed in workplaces with air concentrations below or above 3 mg/m^3 (For58).

The effect of EGDN exposure on the urinary excretion of catecholamines (adrenaline, noradrenaline, and its metabolite vanilyl mandelic acid) was studied in 6 workers in a dynamite factory, aged 31 to 51 years and occupationally exposed to EGDN for 2 to 15 years (mean: 7 years). Six workers without occupational exposure to EGDN served as controls. The dynamite was prepared with a 50:50 glycerol trinitrate/EGDN ratio. Mean EGDN air concentrations in the different work departments of the factory varied from 0.55 to 1.65 mg/m^3. There was also exposure through direct contact with the skin. During the work shift, there was an average decrease of 20 mm Hg in the systolic and of 15 mm Hg in the diastolic blood pressure. The subjects complained only of slight headache when recommencing the work on Mondays after a holiday. The urinary excretion of catecholamines in samples collected during the last working day of the week was higher in the group of EGDN workers compared with the control group, but the increase was statistically significant for vanilyl mandelic acid only. Catecholamine values returned to normal values during the next exposure-free day. Vigliani et al. explained the increase in catecholamine excretion as a result of an EGDN-induced sympathoadrenergic stimulation, secondary to hypotension (Vig68).

In a Japanese study, pulse wave changes in the finger tips of dynamite workers were compared with those in control workers not occupationally

exposed to EGDN. Slight abnormalities were reported in dynamite workers at workplace exposures ranging from 0.25 to 0.42 mg/m^3. There were no complaints of headache during the work (Mor67).

There are also reports of effects on the central nervous system found in workers engaged in the production of dynamite. In a study of Japanese dynamite workers, 7 out of 9 workers exhibited abnormal electroencephalographic (EEG) records, showing fast activity in all areas. The EGDN air concentration in the workplace was below the Japanese occupational exposure limit of 1.27 mg/m^3 (Mat75).

Another study was conducted with 100 workers, who had been employed in a dynamite plant for on average 11.5 years. Most workers had had exposures to mixtures of nitro esters (glycerol trinitrate, EGDN, dinitroglycol, dinitrodiglycol, and pentrite) at total nitro-ester air levels of 1.0-2.0 mg/m^3. Effects were headache, alcohol intolerance, nervousness, and sleep disorders. EEG abnormalities were found in 11% of the workers. Clinical chemical and haematological values did not differ from those of the normal population (Kuz84).

Headache, dizziness, and ECG-abnormalities were reported in 8 workers who were engaged in the use of dynamite in the mining industry. Their ages were between 37 and 55 years, and they had been employed for 8 to 24 years. Air concentrations of EGDN in the workplaces, measured with static air monitoring, ranged between 0.16 and 5.9 mg/m^3 (Ber87). Other authors have also reported ECG abnormalities in workers with long-term exposure to EGDN and glycerol trinitrate (Cai82a, Cai82b, Han65, Mor67, Pre76).

Dynamite workers exposed to EGDN air concentrations of 1.25 to 12.5 mg/m^3, 6 hours/day, did not develop methaemoglobinaemia. *In vitro*, the formation of methaemoglobin, following treatment of haemoglobin with EGDN, was smaller in humans than in any of the animal species studied (Has70).

Various retrospective cohort mortality studies on workers in the dynamite-production industry have been reported. Aiming at cardiac and cerebrovascular diseases due to (long-term) exposure to dynamite, a case-referent study was performed in a Swedish parish with a dynamite factory as the primary industry. In this study, initially including 169 cases and 184 referents covering the period 1955-October 1975, a statistically significant excess mortality from cardio-cerebrovascular diseases was found (crude risk ratio: 2.5; SMR: 3.4; Mantel-Haentzel risk ratio: 3.2, 95% CI: 1.4-7.3). This was due to a statistically significant excess mortality from ischaemic heart disease predominantly found in 55-70-year-old workers with more than 20 years of exposure (crude risk ratio: 2.7; SMR: 3.6; Mantel-Haentzel risk ratio: 3.4, 95% CI: 1.5-7.8). The crude risk

ratio for cerebrovascular disease was 1.6 (not statistically significant) (Hog77). An extension of this study for the period 1976-1980, confirmed the increased mortality from cardiovascular heart disease. In addition, a statistically significant increased mortality from cerebrovascular disease was observed. During the period 1955-1980, the crude risk ratios were 2.9 (95% CI: 0.9-6.4) and 2.7 (95% CI: 1.4-5.4) for cerebro- and cardiovascular diseases, respectively (Hog84).

The increased risk of mortality from cardio-cerebrovascular disease was confirmed by the results of a small cohort study of workers of another Swedish dynamite factory. During the period 1965-1977, there was a significantly increased mortality from cardio-cerebrovascular diseases (9 vs. 4.5 expected; $p<0.05$) among workers with an exposure duration to dynamite of at least one year and an induction-latency time of 20 years. In this study, no increased mortality from cancer was observed (Hog79). Mean 8-hour TWA concentrations of nitrate esters (i.e., EGDN and glycerol trinitrate) in these Swedish dynamite factories during the period 1958-1978 were estimated to range between 0.2 and 1.1 mg/m^3 (Hog80). However, in view of the (huge) difference in vapour pressure and dermal absorption between these two nitrates (Hog84, Lun85), the committee considers that these workers were predominantly exposed to EGDN and that the effects observed are attributable to this compound.

