
Glycerol trinitrate

(CAS No: 55-63-0)

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 glycerol trinitrate (GTN) 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 H Stouten, M.Sc. (TNO Nutrition and Food Research, Zeist, the Netherlands).

The evaluation of the toxicity of glycerol trinitrate has been based on the reviews by the US National Institute for Occupational Safety and Health (NIOSH) (NIO78), the US Environmental Protection Agency (EPA87), and the American Conference of Governmental Industrial Hygienists (ACG99). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, in January 2000, literature was searched in the on-line databases Medline, Toxline, Chemical Abstracts, and NIOSHTIC, starting from 1965-1967, and using the following key words: nitroglycerin and 55-63-0. The final literature search was carried out in Toxline and Medline in October 2004.

In December 2004, the President of the Health Council released a draft of the document for public review. Comments were received from the following individuals and organisations: E Ball (Health and Safety Executive, London, UK). These comments were taken into account in deciding on the final version of the document.

2 Identity

name	: glycerol trinitrate
synonyms	: nitroglycerine; glyceryl trinitrate; nitroglycerol; 1,2,3-propanetriol trinitrate
molecular formula	: C ₃ H ₅ N ₃ O ₉
structural formula	: $\begin{array}{c} \text{H}_2\text{C}-\text{O}-\text{NO}_2 \\ \\ \text{HC}-\text{O}-\text{NO}_2 \\ \\ \text{H}_2\text{C}-\text{O}-\text{NO}_2 \end{array}$
CAS number	: 55-63-0

3 Physical and chemical properties

molecular weight	: 227.09
boiling point	: 218°C (explodes; decomposition starting at 50-60°C)
melting point	: 13.1°C
flash point	: not available
vapour pressure	: at 20°C: 0.04 Pa
solubility in water	: poorly soluble (at 20°C: 0.1 g/100 mL)
log P _{octanol/water}	: 1.62 (experimental); 1.51 (estimated)
conversion factors	: at 20°C, 101.3 kPa: 1 ppm = 9.5 mg/m ³ 1 mg/m ³ = 0.11 ppm

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

At room temperature, GTN is a pale yellow, oily liquid with a sweet, burning taste (ACG99, NLM04).

4 Uses

GTN is highly explosive and used in the production of dynamite and other explosives (ACG99, Lei95). It is also used in rocket propellants. Furthermore, it is employed in medicine as a treatment for angina pectoris, for congestive heart failure (especially when associated with acute myocardial infarction), and hypertension (pulmonary; due to ergotism; perioperative emergencies especially during cardiovascular surgery).

In the Netherlands, GTN-containing products are listed in the 'Geneesmiddelen Repertorium', an overview of information on pharmaceutical specialties registered by the Dutch Medicines Evaluation Board*.

5 Biotransformation and kinetics

Human data

No data were available on the kinetics of GTN following inhalation exposure. In a study on workers exposed to GTN during gunpowder production, uptake of the chemical via the skin was considered to be more important than via the respiratory tract, as no significant correlation was found between airborne GTN levels (range: 1.0-4.0 mg/m³) and plasma GTN concentrations in blood from the

* at: <http://www.geneesmiddelenrepertorium.nl/nefarma/>.

cubital vein (up to 118 µg/L; median: ca. 4 µg/L). However, no data on the correlation between dermal skin exposure and GTN concentrations in plasma were shown (Gje85). In another biological monitoring study, concentrations of GTN metabolites 1,2- and 1,3 glyceryl dinitrate (1,2- and 1,3-GDN) were found in mid- and post-shift urine samples of workers at 2 munitions-manufacturing sites (range: 0-29 µg/g creatinine) and a pharmaceutical-manufacturing site (range: 0-1.5 µg/g creatinine). According to Akrill et al., these results demonstrated GTN skin absorption (Akr02). Quantitative data on dermal absorption have been obtained from clinical studies with the transdermal administration of GTN, as an ointment or, more recently, with transdermal patches. GTN is released from such patches in quantities of 5 to 15 mg/day, at an absorption rate of approximately 0.5 mg GTN/cm²/day. During 24-hour patch application, GTN plasma concentrations increase rapidly during the first few hours, reaching steady-state levels after 3 to 6 hours, after which more or less constant concentrations are seen. In different studies, mean plasma concentrations at 24 hours were of the order of 0.1 to 0.4 µg/L (Bog87, Bog88, Bog94, San00a, Tha88). After removal of the patch, mean elimination half-lives for GTN in plasma of 7 and 28 minutes have been reported (Auc98a, San00b). The systemic bioavailability following transdermal dosing of GTN has been estimated 68 to 76% (Nak87). Following oral application, the bioavailability is less than 1%. GTN plasma concentrations in oral dosing studies were mostly below the analytical detection limit of 0.1 µg/L (Bog94, Bol96). For example, following administration of a 2.5 mg and a 6.5 mg sustained-release oral capsule to a human volunteer, no GMT was detectable in the plasma until 20 minutes after application (Blu77). Following intravenous GTN administration to human volunteers at infusion rates ranging from 10 to 40 ng/min, steady state plasma levels from 0.44 to 4.2 µg/L were found. In patients, the half-life of GTN in plasma was 2 to 3 minutes (Bog87). The rapid disappearance from the plasma involves distribution throughout the body, as well as (first-pass) metabolism (Bog88, Bol96).

GTN is metabolised into 1,2- and 1,3-GDN in the liver as well as in other tissues such as intestinal mucosa, kidneys, vascular endothelial and smooth muscle cells, erythrocytes (Bol96), and in the skin (Auc98b). Following GTN patch application, the plasma levels of 1,2-GDN were about 6 times higher than and those of 1,3-GDN similar to GTN plasma levels (San00a). Following oral GTN administration, 1,2- and 1,3-GDN plasma concentrations were about 100 and 50 times higher, respectively, than those of GTN (Bol96, Noo86). The plasma half-lives of these metabolites are also much longer than that of the parent compound, i.e., 40 to 50 minutes (Auc98a, San00b, Tha88).