The Swedish studies initiated a study on excess mortality among workers of a Scottish explosives factory. The cohort consisted of blasting workers (n=659) aged less than 65 years who were employed at the factory on January 1965. These workers were handling a mixture of glycerol trinitrate and EGDN in a ratio 4:1. The mortality in this cohort was studied over the period 1 January 1965 to 31 December 1980, and compared to an internal control group (n=3159), considered not to have been exposed to either of these compounds. Based on a sharp rise in the occurrence of myocardial infarction of the general population of the county of Ayrshire (external controls), 2 age groups were composed (15-49 and 50-64 years at 1 January 1965). In addition, exposed groups were divided into categories with ‘low’ and ‘high’ exposure (not further quantified). The major finding in the blasting workers was a statistically significant excess of mortality for acute myocardial infarction in the high-exposed younger age groups, when compared with the internal controls. This excess still remained when compared with the general male population of the same age in Ayrshire (not significant). When older workers were examined, the excess mortality in acute myocardial infarction in blasting workers was only found in the low-exposure group, compared to internal controls. When compared with the older Ayrshire population this excess could not be found. Since EGDN is considerably more volatile and more readily absorbed through the skin than glycerol trinitrate,

EGDN was considered to be the more important compound in causing effects in the blasting workers (Cra85).

The results of the above-discussed studies are summarised in Table 1.

Table 1 Overview of human studies on EGDN.

route of exposure material	subjects (number)	EGDN exposure level (mg/m^3)	critical effect	NOAEL (mg/m^3)	reference
inhalation					
EGDN	volunteers	0.4, 0.74, 2.0[a]	headache	LOAEL: 0.4	Lam93
dynamite	volunteers	0.35 and 0.5 (for 25 minutes); 1.4[b, c]	headache, decreased systolic BP	LOAEL: 0.35	Tra66
dermal					
dynamite	volunteers	1.5 gram applied on gloves	headache, dizziness, nausea	LOAEL: 1.5 gram	Hog80
mixed exposures					
dynamite manufacture	plant workers	0.06-1.6[a]	headache	1.6	Lam93
dynamite manufacture	plant workers (37); controls (19)	<0.25, 0.25-0.75, >0.75[a]	headache decreased systolic BP, increased pulse rate	LOAEL: 0.25 NOAEL: 0.25	Ein63
dynamite manufacture	plant workers (3)	0.13-0.63[b]	decreased systolic BP	not established	Fuk81
dynamite storage	workers (8)	0.07-0.37	headache blood pressure	LOAEL: 0.07 NOAEL: 0.37	Tra66
dynamite manufacture	plant workers (276)	<5[b]	headache, dizziness	not established	For58
dynamite manufacture	plant workers (6); controls (6)	0.55-1.65[b]	decreased systolic BP, increased catecholamine excretion in urine	not established	Vig68
dynamite manufacture	plant workers (200); controls (not given)	0.13-0.42[b]	abnormal pulse wave at the finger tip	0.25	Mor67
dynamite manufacture	plant workers (9)	<1.27[b]	EEG abnormalities	not established	Mat75
dynamite manufacture	plant workers (100)	1.0-2.0[d]	headache, EEG abnormalities	not established	Kuz84
dynamite use	mine workers (8)	0.16-5.9[b]	headache, dizziness, ECG abnormalities	not established	Ber87
dynamite manufacture	plant workers	1.25-12.5[b]	MetHb	12.5	Has70
dynamite manufacture[e]	plant workers (169): controls (184)	0.2-1.1[a,b]	cardio-cerebrovascular disease	not established	Hog77, Hog79, Hog84
dynamite manufacture[e]	blasting workers	high category low category	myocardial infarction no changes	not established	Cra85

BP = blood pressure; MetHb = methaemoglobinaemia

[a] Breathing zone of worker (sampling time not given).
[b] Static air monitoring.
[c] glycerol trinitrate + EGDN, expressed as mg EGDN/m^3.
[d] Total nitro esters, including EGDN.
[e] Epidemiological study.

Animal data

Irritation and sensitisation

The committee did not find data from experimental animal skin- or eye-irritation or skin-sensitisation studies on EGDN.

Acute toxicity

Oral LD_{50} values of 460 and 540 mg/kg bw have been reported for rats and mice, respectively; for rats, the dermal LD_{50} was 3800 mg/kg bw (NIO04). Rabbits and cats, treated by subcutaneous injection with 400 and 100 mg/kg bw, respectively, all died (Gro42).

When rats (n=75) were given EGDN as a single subcutaneous injection of 65 mg/kg bw, blood pressure fall immediately, reaching its minimal value at 30 minutes after the injection. The time course of the fall in blood pressure coincided with the increase of EGDN concentrations in the blood of the animals (Cla67). Another effect in rats, following a single subcutaneous injection of 65 mg EGDN, was a large increase in plasma corticosterone within a few minutes, which reached a peak level at 15-30 minutes after the administration and returned to normal levels after 4 hours (Cla72). Methaemoglobinaemia (MetHb) is also produced in rats treated subcutaneously with EGDN (60 mg/kg bw). The maximal level of about 24% MetHb was attained about 3 hours after administration. Thereafter, it decreased rapidly to about 13% MetHb at 5 hours after administration. MetHb arising from EGDN administration is formed principally by the action of inorganic nitrite, formed by metabolism of EGDN (Cla73).

In an *in vitro* study, EGDN showed a monophasic concentration-effect curve for relaxation of isolated bovine mesenteric arteries. This may indicate that EGDN exerts its effect on smooth muscle relaxation through a single mechanism. Other nitro esters, i.e., dinitratopropane and tetranitratopropane, act according to the same mechanism. In contrast, glycerol trinitrate exhibited a biphasic concentration-effect relationship, indicating that this compound has a partly unique mechanism for vascular smooth muscle relaxation (Axe92).

To elucidate the action of EGDN on cardiac muscles, the *in vitro* contractile and chronotropic responses of isolated rat cardiac muscles to EGDN were investigated. EGDN produced negative chronotropic (change in heart rate) and inotropic (change in contractility) effects on spontaneously beating right atria in

concentrations ranging from 10^{-7} to $3x10^{-4}$ M. EGDN also produced dose-dependent negative inotropic effects on electrically driven left atrial muscles. In contrast, in right ventricle muscles, positive inotropic effects were induced. Tai and Tsuruta conclude that EGDN acts directly on the cardiac muscles as well as on vascular smooth muscles (Tai97).

Subacute and subchronic toxicity

Rats and guinea pigs were exposed to an EGDN air concentration of 500 mg/m^3 for 6 months. Clinical signs reported were drowsiness and Heinz body formation in the red blood cells, indicating MetHb formation. Microscopic examination revealed fatty changes in the liver, heart, muscle, and kidney, with pigment deposits in the liver and spleen, similar to those seen in anaemia. No further information was given (Dav93).

When 4 cats were exposed to air levels in the range of 134 to 170 mg/m^3, 8 hours/day, 5 days/week, 3 died after 97, 102, and 273 days, respectively. The fourth cat survived exposure up to 1000 days. Clinical signs of toxicity included nausea, decreased food consumption, and decreased body weights. Animals showed decreased erythrocyte count and haemoglobin concentrations and increased reticulocyte count. MetHb was detected in all animals. Microscopic examination showed internal haemorrhages and liver and renal injury. One cat was exposed to EGDN at an air concentration of 13 mg/m^3, 8 hours/day, 5 days/week, for 1000 days. The animal did not show clinical signs of toxicity. A temporary, moderate, decrease in erythrocyte count, and an increase in reticulocyte count were observed. No methaemoglobin formation was detected and microscopic examination did not reveal abnormalities (Gro42).

When cats were given daily subcutaneous injections of 0.1 mg/kg bw of EGDN for 50 days, 6 days/week, the only noticeable effect was a slight anaemia. Dosing of 1 mg/kg bw for 20 days or of 30 mg/kg bw for 5 days caused mortality (Gro42).

Several studies have been reported on possible mechanisms of the effects of EGDN on the cardiovascular system.

Rats receiving subcutaneous injections of 65 mg/kg bw EGDN, 5 days/week, for 10 weeks, showed a marked fall in blood pressure after the first injection. However, tolerance developed after repeated injections. This tolerance was lost after a period of 60 hours free from injection, and there was a return to the original susceptibility (Cla69). Prolonged depression of blood pressure in rats (n=6) was observed following subcutaneous re-injection of EGDN, 1 to 5 days

after subcutaneous administration of 65 mg/kg bw/day EGDN for 5 successive days. A less severe blood pressure response was observed following EGDN re-injection of animals treated with 65 mg/kg bw/day of EGDN for 10 consecutive days. After 5 successive doses of EGDN, noradrenaline levels in heart and brain, and adrenaline levels in adrenals were significantly higher for the first 3 days after the end of treatment than in untreated animals, but no differences were observed when rats were treated for 10 consecutive days. The urinary concentration of catecholamines during the 5 days after 5 days' EGDN injection was also higher than the concentration after 10 days' EGDN injection, or than in the controls (Min72).

To study the effect of EGDN on adrenaline and noradrenaline concentrations in the myocardium of rats, groups of Sprague-Dawley rats (n=20/group/time point) were given EGDN in propylene glycol by intramuscular injection at doses of 0 and 20 mg/kg bw, 3 times/day for 5 days. The animals were sacrificed at 3, 6, 24, and 36 hours after the end of treatment. Noradrenaline and adrenaline concentrations started to increase after completion of treatment, reaching a maximum increase of 125% and 92%, respectively, with regard to the control values, at 24 hours after the end of treatment. The time-course of increases in catecholamine concentrations in the myocardium was similar to that observed in rats after administration of an inhibitor of the monoamine oxidase (MAO) enzyme activity, indicating that EGDN may inhibit the MAO activity in the myocardium. The authors concluded that repeated administration of EGDN to rats caused an accumulation of catecholamines in the storage sites of the sympathetic nerve endings in the heart. The induction and maintenance of a high level of stored catecholamines may be due to an inhibitory effect of EGDN on MAO. The sudden release of large amounts of catecholamines stored in the heart may explain the adverse effects of chronic EGDN exposure on the heart in dynamite workers (Vig68).