Animal data

In a dermal absorption study in rats, amounts of 100-800 mg of a gelatine mixture comprising 93% GTN and 7% nitrocellulose were applied to 1 cm² of clipped, occluded back skin, for 1 to 4 days. After 4 days, the amount of absorbed GTN, determined indirectly by measurement of the residual amount of GTN on the skin and in the cover, varied from 57% to 11% of the dose, after administration of 100 and 800 mg, respectively. The mean absorption rate was 0.85 mg/cm²/hour. When 100-400 mg of a paste containing 22% GTN, 6% dinitrotoluene, 5% trinitrotoluene, and 65% NaCl was applied for 8 days, the amount of absorbed GTN after 8 days was about 18% of the applied doses. The mean absorption rate was 0.63 mg/cm²/hour. Contrary to the experiments with the gelatine, absorption curves were not linear over the experimental period but levelled off after day 1 (Gro60).

When CD female rats were given a single oral dose of 180 mg/kg bw of radiolabelled [1,3-¹⁴C] GTN (purity: 98.3%), 39.8% of the radioactivity was excreted in the urine, 6.3% in the faeces, and 25.5 % in expired air as ¹⁴CO₂ within 24 hours. At 24 hours after administration, the amount of radioactivity remaining in the gastrointestinal tract was 3.0% of the dose. A significant amount (4.3% of the dose) was found in the liver, and only small amounts (<1% of the dose) were detected in the blood, kidneys, brain, or lungs. Radioactivity retained in the carcass amounted to 5.4% of the dose. The authors concluded that 80-90% of the oral dose was absorbed through the gastrointestinal tract at 24 hours after administration. At 4 hours after dosing, the radioactivity ratios in the tissues, relative to plasma (tissue/plasma ratios) were in the following order: liver (4.4), kidney (2.4), lungs (1.2), brain (1.1), and muscle (0.6). The authors showed that the major urinary metabolites were unconjugated glyceryl mononitrate (GMN; 10.6 % of the dose), 1,2-GDN glucuronide (10% of the dose), and glycerol (6.9% of the dose). Minor metabolites were 1,3-GDN glucuronide (3.5% of the dose), GMN glucuronide (1.5% of the dose), and unconjugated 1,2- and 1,3 GDN (<1% of the dose). A negligible amount of GTN was detectable (<0.1% of the dose) (Hod75).

In a previous study in rats, more than half of the radioactivity was removed from the gastrointestinal tract within 30 minutes after administration of a single oral dose of 10 mg/kg bw of [1,3-¹⁴C] GTN. At 4 hours after administration, 21% of the radioactivity was excreted in the urine, and 20% in expired air as ¹⁴CO₂. The major tissue concentrations of radiolabel were found in the liver and the carcass (DiC68). When mice, rabbits, dogs, and monkeys were given single doses of 180-200 mg/kg bw of [1,3-¹⁴C] GTN, absorption was essentially

complete within 24 hours. Radioactivity excreted in the first 24-hours urine after administration was highest in rabbits and dogs (72% of the dose), followed by monkeys (45%) and mice (19%). Excretion in the faeces ranged from 0.1% of the dose in rabbits to 28.5% in mice. The highest amount of excreted radioactivity in expired air (as $^{14}\text{CO}_2$) was found in mice (19.2%), followed by rabbits (7.8%), monkeys (3.6%), and dogs (2.5%). At 24 hours after administration, 2.2 % (mice) to 8.4 % (monkeys) of the dose was found in the gastrointestinal tract. In other tissues, high amounts were found in the liver (varying from 4.8% in rabbits to 6.8% in monkeys), and in the skeletal tissues (9.5% of the dose in dogs and 13% in monkeys vs. 2.5% in mice and rabbits). Tissue/plasma radioactivity ratios were highest in the liver, especially in mice (ratio: 30) and rabbits (ratio: 21), vs. 7.5 in dogs, and monkeys. In the kidneys ratios varied from 2.2 (monkeys) to 4.3 (rabbits). GTN and free 1,2- and 1,3-GDN were excreted only in small amounts (1.2% or less of the dose) in the urine of mice, and rabbits, and in slightly higher amounts in the urine of dogs and monkeys (4.3% and 2.8%, respectively). Mice excreted only small amounts of free GMN, GMN glucuronide, and GDN glucuronides (4.6% of the dose). Most of the urinary metabolites in rabbits were free GMN, and 1,2- and 1,3-GDN glucuronides. Dogs and monkeys excreted mostly free GMN and GMN glucuronide (EPA87).

The mechanism of GTN denitration into GDNs and inorganic nitrite and nitrate involves a reaction with glutathione, either spontaneously or linked with the liver enzyme organic nitrate reductase (Nee76). Nitrate enters into the cell and is cleaved to inorganic nitrite and then to nitrous oxide (NO). NO or its further combination with thiol groups leading to production of nitrosothiol activates guanylate cyclase, resulting in increased synthesis of cyclic monophosphate (cGMP), which induces vascular smooth muscle dilation (Tha88).

6 Effects and mechanism of action

Human data

Irritation and sensitisation

In an old report describing effects of GTN in pharmaceutical workers, it was stated that prolonged contact might result in skin eruptions of variable severity, in particular ulcerations of the fingertips and below the nail (Bre49). When transdermal patches, with 31 or 80 mg GTN, were applied to the skin of the

antero-lateral thorax of human volunteers (n=24) for 24 hours, local erythema was observed in nearly all subjects, which disappeared within a few hours after patch removal. According to Santoro et al., erythema on the absorption site of the skin was due to vasodilation of the blood vessels in the dermis (San00b).

In a skin irritation and sensitisation study in human volunteers (n=11 males; 17 females), transdermal patches with 31 mg GTN were applied to the skin of the antero-lateral thorax, 12 hours/day, for 14 days. Two weeks after the last application, the subjects were challenged by another 12-hour skin application. Only very mild or transient erythema on the application site in less than 30% of the subjects, but no skin sensitisation was observed (San01).

In a case report, 4 dynamite workers with allergic contact dermatitis were positive in a patch test with GTN (Kan91). In addition, several reports on allergic contact dermatitis from topical medical treatment with GTN (transdermal delivery systems, plaster, patches) have been published (Car89, DiL89, Fue94, Kan91, Kou96, Mac99, McK00, Pér02, Sau78, Sil01, Wei86).

Systemic effects

GTN has been in occupational use in the manufacture and production of explosives and pharmaceutical agents since the middle of the 19th century. Health effects, especially in explosive workers, have been described in case reports and epidemiological studies and reviewed - amongst others - by Daum (Dau92), Fine (Fin92), Kristensen (Kri89), Morton (Mor77), and NIOSH (NIO78).