In a study in rats given subcutaneous doses of EGDN of 75 mg/kg bw/day for 14 to 28 days, tryptamine excretion in urine, which well reflects the MAO activity *in vivo*, was not changed compared with untreated animals. The MAO activity in liver and heart and in the adrenergic nerves in the iris of the rat remained unaffected in EGDN-treated animals. In conclusion, no effects were observed of EGDN on the uptake, storage, release, or re-synthesis of noradrenaline in the adrenergic nerves. *In vitro* experiments showed that EGDN inhibited the MAO activity in rabbit liver mitochondria, but not in adrenergic nerves (Kal69).

The cardiovascular effects of prolonged exposure to EGDN and the influence of adrenaline administration on the cardiovascular system at various intervals

after cessation of EGDN exposure was studied in female Alderley Park rats, given a daily subcutaneous injection of 65 mg/kg bw EGDN, 5 days/week, for 5 weeks. No changes in resting heart rate or in ECG were found until 96 hours after the last injection of EGDN. Resting blood pressure was only depressed 5 hours after the last injection, which coincided with the high EGDN blood concentrations at that time point (see Chapter 5). However, when the rats were given intravenous injections of adrenaline (2.5-5 μg/kg bw), 9 out of 10 rats showed ECG abnormalities in the form of ventricular extrasystoles at 24 hours after the last injection of EGDN, which occurred at or near the maximum of the blood pressure response. In control animals, 2 out of 10 showed ECG abnormalities. This super sensitivity of the cardiovascular system to adrenaline following repeated EGDN administration was not seen in pithed rats that were free from effects of nervous control and reflexes resulting from changes in blood pressure. The authors suggest that this supersensitivity to the pressor effects of adrenaline are not due to a direct action on the muscle cells of the heart, but must involve the nervous system in some way (Cla70).

The effects of EGDN on the pituitary-adrenocortical function was studied in 2 groups of female Alderley Park rats, given daily subcutaneous injections of EGDN of 65 mg/kg bw, 5 days/week, for either 1 or 8 weeks. At 24 or 72 hours after the last injection, rats were re-injected with a single subcutaneous dose of 65 mg/kg bw, and plasma corticosterone levels were measured at 15, 30, and 60 minutes after this re-injection. A decrease in plasma corticosterone levels was found in both groups compared with control animals, which was in sharp contrast with the increase in plasma corticosterone levels following a single injection of EGDN (see Section ‘Acute toxicity’). Also when rats were given a ‘standard stress’ of histamine, at 24 or 72 hours following repeated injections of EGDN, plasma corticosterone levels were lower compared with control animals, not treated with EGDN. Clark suggested that the reduced corticosterone response to EGDN following repeated EGDN administration was due partly to tolerance to the hypotensive action of EGDN and partly to some deficiency in the hypothalamo-pituitary-adrenal axis (Cla72).

The effects of repeated EGDN exposures on vascular responsiveness, on catecholamines (adrenaline, noradrenaline, dopamine, L-DOPA (3,4-dihydroxyphenylalanine)) and DOPAC (3,4-dihydroxyphenylacetic acid) levels in brain, heart, and adrenals, and on noradrenaline uptake into brain synaptosomes were investigated in male Sprague-Dawley rats at various times after cessation of EGDN exposure. Tolerance was induced by subcutaneous administration of 50 mg/kg bw EGDN, twice a day, for 10 days. At 2 hours after cessation of EGDN, mean arterial blood pressure was reduced and heart rate was

faster, compared with control rats. However, at 24 hours after cessation of EGDN, the mean arterial blood pressure was slightly higher than in controls and heart rate was still elevated. In a separate experiment, an acute intravenous dose of EGDN, given after cessation of prolonged EGDN treatment, did not induce a significant decrease of mean arterial blood pressure in conscious rats. *In vitro*, aortic strips showed a decreased responsiveness to EGDN-induced relaxation of strips pre-contacted with phenylephrine, and were more sensitive to noradrenaline, compared with strips from control animals at 2, 24, and 96 hours after cessation of EGDN exposure. EGDN treatment resulted in a significant decrease in accumulation of L-DOPA and DOPAC in all brain structures measured, in particular at 2 hours after cessation of EGDN. Lower levels of catecholamines were measured in heart and adrenals, but the changes were not statistically significant. No consistent effects of EDGN treatment on the neuronal uptake of noradrenaline into the brain could be detected. It was concluded that repeated EGDN treatment induces tolerance at the cellular level, resulting in a decrease in blood pressure and a reflexogenic increase in heart rate. In addition, repeated EGDN treatment interferes with catecholamine formation and possibly receptor functions, as indicated by the increase in noradrenaline sensitivity on isolated aorta and vena cava strips (Joh87).

The committee did not find data from chronic, including carcinogenicity, reproduction toxicity, or mutagenicity or genotoxicity studies with EGDN.

7 Existing guidelines

The current administrative occupational exposure limit (MAC) of ethylene dinitrate (EGDN) in the Netherlands is 0.3 mg/m^3, 8-hour TWA, with a ‘skin’ notation.

Existing occupational exposure limits for EGDN in various countries are summarised in the annex.