GTN is a potent vasodilator of both arterial and venous smooth muscle. As for other aliphatic nitrates (e.g., ethylene dinitrate), its outstanding effect is a severe throbbing headache that can already be produced at relatively low exposure levels. Accompanying symptoms included nausea, vomiting, and abdominal pain. Exposures to higher levels may cause hypotension, depression, confusion, occasionally delirium, methaemoglobinaemia, and cyanosis. Use of alcohol aggravates these symptoms causing hallucinations or mania, or evokes them where they were initially absent. Characteristic is tolerance developing after repeated exposure for 3 to 4 days but disappearing after a 2-day exposure-free period resulting in the phenomenon described as 'monday morning angina' or 'monday morning death'. Because of this time lag between end of exposure and onset of effects, the term 'nitrate withdrawal symptoms' has been used as well, which included various conditions such as angina, coronary spasm, myocardial infarction, arrhythmia, and sudden death. Other effects (occasionally) described are methaemoglobinaemia, leucopenia, abnormal liver

function tests and albumin/globulin ratio, acute renal insufficiency, symptoms of Raynaud's phenomenon, peripheral neuropathy, paraesthesia, transient hemiparesis, epilepsy, and aphasia (Dau92, Dav93, Kri89).

An acute lethal dose of 200 mg has been reported, but humans also survived acute doses up to 1200 mg (Bol96). In one case, an acute dose of 24 mg GTN caused convulsions (Gos84). Therapeutic doses of GTN, given as a sublingual tablet, are up to a total of 6 mg/day (Lau87). Dermal patches, with 16, 31, or 47 mg GTN, were applied on the skin of the antero-lateral thorax of human volunteers (n=18/dose) for 24 hours. These patches are designed to deliver 5, 10, or 15 mg during the application period, respectively. Headache was reported by 13, 18, or 17 subjects, nausea by 1, 1, or 2 subjects, vomiting by 1, 2, or 1 subject, and dizziness by 0, 0, or 1 subject, respectively (San00a).

Gjesdal et al. conducted a study on 7 male and 5 female gunpowder-production workers, to examine, amongst others, the effects of GTN on pulse rate, blood pressure, and headache during working hours, in relation to airborne and plasma GTN levels (cf. Section 5). Air sampling showed concentrations ranging between 1.1 and 4.0 mg/m³ (mean: 2.4 mg/m³). Plasma GTN concentrations in blood from the cubital vein were up to 118 µg/L (median: ca. 4 µg/L). None of the subjects had a morning headache. During the working day, almost all workers experienced an increasing headache but this was not significantly correlated with GTN concentrations in air or in the plasma. Neither significant correlations were found between GTN concentrations in plasma and blood pressure or pulse rate. According to Gjesdal et al., the lack of such correlations is due to the short half-life of GTN in plasma and the fact that effects were induced by dermal absorption rather than by inhalation of GTN (Gje85). In dynamite workers (n=8) exposed to total air levels of GTN and ethylene dinitrate (EGDN) in the range of 0.10 to 0.53 mg/m³, as measured by static monitoring and calculated as mg GTN/m³, headache, but no effect on blood pressure was observed. As a follow-up, the effects of these dynamite vapours were examined by exposing 6 to 10 workers voluntarily to average total air concentrations of EGDN and GTN, expressed as mg GTN/m³, of 0.5 or 0.7 mg/m³ (range: 0.65-0.74 or 0.40-0.67 mg/m³, respectively) for 25 minutes, or 2.0 mg/m³ (range and duration of exposure not specified). Skin contact with the dynamite was avoided. At 2.0 mg/m³, headache developed within 3 minutes in 5 subjects, and decreases in systolic and diastolic blood pressure were measured in 5 and 4 subjects, respectively. One subject did not have a headache or effects on blood pressure. All 10 volunteers exposed to 0.7 mg/m³ developed headache or pulsating feelings or dullness in the head, and decreases in systolic and diastolic blood pressure were seen in 8 and 7 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 GTN, EGDN completely predominates the vapour phase from a mixture of them in dynamite production, irrespective of the ratios used (Hog84a). Therefore, the committee considers that the effects observed are attributable to EGDN. In a previous study, an extensive investigation was conducted of complaints of irritation and headaches among workers manufacturing GTN tablets 2 to 3 times a week. Breathing zone air levels of $0.3\text{-}1.0 \text{ mg/m}^3$ were associated with headache and irritation (not further specified), and these complaints disappeared when changes in manufacture operation resulted in GTN air levels below 0.1 mg/m^3 (Han66).

Aiming at cardiac and cerebrovascular diseases due to (long-term) exposure to GTN, 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 (Hog84b).

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., GTN and EGDN) 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 (Hog84a, 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 workers aged less than 65 years who were employed at the factory on January 1965. The mortality in this cohort (n=4042) was studied over the period 1 January 1965 to 31 December 1980. Workers were divided into 3 groups: the blasting workers (n=659), who were handling a mixture of GTN and EGDN in a ratio 4:1, the propellants workers (n=224), considered to have been exposed to GTN only, and the internal controls (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 made (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). As to the propellants workers with high exposure, a not statistically significant increase in mortality from cerebrovascular disease was found in the workers of the older age group (6 observed, vs. 4 or 3 expected in the external or internal controls, respectively). Figures for mortality from ischaemic heart disease were similar to those of the control groups (9 observed, vs. 12 or 8 expected, respectively). There was no excess mortality from all cancers (6 observed vs. 7 or 6 expected, respectively), or from lung cancer (1 observed vs. 3 or 2 expected). In the low-exposure category, there were no deaths from cerebrovascular diseases and 1 from ischaemic heart disease (vs. 3 or 1 expected, respectively), and 3 deaths from all cancers (vs. 2 or 1 expected, respectively), all being lung cancers (1 or 2 expected, respectively). In the younger age group, the mortality rate for cardio-cerebrovascular diseases of the propellant workers was similar to that of both control groups. There was no mortality from cancer in the low-exposure group. In the high-exposure group, 4 workers died from all cancers (vs. 2 expected in both control groups), and 2 died from lung cancer (vs. 1 expected in both control groups). The major finding in the blasting workers was a significant excess of mortality for acute myocardial infarction found in the high-exposed younger age group when compared with the internal controls ($p < 0.05$). Since EGDN is considerably more volatile and more readily absorbed through the skin than GTN, EGDN was considered to be the more important compound in causing effects in the blasting workers (Cra85).