8 Assessment of health hazard

Occupational exposure to EGDN may occur by inhalation of the vapour or by skin contact with the vapour or the liquid during manufacture and use of the compound. In human volunteers, about 14% of EGDN was absorbed when 22 mg was placed on the skin under occlusion for 7 hours. When the bare hands of a human volunteer were exposed for 1.5 hours to EGDN air concentrations, varying from 4.1 mg/m^3 at the beginning to 2.3 mg/m^3 at the end of the

experiment, EGDN was detected in the blood at a concentration of 26 µg/L, indicating skin absorption of the vapour. EGDN may also penetrate through rubber and cotton gloves. In rats exposed to high air levels of EGDN, about 20% of the inhaled dose was absorbed. Following dermal application of EGDN to rats, an absorption rate of 6.5-10 mg/cm^2/day has been estimated, which was 3- to 4-fold higher than in human volunteers. After absorption, EGDN is rapidly metabolised into inorganic nitrite and nitrate and probably ethylene glycol. Following repeated subcutaneous injections with EGDN, about 57% of the dose was excreted in the urine as inorganic nitrate and <0.1% as inorganic nitrite or unchanged EGDN.

In humans, one case has been published of possible EGDN-induced allergic contact dermatitis.

The cardiovascular system is the prime target of EGDN. Effects are induced by vasodilation, which initiates symptoms like throbbing headache, increased pulse rate, decreased systolic blood pressure, decreased pulse pressure, dizziness, and nausea. The symptoms usually have a typical sequence of occurring during the first few days of the week and then tolerance develops for the rest of the week. However, on Monday morning, after an exposure-free weekend, the first contact with EGDN induces the symptoms again. In more serious cases, angina pectoris or even sudden death may occur.

The relationship between EGDN exposure and the above effects have been reported in several studies. In a volunteer study, exposure to EGDN concentrations of 0.35 and 0.5 mg/m^3 caused very slight to slight or transient headache or dullness in 6/7 dynamite workers and more severe headache or dullness in 10/10 dynamite workers, respectively, while at exposure to 2 mg/m^3, headache developed in 5/6 subjects within 1-3 minutes. However, short-term personal exposures to EGDN air concentrations between 0.40 and 1.64 mg/m^3 during the production of dynamite did not induce headache in any of a group of 62 dynamite workers. In a study conducted in a dynamite-manufacturing plant in California, airborne EGDN concentrations at the breathing zone of a group of 37 workers varied from 0.03 to 4.35 mg/m^3 and skin exposures from <0.1 to 1.0 mg (as total EGDN and glycerol trinitrate). An exposure-related increased incidence of headache, rise in pulse rate, and drop in systolic blood pressure was observed in the workers. Statistical evaluation of the data, however, was not performed. The LOAEL for the induction of headache was 0.25 mg/m^3 and the NOAEL for the other effects was 0.25 mg/m^3 in the absence of noticeable skin exposure. An increased urinary excretion of catecholamines was measured in 6 workers in an Italian dynamite factory. Airborne exposures in the different areas of the plant varied from 0.55 to 1.65 mg/m^3. Symptoms of EGDN exposure were slight

headache and reduced blood pressure. Abnormal electroencephalographic (EEG) records were found in Japanese dynamite workers at EGDN concentrations in the workplace below 1.27 mg/m^3. ECG abnormalities were observed in a group of miners, who worked at places where EGDN air concentrations were between 0.16 and 5.9 mg/m^3.

Chronic effects of EGDN exposure concern cardio-cerebrovascular diseases. In the Swedish dynamite-production industry, with mean 8-hour TWA air concentrations of nitrate esters ranging between 0.2 and 1.1 mg/m^3, an excess mortality due to cardio-cerebrovascular diseases was found among subjects with more than 20 years of exposure, i.e., the excess might be associated with much higher exposures during earlier decades. No significant excess mortality from cardio-cerebrovascular diseases was observed in Scottish explosives (blasting) workers exposed to mixtures of EGDN and glycerol trinitrate, but in workers aged 15-49 years with 'high-exposure' (not defined), there was a significant excess mortality from ischaemic heart disease, particularly acute myocardial infarction.

No data were found on eye or skin irritation or on skin sensitisation potential of the compound in test animals. Results of acute lethal toxicity studies (oral LD_{50} rat and mice: about 500 mg/kg bw; dermal LD_{50} rat: 3800 mg/kg bw) indicated that EGDN is harmful if ingested and of low toxicity following dermal exposure. In rats, an acute subcutaneous injection of a high dose (65 mg/kg bw) of EGDN caused a fall in blood pressure and an increase in plasma corticosterone concentrations. The maximum effects were reached at 15-30 minutes after administration. Methaemoglobinaemia was also observed with a maximal level of 24% reached about 3 hours after administration.

The committee did not find repeated-dose toxicity studies suitable for EGDN risk assessment. Most published short-term studies dealt with experiments to elucidate the mechanisms of the observed cardiovascular effects after cessation of prolonged exposure to EGDN. The committee's view is that an increased activity of the sympathetic nerves and/or an increased vascular sensitivity to noradrenaline after cessation of EGDN exposure may be responsible for the cardiovascular effects. *In vitro* experiments demonstrated that EGDN acts directly on rat cardiac muscles, causing a change in contractility.