In a retrospective cohort mortality study, the possible relationship of exposure to GTN and the risk of cardiovascular disease mortality was examined in white male workers (n=5529) from a US munitions facility. Mortality data were compared with those of the US population and of an unexposed internal

control group (n=5136). Mortality from ischaemic heart and cerebrovascular diseases were close to those expected. SMRs were 1.07 and 0.90, and standardised rate ratios (SRRs) 1.07 and 0.87, respectively. A significant interaction between age and exposure to GTN was detected for ischaemic heart disease, especially for workers under 45 years of age in the high-exposure group (SRR: 3.30, 95% CI: 1.29-8.48). No increased mortality from all malignancies or from lymphatic and haematopoietic neoplasms (only selection presented) was observed (SMR: 0.84 and 1.06, respectively) (Sta92).

In testing associations of 215 prescription drugs or drug groups with subsequent incidence of cancer at 56 sites, by using computerised pharmacy records for a cohort of more than 140,000 members of a medical care programme in Northern California, GTN was listed among compounds having a statistically significant positive drug-cancer association. Based on 1999 users, 42 cases of lung, trachea, or bronchus cancer were observed in the period 1969-1984 vs. 29.4 expected (no more data available) (Sel89).

Animal data

Irritation and sensitisation

In an unpublished study, a 7.3% GTN paste (25% peanut oil and 75% of 9.7% GTN in lactose) was not irritating to the eyes of rabbits. When applied to the intact or abraded shaved skin of rabbits, this paste was found only very mildly irritating (Lee75). Application of transdermal patches with 31 mg GTN (2.5 mg/cm²) and 4 mg GTN per cm² of release area, respectively, to the clipped dorsal intact skin of rabbits resulted in primary irritation scores (obtained combining and averaging erythema and oedema scores recorded 24, 48, and 72 hours after removing patches) of 0.56 and 0.0, respectively. Repeated application of the 31 mg-containing patch, 21 hours/day, for 28 days, resulted in very slight erythema (average score: 0.9) and no oedema (average score: 0.02). After 4 days of application of this patch to the shaved skin of mice followed by UV radiation, no evidence of phototoxic reactions was observed (San01).

Using the Magnusson-Kligman maximisation test, a 40% positive response indicated that GTN (3.4%; as 9.7% GTN in lactose suspended in peanut oil) applied to the clipped skin of guinea pigs was a moderate skin sensitising compound (no more details presented) (Lee75). No skin sensitising or skin photosensitising were seen when transdermal patches with 31 mg GTN were tested in guinea pigs (San01).

Acute toxicity

The oral LD₅₀ values were 822 and 884 mg/kg bw in male and female rats, respectively, and 1188 and 1055 mg/kg bw, in male and female mice, respectively. Signs of toxicity within 1 hour after dosing included cyanosis, ataxia, pale ears, nose, eyes, paws, and tails, and depressed respiration. Death followed usually within 5-6 hours. The survivors recovered mostly within 24 hours. No gross pathology was seen in the treatment-related deaths (Lee75). In other unpublished studies (originating from Japanese sources), oral LD₅₀ values of 105, 115, and 1607 mg/kg bw were reported for rats, mice, and rabbits, respectively. Dermal LD₅₀ values of >29, >35, >280 mg/kg bw were found for rats, mice, and rabbits, respectively. No further details were given (NIO04). Following single intravenous injections, LD₅₀ values of 17.3 and 18.2 mg/kg bw were found in male and female mice, respectively, and of 24.4 and 23.2 mg/kg bw in male and female rats, respectively. All deaths occurred within 5 minutes after injection. In mice, sedation, prostration, and weight loss, and, at necropsy, depletion of fat depots (in 2 animals given 15.9 mg/kg bw) were observed. Surviving animals were normal within 2 hours. In rats, there were incoordination, opisthotonos, prostration, sedation, and tremors, and no gross pathology. Surviving animals were normal within 1 hour after dosing (And83). In other unpublished studies, intravenous LD₅₀ values were reported of 10.6, 19, and 45 mg/kg bw for mice, dogs, and rabbits, respectively (NIO04).

Methaemoglobinaemia (MetHb) was produced in female Alderley Park rats treated subcutaneously with GTN (120 mg/kg bw). The maximal level, being approximately 26% MetHb, was attained about 4 hours after administration. Thereafter, there was a rapid decrease, and approximately 13% MetHb was left at 8 hours after administration. MetHb arising from GTN administration is formed principally by the action of inorganic nitrite, formed by metabolism of EGDN (Cla73).

Short-term toxicity

The committee found only one study, of limited significance, on the effects following repeated inhalation exposure to GTN. In this study, 1 cat was exposed to saturated air (ca. 5 mg/m³), 8 hours/day, 5 days/week, for 31 days, 1 cat for 68 days, and 1 cat for 156 days. At 31 and 168 days, slight to moderate anaemia was observed, indicated by decreased haemoglobin and erythrocyte levels, but no MetHb or formation of Heinz bodies was found. In the animal exposed for 156 days, increased normoblast and reticulocyte count was reported. In addition, this

cat showed decreased food consumption and body weight gain. In the third cat, exposed for 68 days, only a moderate lymphocytosis was seen (Gro42).

Beagle dogs (n=4 sex/group) were given daily capsules containing 0, 0.01, 0.1, or 1.0 mg/kg bw. After 4 weeks, no signs of toxicity were observed, and no changes in urinalysis, haematology, or clinical chemical tests were found in any of the dogs. Macroscopic and microscopic examination did not reveal abnormalities in any of the animals sacrificed (i.e., n=11/sex/group). Thereafter, doses were increased to 0.05 and 0.5 mg/kg bw/day in the low- and mid-dose groups (n=3/sex), and to 5 mg/kg bw/day in the high-dose group (n=2/sex) for another 9 weeks. Since there were no adverse effects in any of the dogs or macroscopic or microscopic changes in any of the animals sacrificed (n=1/sex/group), another experiment was conducted in Beagle dogs (n=2/sex), given 0, 25, 50, 100, or 200 mg/kg bw/day in capsules, for 5 consecutive days. After each dose, blood samples from each dog were taken at several time points for the measurement of haemoglobin (Hb) and MetHb levels. Peak MetHb levels were observed at 4 hours after dosing and were dose related. In dogs given up to 100 mg/kg bw, MetHb levels returned to zero within 24 hours on all days, while incomplete recovery was seen in the high-dose group on day 3. In this group, animals had cyanosis and clinical signs of such severity that treatment was discontinued on day 4. At 100 mg/kg bw, there was cyanosis as well. In both groups, the cyanosis corresponded with the MetHb peaks levels amounting to roughly 30-40% of total Hb (EII84, EPA87).