The committee did not find data on the potential mutagenicity and genotoxicity or reproductive toxicity of EGDN.

Based on the above data, the committee concludes that the critical effect of exposure to EGDN is vasodilation as indicated by the development of throbbing headache or blood pressure decreases. However, it is very difficult to assess the

levels of exposure to EGDN in occupational situations that induce symptoms and effects, not only because exposure is usually to mixtures of organic nitrate esters, but also because of both respiratory tract and skin absorption of EGDN vapours. It is even suggested that workers who handle dynamite directly may absorb more glycerol trinitrate and EGDN mixtures through the skin than through the lungs (NIO78). Nevertheless, exposure to levels as low as 0.25 (Ein63) or 0.35 mg/m^3 (Tra66) appeared to induce headaches. The committee considers 0.25 mg/m^3 to be the LOAEL to be taken as a starting point in establishing health-based recommended occupational exposure limit (HBROEL). At this air level, no changes in the incidences of systolic blood pressure or pulse rate at the end of the work shift were observed. For extrapolation to an HBROEL, the committee applies an overall assessment factor of 4, covering the following aspects: inadequacies in the database (e.g., workplace exposures instead of personal exposures) and the absence of a NOAEL. Thus applying this factor of 4 and the preferred-value approach, a health-based occupational exposure limit of 0.05 mg/m^3 is recommended for ethylene dinitrate. Since sampling (Ein63) or exposure (Tra66) were about 20 minutes and headache developed within 1-3 minutes at exposure to 2 mg/m^3 (Tra66), the committee recommends this health-based occupational exposure limit in the form of a 15-minute average.

The committee recommends a health-based occupational exposure limit for ethylene dinitrate of 0.05 mg/m^3 (0.008 ppm), as a 15-minute time-weighted average.

Due to the great accessibility through the skin, the committee also recommends a ‘skin notation’.

References

ACG99 American Conference of Governmental Industrial Hygienists (ACGIH). Ethylene glycol dinitrate. In: TLVs and other occupational exposure values - 1999. [CD ROM]. Cincinnati OH, USA: ACGIH®, 1999.

ACG04 American Conference of Governmental Industrial Hygienists (ACGIH). Guide to occupational exposure values - 2004. Cincinnati OH, USA: ACGIH®, 2004: 64.

ACG05 American Conference of Governmental Industrial Hygienists (ACGIH). 2005 TLVs® and BEIs® based on the documentation of the Threshold Limit Values for chemical substances and physical agents & Biological Exposure Indices. Cincinnati OH, USA: ACGIH®, 2005: 29.

Arb02 Arbejdstilsynet. Grænseværdier for stoffer og materialer. Copenhagen, Denmark: Arbejdstilsynet, 2002: 26 (At-vejledning C.0.1).

Axe92 Axelsson KL, Andersson C, Ahlner J, et al. Comparative in vitro study of a series of organic nitroesters: unique biphasic concentration-effect curves for glyceryl trinitrate in isolated bovine arterial smooth muscle and lack of stereoselectivity for some glyceryl trinitrate analogues. J Cardiovasc Pharmacol 1992; 19: 953-7.

Bar67 Bartalini M, Cavagna G, Foa V. Epidemiological and clinical features of occupational nitroglycerin poisoning in Italy. Med Lav 1967; 58: 618-23.

Ber87 Bergert KD, Friedrich K, Geschke U, et al. Kardiovaskuläre Erkrankungen bei Exposition gegenüber dem Salpetersäureester Ethelenglycoldinitrat. Z Gesamte Inn Med 1987; 42: 581-3.

Bil63 Bille S, Sivertssen E. Mors subita hos sprengstoffarbeider. Nord Med 1963; 70: 842-3.

Cai82a Caillard JF, Mereau P, Derzko G, et al. Exposition au nitroglycol et à la nitroglycerine. Étude bibliographique. Bilan d'une enquête transversale dans cinq dynamiteries. Cah Notes Doc 1982; 107: 189-206.

Cai82b Caillard JF, Delebarre P, Cramer J, et al. Exposition au nitroglycol et à la nitroglycerine. Syndrome de sevrage. Étude d'enregistrements electrocardiographiques continus. Cah Notes Doc 1982; 109: 555-67.

Car63 Carmichael P, Lieben J. Sudden death in explosive workers. Arch Environ Health 1963; 7: 424-39.

Cla67 Clark DG, Litchfield MH. Metabolism of ethylene glycol dinitrate and its influence on blood pressure of the rat. Br J Ind Med 1967; 24: 320-5.

Cla69 Clark DG, Litchfield MH. Metabolism of ethylene glycol dinitrate (ethylene dinitrate) in the rat following repeated administration. Br J Ind Med 1969; 26: 150-5.

Cla70 Clark DG. The supersensitivity of the rat cardiovascular system to epinephrine after repeated injections of ethylene glycol dinitrate. Toxicol Appl Pharmacol. 1970; 17: 433-42.

Cla72 Clark DG. Effects of ethylene glycol dinitrate on pituitary-adrenocortical function in the rat. Toxicol Appl Pharmacol 1972; 21: 355-60.

Cla73 Clark DG, Litchfield MH. Role of inorganic nitrite in methaemoglobin formation after nitrate ester administration to the rat. Br J Pharmacol 1973; 48: 162-8.

Cra31 Crandall LA Jr, Leake CD, Loevenhart AS, et al. Acquired tolerance to and cross-tolerance between the nitrous and nitric acid esters and sodium nitrite in man. J Pharmacol Exp Ther 1931; 41: 103.

Cra85 Craigh R, Gillis CR, Hole DJ, et al. Sixteen year follow up of workers in an explosives factory. J Soc Occup Med 1985; 35: 107-10.

Dav93 Davis RA. Aliphatic nitro, nitrate, and nitrite compounds. In: Clayton GD, Clayton FE, eds. Toxicology. 4th ed. New York, USA: John Wiley & Sons, Inc, 1993: 599-662 (Patty's industrial hygiene and toxicology; Vol II, Pt A).

DFG05 Deutsche Forschungsgemeinschaft (DFG): Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area. List of MAK and BAT values 2005. Maximum concentrations and biological tolerance values at the workplace. Weinheim, FRG: Wiley-VCH Verlag GmbH & Co. KGaA, 2005: 63 (rep no 41).

EC05 European Commission: Directorate General of Employment, Social Affairs and Equal Opportunities. Indicative occupational exposure limit values. http://europe.eu.int/comm/employment_social/health_safety/docs/oels_en.pdf.

Ein63 Einert C, Adams W, Crothers R, et al. Exposures to mixtures of nitroglycerin and ethylene glycol dinitrate. Am Ind Hyg Assoc J 1963; 24: 435-47.

For58 Forssman S, Masreliez N, Johansson G, et al. Untersuchungen des Gesundheidszustandes von Nitroarbeitern bei drei schwedischen Sprengstoffabriken. Arch Gewerbepathol Gewerbehyg 1958; 16: 157-77.

Fri60 Frimmer M, Gross E, Kiese M, et al. Resorption von Äthylenglykoldinitrat durch die Lunge. Arch Toxikol 1960; 18: 200-4.

Fuk81 Fukuchi Y. Nitroglycol concentrations in blood and urine of workers engaged in dynamite production. Int Arch Occup Environ Health 1981; 48: 339-46.

Fur83 Furuno J. Nitroglycol poisoning. Nippon Hoigaku Zasshi 1983; 37:491-503 (in Japanese with abstract, figures, tables in English).

Gro42 Gross E, Bock M, Hellrung F. Zur Toxikologie des Nitroglykols im Vergleich zu der des Nitroglycerins. Arch Exp Path Pharmakol 1942; 200: 271-304.

Gro60 Gross E, Kiese M, Resag K. Resorption von Äthylglykoldinitrat durch die Haut. Arch Toxikol 1960; 18: 194-9.

Han65 Hanova M.[Electrocardiographic changes due to ethyleneglycol dinitrate and glycerol trinitrate]. In Slowak. Bratisl Lek Listy 1965; 45: 220-4; cited in NIO78.

Has70 Hasegawa M, Sato M, Tsuruta H. Methemoglobin formation in man and animal by nitroglycol. Ind Health 1970; 8: 153-4.

Hog77 Hogstedt C, Axelson O. Nitroglycerine-nitroglycol exposure and the mortality in cardio-cerebrovascular diseases among dynamite workers. J Occup Med 1977; 19: 675-8.

Hog79 Hogstedt C, Andersson K. A cohort study on mortality among dynamite workers. J Occup Med 1979; 21: 553-6.

Hog80 Hogstedt C, Ståhl R. Skin absorption and protective gloves in dynamite work. Am Ind Hyg Assoc J 1980; 41: 367-72.

Hog84 Hogstedt C, Axelson O. Mortality from cardio-cerebrovascular diseases among dynamite workers - An extended case-referent study. Ann Acad Med Singapore 1984; 13 (2, suppl): 399-403.

HSE03 Health and Safety Executive (HSE). EH40/2002. Occupational exposure limits supplement 2003. Sudbury (Suffolk), England: HSE Books, 2003: 4.

Joh87 Johansson P, Ehrenström F, Ungell AL. Study on adrenergic function after development of tolerance to ethylene glycol dinitrate (EGDN) in rats. Pharmacol Toxicol 1987; 61: 172-81.

Kal69 Kalin M, Kylin B, Malmfors T. The effect of nitrate explosives on adrenergic nerves. Arch Environ Health 1969; 19: 32-5.

Kan91 Kanerva L, Laine R, Jolanki R, et al. Occupational allergic contact dermatitis caused by nitroglycerin. Contact Dermatitis 1991; 24: 356-62.

Kri89 Kristensen TS. Cardiovascular diseases and the work environment. A critical review of the epidemiologic literature on chemical factors. Scand J Work Environ Health 1989; 15: 245-64.

Kuz84 Kuželová M, Kovařík J, Fiedlerová D, et al. Vliv nitroesterů na nervový systém exponovaných osob. Prac Lek 1984; 36: 166-70.

Lam93 Lamm SH, Grumski KS, Fethers RF. Short-term exposures to ethylene glycol dinitrate concentrations greater than 0.4 mg/m^3 show no evidence of nitrate-induced headaches (abstract). Am J Epidemiol 1993; 138: 653.