In a final experiment, groups of 6 male and female dogs were given 0, 1, 5, or 25 mg/kg bw/day of GTN per capsule, for 12 months. No clinical signs of toxicity or body weight changes were observed. The only notable effect found was MetHb, usually less than 3%, after 9 months, but not after 12 months. The incidence was dose related and even found in the low-dose group (EII84, EPA87). From these data, the committee concludes that no significant effects occur in dogs exposed up to a maximum tested level of 25 mg/kg bw/day for 12 months. Although no tumours were found, the committee is of the opinion that the exposure duration was too short with respect to the life span of dogs to justify conclusions with respect to the potential carcinogenicity of GNT in dogs.

CD rats (n=6/sex/group) were fed diets containing GTN at doses equivalent to 0, 0.9, 6, and 59 mg/kg bw/day. After 4 weeks of treatment, only significantly decreased food consumption and body weight gain were seen in the high-dose animals. There were no macroscopic and microscopic changes in any of the animals sacrificed at this time point (n=4/sex/group). Thereafter, the remaining animals were given GTN via the diet at doses equivalent to 3, 25, 230 mg/kg bw/day, for another 8 weeks. Apart from decreased feed consumption and

somewhat lower body weight gain found in the animals of the high-dose group, no treatment-related effects were seen in haematological and clinical chemical tests, and at macroscopic and microscopic examinations in any of the treated groups. Because no clear toxicity was observed in these experiments, an additional group of rats (n=3/sex) was fed GNT via the diet at ca. 1400 mg/kg bw/day, for 13 weeks. During the first 8 weeks, feed consumption was half that of controls and animals lost weight. They were less active and had a rough coat. Thereafter, consumption increased and animals were gaining weight slowly. Significant increases in erythrocyte and reticulocyte count, haematocrit, haemoglobin concentrations, and serum alkaline phosphatase, and a significant decrease in fasting blood glucose were found. There were no changes in MetHb levels. Upon macroscopic and microscopic examinations, increased absolute and relative liver, kidney, and brain (males only) weights, pigment deposits in liver and spleen, and moderate to severe testicular degeneration and/or atrophy with severe to complete aspermatogenesis were found (E1184, EPA87). Since dietary exposure to 6 mg/kg bw for 5 weeks followed by 25 mg/kg bw for another 8 weeks does not induce adverse effects, the committee derives a NOAEL for rats of 25 mg/kg bw from this study.

CD1 mice (n=16/sex/group) were fed initial doses equivalent to 0, 1.3, 11, and 100 mg/kg bw/day. After 3 weeks, when no adverse effects were seen in any of the mice, doses were increased to ca. 6.5, 59, and 580 mg/kg bw/day. Treatment caused a mild to moderate extramedullary haematopoiesis in the livers and/or spleen of all mice of the mid- and high-dose group, and of one male and one female animal of the low-dose group, while no such effects were seen in any of the control mice. In addition, there was an increase in relative and absolute spleen weights of the female mice of the mid- and high-dose group when compared to those of controls, but these changes did not reach statistical significance (E1184, EPA87). Based on the haematopoiesis seen at all dose levels, the committee concludes that no NOAEL can be derived from this study for mice and places the LOAEL at 6.5 mg/kg bw, the lowest dose tested.

When daily doses of 0, 2.5, 5, or 10 mg/kg bw were administered by intravenous infusion to rats (n=10/sex/group) for 14 days, no differences were seen in biochemical, haematological, and urinalysis parameters, in body weights, or in relative and absolute organ weights when compared with those of untreated or vehicle-treated control groups. At necropsy, there were no gross or microscopic, compound-related changes. Two animals of the high-dose group died during the first week but the cause of death could not be ascertained (And83).

In dogs (n=2/sex/group), given intravenously daily doses of 1 and 3 mg/kg bw for 14 days, no significant electrocardiographical, ophthalmic, clinical chemistry, body weight, organ weight, or histological changes were observed (And83).

Long-term toxicity and carcinogenicity

Rats (Sprague-Dawley; 50 males; 48 females) were given 0.03% GTN in the drinking water for 10 months followed by an exposure-free period of 8 months. Based on the daily consumption of the solution and animal body weights, Takayama calculated the actual intake of GTN to be 31 mg/kg bw/day. Controls (53 males, 48 females) received tap water ad libitum for 18 months. Treatment did not induce remarkable behavioural or physical abnormalities or effects on survival rates and body weights. Severe pneumonia with abscess was considered to be the cause of death of the animals that died during the study (viz., 38 males and 23 females). In these animals, no lesions were found in the visceral organs such as liver, kidney, and spleen. Macroscopic and microscopic examination of all animals, and haematological and clinical chemical examination of animals (n=5/sex) surviving up to 18 months, did not show differences between the treated and the control group. The treatment did not cause statistically significant increases in tumour incidences (Tak95).

In a 2-year study, CD rats (n=38/sex/group) were given GNT via the diet at doses equivalent to 0, 3.0, 32, 363 mg/kg bw/day for males and 4.0, 38, and 434 mg/kg bw/day for females. At regular times, clinical signs, behavioural changes, body weights, and feed intake were recorded and blood samples (n=4/sex/group) were collected for haematological and clinical chemical testing. An interim kill (n=8/sex/group) was performed after 12 months. All female and some male rats of the high-dose group lost weight in the first week due to decreased feed consumption. During the subsequent weeks, feed consumption increased but never reached control levels again. At termination, body weights were roughly 25-40% lower than those of controls. In the animals of the mid-dose group, there was some decrease in body weights, but feed consumption was obviously not affected. The high-dose rats had a tan, rough, and matted fur. Some of them occasionally showed a bluish skin, especially around the nose. Haematological or clinical chemical tests did not show changes in the animals of the mid- and low-dose groups. In the high-dose animals, MetHb (10-30% of total Hb), reticulocytosis, increased erythrocyte count, haematocrit, and haemoglobin concentration, but no Heinz bodies were found after 3 months. After 12 months, there was still a moderate MetHb but erythrocyte count was within normal limits.

After 24 months, MetHb had disappeared, but increased levels of serum transaminases (ALAT and ASAT) and of alkaline phosphatase were found in the male animals. Most of the untimely dying high-dose rats had MetHb and/or elevated serum enzyme levels. High-dose female rats were reported to have a significantly longer life span than control animals, which was attributed to decreased incidences of spontaneous pituitary chromophobe adenomas and mammary tumours. At the 12-month interim sacrifice, there was a dose-response relationship in the incidence and severity of pre-neoplastic hepatocellular alterations (areas and foci). Neoplastic nodules were seen in 3 high-dose males, 1 high-dose female, and 1 mid-dose male, while hepatocellular carcinoma was observed in 1 high-dose male. All but 2 rats of the high-dose group had cholangiofibrosis, proliferation of the bile ducts, and fibrous tissue. Enlarged livers were observed in the high-dose rats. Finally, excessive pigmentation was found in the spleen of most and in the renal epithelium of many of the high-dose animals. Similar, but further developed lesions were seen in the rats killed at study termination (24 months). In the high-dose group, absolute and relative liver weights were increased. The major lesion in this group of rats was cholangiofibrosis in 18/21 males and 24/25 females, while not found in any of the other groups. Furthermore, treatment induced an increased incidence of hepatic hyperplastic foci (males: low dose: 18/34, mid dose: 23/33, high dose: 17/29 vs. 6/32 in controls; females: 10/40, 24/36, 28/33 vs. 8/37, respectively), of hepatocellular carcinomas and/or neoplastic nodules (males: 0/28, 4/26, 15/21 vs. 1/24, respectively; females: 1/32, 3/28, 16/25 vs. 0/29, respectively), and of interstitial cell tumours of the testis (1/28, 3/26, 11/21 vs. 2/24, respectively). These testis tumours were thought to produce an incidence of atrophy and aspermatogenesis greater than normally seen in old rats. Finally, excessive splenic and renal epithelial pigmentation was found with a high incidence in the high-dose group. Statistical treatment of the data was not reported (E1184, EPA87).

In another study using F344/NCr rats, animals given a single oral dose (by gavage) of 1200 mg/kg bw at 6 weeks of age did not develop tumours. Partial hepatectomy performed at 9 weeks of age to induce rapid hepatic tissue proliferation did not affect these results. In rats given GTN via the diet at a dose equivalent to 500 mg/kg bw/day for up to 70 weeks (from 8 up to 78 weeks of age, final sacrifice at 84 weeks of age), hepatocellular adenomas and carcinomas were seen, beginning at weeks 52 and 78 of age, respectively. Preneoplastic lesions, viz. glutathione-S-transferase-P (GST-P) positive foci, mainly of the clear cell and mixed cell type, were seen in almost all animals at the first interim sacrifice at 14 weeks of age. Beginning at weeks 52 of age, focal eosinophilic

areas (atypical foci) composed of atypical hepatocytes that often extended into veins were observed. Eighteen tumours (8 carcinomas, 9 adenomas, 1 atypical focus) were selected for examination for mutations in coding regions of the *K-ras* and *p53* genes. No *p53* mutations were found while *K-ras* mutations were seen in 8 of the tumours (3 carcinomas, 5 adenomas). The mutations all found in codon 12 of exon 1 were first or second position GT transversions or second position GA transitions (Tam96).

From these oral rat studies, the committee concludes that GTN is carcinogenic to rats inducing increases in the incidences of hepatocellular tumours in male and female rats and of interstitial cell tumours of the testes in male rats at an average dose of 400 mg/kg bw/day. However, in view of the severe toxicity observed at this dose level, the committee is of the opinion that the findings concerning the tumour formation are of questionable relevance. No NOAEL could be established since exposure to an average dose of 3.5 mg/kg bw/day, the lowest dose tested, resulted in increased incidences of hepatic hyperplastic foci.

Mice (C57BL/6Jms; n=49-66 males and 45-50 females/group) were given 10, 40, and 330 mg/L of GTN via the drinking water, resulting in actual dose levels as calculated by Suzuki et al. of 1.5, 6.2, and 58.1 mg/kg bw/day, respectively. The animals of the high-dose group were treated for 12 months and observed for another 6 months; those of the 2 other dose groups were treated for 18 months. A control group consisting of 60 males and 63 females was included. Data on survival rates were not presented. Treated animals did not show abnormal behaviour. In the animals of the high-dose group, average body weights were lower than those of controls. Generally, treatment did not induce differences in the incidence of tumour-bearing animals, the incidence of microscopically defined tumours, the number of tumours per animal, and the pattern of tumours between the treated and control groups. Only in the high-dose females, there was an increase in the number of animals with macroscopically defined tumours (24/34, 70.6% vs. 22/56, 39.3% in controls), mainly caused by the presence of pituitary gland tumours in 5/34 (15%) animals. Upon microscopic evaluation, pituitary gland adenomas were diagnosed in 6/34 high-dose female, 3/39 mid-dose female, 1/40 low-dose female, and in 1/50 control female animals. Non-neoplastic lesions including inflammatory and degenerative changes did not differ between treated and control groups (Suz75).

In a 2-year study, CD1 mice (n=58/sex/group) were fed GTN via the diet at daily doses equivalent to 0, 11, 115, and 1022 mg/kg bw for males and 9.7, 96, and 1058 mg/kg bw for females. Physical and behavioural changes, body weights, and feed intake were recorded regularly. An interim kill

(n=8/sex/group) was performed after 12 months. In the high-dose group, feed intake was severely decreased during the first week, and the animals lost weight. Thereafter, feed consumption and weight gain returned to almost control levels, but terminal body weights were roughly 15-25% lower than those of controls. In this group, tan matted fur was observed. There were no significant differences as to survival rates between groups, although the high-dose group had slightly fewer survivors. Females lived longer than males. Examinations at the 12-month interim and 24-month terminal sacrifice showed similar effects, mainly limited to the high-dose group. They included a compensated anaemia, normal erythrocyte count, elevated reticulocyte count (in males only, not statistically significant), Heinz bodies, MetHb (in males only), and hepatic, splenic, and renal pigmentation. Pigmentation was found in some mid-dose animals as well. There were no indications of treatment-related increases in tumour incidences. Pituitary tumours as reported above (Suz75) were found, but in the low-dose group only (6 in total) (Ell84, EPA87).