Lit73 Litchfield MH. Recent views on the mechanisms of nitrate ester metabolism. Drug Metab Rev 1973; 2: 239-64.

Lun85 Lundberg P, ed. Consensus report for nitroglycol and nitroglycerin. In: Scientific basis for Swedish occupational standards. VI. Arbete och Hälsa 1985; (32): 48-57.

Mat75 Matsushita T, Tadokoro Y. An electroencephalographic study for chronic nitroglycol poisoning. Ind Health 1975; 13: 237-41.

McG61 McGuiness BW, Harris EL. 'Monday head': An interesting occupational disorder. Br Med J 1961; 2: 745-7.

Min72 Minami M, Akada A, Takizawa A, et al. Effect of ethylene glycol dinitrate on metabolism of catecholamines and on blood pressure reaction to re-exposure. Br J Ind Med 1972; 29: 321-7.

Mor67 Morikawa Y, Muraki K, Ikoma Y, et al. Organic nitrate poisoning at an explosive factory. Arch Environ Health 1967; 14: 614-21.

NIO78 US National Institute of Occupational Safety and Health (NIOSH). Criteria for a recommended standard .... Occupational exposure to nitroglycerin and ethelene glycol dinitrate. Cincinnati OH, USA: US Dept of Health, Education and Welfare, Public Health Service, Center for Disease Control, NIOSH, 1978; DEHW (NIOSH) Publ No 78-167 (report available from NTIS, Springfield VA, USA; order no PB81-225526).

NIO04 US National Institute of Occupational Safety and Health (NIOSH), ed. Ethylene glycol, dinitrate. In: The Registry of Toxic Substances and Disease Registry (RTECS) (last update ethylene dinitrate file: October 2002; http://www.cdc.gov/niosh

NLM04 US National Library of Medicine (NLM), ed. Ethylene glycol dinitrate. In: The Hazardous Substances Databank (HSDB). (last revision date ethylene glycol dinitrate file: February 14, 2003; last review date file: September 19, 1996); http://toxnet.nlm.nih.gov.

Pre65 Přerovská I, Teisinger J. Klinický obraz chronické otravy dinitroglykolem. Prac Lek 1965; 17: 41-3.

Pre76 Přerovská I, Pícková J. Vývoj klinických nálezù u dlníkù pc chronické otrav dinitroglykolem. Prac Lek 1976; 28: 21-4.

Swe00 Swedish National Board of Occupational Safety and Health. Occupational exposure limit values and measures against air contaminants. Solna, Sweden: National Board of Occupational Safety and Health, 2000: 42 (Ordinance AFS 2000:3).

SZW05 Ministerie van Sociale Zaken en Werkgelegenheid (SZW). Nationale MAC-lijst 2005. The Hague, the Netherlands: Sdu Uitgevers, 2005: 26.

Tai97 Tai T, Tsuruta H. The effects of nitroglycol on rat isolated cardiac muscle. Ind Health 1997; 35: 515-8.

Tra66 Trainor DC, Jones RC. Headaches in explosive magazine workers. Arch Environ Health 1966; 12: 231-4.

TRG04 TRGS 900. Technische Regeln für Gefahrstoffe. Grenzwerte in der Luft am Arbeitsplatz. BArbBl 2004; (7/8).

Tsu70a Tsuruta T, Hasegawa H. Studies on nitroglycol poisoning. On some properties of an enzyme which decomposes nitroglycol into inorganic nitrate. Ind Health 1970; 8: 99-118.

Tsu70b Tsuruta T, Hasegawa H. Studies on nitroglycol poisoning. Decomposition mechanism of nitroglycol by nitrite forming enzyme. Ind Health 1970; 8: 119-40.

Vig68 Vigliani EC, Cavagna G, Locati G, et al. Biological effects of nitroglycol on the metabolism of catecholamines. Arch Environ Health 1968; 16: 477-84.

Annex

Occupational exposure limits for ethylene dinitrate in various countries.

country - organisation	occupational exposure limit		time-weighted average	type of exposure limit	note[a]	reference[b]
	ppm	mg/m^3				
the Netherlands						
- Ministry of Social Affairs and Employment	0.05	0.3	8 h	administrative	S	SZW05
Germany						
- AGS	0.05	0.32	8 h		S,[c]	TRG04
	0.2	1.28	15 min			
- DFG MAK-Kommission	0.05	0.32	8 h		S,[c]	DFG05
	0.05	0.32	15 min			
Great-Britain						
- HSE	-	-				HSE03
Sweden	0.03	0.2	8 h		S	Swe00
	0.1	0.6	15 min			
Denmark	0.02	0.12	ceiling		S	Arb02
USA						
- ACGIH	0.05	-	8 h	TLV	S	ACG05
- OSHA	0.2	1	ceiling	PEL	S	ACG04
- NIOSH	-	0.1	ceiling	REL	S	ACG04
European Union						
- SCOEL	-	-				EC05

[a] S = skin notation; which means that skin absorption may contribute considerably to body burden; sens = substance can cause sensitisation.

[b] Reference to the most recent official publication of occupational exposure limits.

[c] Limit holds only for workplaces without skin contact.