From these mouse studies, the committee concludes that there is no consistent, convincing evidence of a carcinogenic potential in mice. Based on body weight changes and haemosiderosis, a NOAEL of 9.7 mg/kg bw/day while the next higher dose of 96.4 mg/kg bw/day is considered to be a LOAEL.

Mutagenicity and genotoxicity

- *In vitro* studies

In an unpublished study, a saturated aqueous solution of GTN did not induce reverse mutations in several strains of *S. typhimurium* (TA1535, TA1537, TA1538, TA98, and TA100), with and without S9 metabolic activation (Sim77). In another unpublished study, weakly positive results were found in 2 out of 5 *S. typhimurium* strains, viz., TA1535 and TA1537, at a concentration of 1000 µg/plate, in the presence or absence of a metabolic activation system (Ell78a). The weakly positive result in *S. typhimurium* strain TA1535 was confirmed in another report (Win91). In a follow-up study designed to reveal the mechanism of action, GTN was negative in strains TA1538, TA100, TA100NR, YG1026, TA1975, and TA102 when tested in the absence of a S9 mix at doses of 0.1 to 12.5 µmol/plate. In strain TA1535, at a dose of 5 µmol/plate GTN, an increased number of His⁺ revertants to a maximum of 4 times over background values was found. Higher levels were toxic. Addition of a hamster liver S9 mix reduced the toxicity at the higher doses and induced a maximum response of 5 times over background at 10 µmol/plate. Further experiments showed that virtually all of the GTN-induced mutants contained CT transitions in 1 of the first 2 bases of the

hisG46 (CCC) target codon for which intracellular nitric oxide was considered to be responsible (Mar93). GTN not cause an increase in mutation frequency in extracellular bacteriophage T4B of *E. coli* (mutation frequency: 0.05-0.07/1000 exposed bacteria vs. ca. 0.1/1000 untreated bacteria). The phage was exposed to a 0.084 M solution (Kon72). The compound was negative in *S. cerevisiae* D3 (Sim77).

GTN did not induce mutations in wild type Chinese hamster (CHO-K1) ovary cells when tested at concentrations of 50.0 and 144.8 µg/mL in the absence of a metabolic activation system (Lee76).

- *In vivo* studies

In a dominant lethal assay, no mutagenic effect or impaired male fertility was observed in male rats, fed at GTN doses of 3, 32, and 363 mg/kg bw/day for 13 weeks and subsequently mated to virgin females (Ell78b).

In an unpublished study, rats fed ca. 59 mg/kg bw/day for 5 weeks and ca. 230 mg/kg bw/day for an additional 8 weeks (cf. above short-term studies by Ellis et al., Ell84) did not show numerical or structural chromosomal aberrations in peripheral blood lymphocytes or kidney cultures (Lee76). In another unpublished study, rats fed with ca. 400 mg/kg bw/day for 24 months (see above long-term study by Ellis et al., Ell84) did not show statistically significant changes in the number of tetraploids, the frequency of chromatid breaks and gaps, or translocations in bone marrow cells or kidney cell cultures compared to untreated controls (Ell78b).

The committee concludes that the above data are inadequate for a proper evaluation of the mutagenicity/genotoxicity of GTN.

Reproduction toxicity

Data on reproduction toxicity of GTN were from unpublished studies discussed in EPA87 and from Japanese papers provided with English abstracts, tables, and figures (Oke81a-d, Sku85).

In a 3-generation study, parental F0 rats (n=10/sex/group) were fed GTN at doses equivalent to 0, 3-4, 32-38, and 363-434 mg/kg bw/day for 6 months prior to mating, during pregnancies, and through weaning of their F1b offspring (2nd litters). However, EPA noted that, according to a table, the age of the F0 generation at the first mating was 5 months. Thereafter, 10 to 12 pairs of the F1b generation were selected to produce an F2b generation and a similar number of F2b rats to produce an F3b generation. Exposure continued through weaning of

the F3b generation. Body weights of the parental (F0) animals of the high-dose group were significantly decreased at all matings. There were no specific effects on the fertility of the F0 animals. A severely impaired fertility was observed in the high-dose males of the F1 and F2a generation, which was attributed to severe aspermatogenesis accompanied by increased interstitial tissue and significantly smaller testicular size. This infertility attributed to high-dose males was confirmed by a third mating of high-dose F2a females with control males, which resulted in a pregnancy rate of 13/14. Implantation and implant viability indices were not affected. Reproduction toxicity parameters including litter size, live-born index, birth weight, viability and lactation indices, and weaning weight (but not sex ratio) were impaired in the high-dose F1a and, to some extent, F1b and F2a litters. These effects were attributed to the poor nutritional status of the high-dose female animals. However, the reproductive performance was not affected at a third mating of high-dose F0 females - with a body weight 76% of controls on Day 0 - with control males. The committee concludes that the NOAEL for parental and reproductive toxicity was 32-38 mg/kg bw/day (E1178b).

A teratogenicity study was included as well. In the high-dose group, only a single malformation, diaphragmatic hernia, was found at examination of the soft tissue of one-half of the fetuses (not significant). At examination of the skeleton in the other half, the only effect observed was a statistically significant increase in the incidence of absent and incomplete ossification of the hyoid bone. EPA noticed some inconsistencies in this teratology study hampering a proper evaluation. According to the study protocol, virgin females should be treated during the organogenesis period (days 6-15). Outlining the experimental methods, it was indicated that the F0 females of the reproduction study should be discarded following weaning of the 2nd litter. The body of the report, however, indicated that these females were mated for a third time and subsequently used for the teratogenicity study (EPA87).

Dermal application of a GTN-containing ointment to rats on gestational days 7 through 17 at doses of 1000, 2000, or 4000 mg/kg bw/day did not have effects on F0 Caesarean section examination parameters, fetal malformations or variations, and neonatal behaviour, viability, growth and reproductive capabilities (including F1 Caesarean section parameters, F2 fetal morphology) of the F1 generation (Sku85).

Intravenous injection of 0.5, 1, or 4 mg/kg bw/day into rabbits from gestational days 6 through 18 did not affect pregnancy outcome parameters or fetal morphology. Apart from transient convulsions in the animals of the high-dose groups, no signs of maternal toxicity were reported (Oke81a).

No effects on fertility, peri- and post-natal parameters were observed when doses of 0, 1, 10, or 20 mg/kg bw/day were injected intraperitoneally into male rats (SD-S1c) for 63 days prior to mating and female rats 14 days prior to mating and through up to gestational day 7. As to parental toxicity, body weight and food and water intake were not affected, but some occasional and transient convulsions or sedation were seen in the animals given 20 mg/kg bw (Oke81b). Similar treatment on gestational days 7 through 17 or from gestational day 7 to lactational day 21 did not have effects on pregnancy outcome parameters and fetal morphology or on post-natal development, growth, fertility, pregnancy outcome parameters, and fetal morphology of the F1 generation. In the high-dose F0 animals, there were occasional and transient convulsions or sedation (Oke81c, Oke81d).

Immunotoxicity

Beagle dogs given dietary doses of 0.01 to 5.0 mg/kg bw/day, for 13 weeks (cf. above studies of Ellis et al., Ell84), did not show significant changes in serum IgE concentrations, or sensitisation, or allergic reactions in dogs. Similarly, rats fed ca. 1400 mg/kg bw/day, for 13 weeks, did not show changed serum IgE concentrations in rats (EPA87).

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for GTN in the Netherlands is 0.5 mg/m³ (0.05 ppm), 8-hour TWA. A skin notation is added.

Existing occupational exposure limits for GTN in some European countries and in the USA are summarised in the annex.

8 Assessment of health hazard

Occupational exposure to GTN will take place by inhalation of the vapour and in particular by skin contact during manufacture and use of the compound. The committee did not find data on the toxicokinetics of GTN in humans or experimental species following exposure by inhalation.

Both human and experimental animal data showed that GTN can penetrate the skin. When GTN is used as a drug in clinical medicine, the systemic bioavailability is estimated to be 68 to 76% following transdermal application. After removing patches, GTN rapidly disappeared from the blood with half-lives varying from about 5 to 30 minutes. In rats, dermal absorption rates of 0.6-0.9

mg/cm²/hour were estimated. Following oral (clinical medicine) administration, the bioavailability in humans was estimated to be less than 1%. In several animal species, GTN was readily absorbed from the gastrointestinal tract, absorption being essentially complete 24 hours after an oral dose of 180-200 mg/kg bw. In rats, following an oral dose of 10 mg/kg bw, half of the dose was absorbed within 30 minutes. The metabolism of GTN occurs in the liver as well as in intestinal mucosa, kidneys, vascular endothelial and smooth muscular cells, and the skin. Via non-enzymatic redox reactions, in which glutathione is involved, GTN is denitrated and inorganic nitrite and nitrate, glycerol dinitrates (GDNs), glycerol mononitrates (GMNs), glycerol, and carbon dioxide are formed. In humans, following oral administration of GTN, relatively high plasma concentrations of both 1,2- and 1,3-GDN were found. Following dermal application, the plasma concentration of 1,2-GDN was 6 times higher than those of GTN or 1,3-GDN. In experimental animals given 1,3-[¹⁴C]-GTN, the urine was the major excretion route accounting for 40% (rats) to 72% (dogs, rabbits) of the administered dose. In rats, ca. 25% of the radiolabel was excreted in expired air. The committee did not find data on the metabolic fate or excretion pattern of GTN in humans.

In one, old report, skin irritation due to prolonged contact to GTN has been described. Several cases of allergic contact dermatitis from occupational handling and topical medical treatment have been reported.

The most outstanding effect of exposure to aliphatic nitrates including GTN and EGDN is vasodilation as indicated by the development of severe throbbing headache and decreased blood pressure, produced already at relatively low levels. In a Swedish study on gunpowder workers, air concentrations of 1.1 to 4.0 mg/m³ (mean: 2.4 mg/m³) were found to cause an increasing headache during the working day. In US pharmaceutical workers, complaints of irritation and headaches, associated with breathing zone air levels of 0.3-1.0 mg/m³, disappeared when measures reduced concentrations to below 0.1 mg/m³. Headache and, to a less extent, nausea were reported by human volunteers who received doses of 5 mg GTN following 24-hour application of dermal patches. Higher, not specified, levels may cause hypotension, depression, confusion, occasionally delirium, methaemoglobinaemia, and cyanosis. Characteristic is tolerance that develops after repeated exposure for 3 to 4 days, but disappears after a 2-day exposure-free period resulting in so-called 'nitrate withdrawal symptoms' or 'monday morning angina' or 'monday morning death'.

Based on investigations in occupationally exposed Swedish, Scottish, and US workers, the committee concludes that there are no indications for an increased risk of mortality from cardio-cerebrovascular diseases or malignancies due to

long-term occupational exposure to GTN. The observed effects in the Swedish study were most likely to be due to the predominant exposure to EGDN.

Unpublished data from experimental animal studies showed that GTN instilled or applied as a paste was not irritating to the eyes and very mildly irritating to the skin of rabbits and moderately sensitising to the skin of guinea pigs.

The committee did not find valid data on the effects of GTN in experimental animals following single or repeated inhalation exposure. From acute lethality data, the committee considers GTN to be harmful if swallowed (LD_{50} rat: ca. 850 mg/kg bw). From dermal studies, no conclusions can be drawn ($LD_{50} > 29$ and > 280 mg/kg bw in rats and rabbits, respectively). Intravenous injections appeared to be very toxic (LD_{50} rat: ca. 24 mg/kg bw) inducing death within 5 minutes. Methaemoglobinaemia was observed following a single subcutaneous injection of 120 mg/kg bw. A maximum level of 26% was reached about 8 hours after administration. Repeated administration of 100 and 200 mg/kg bw for 5 days also caused significant elevated methaemoglobin levels (up to 30-40% of total Hb) and accompanying cyanosis in dogs.

Short-term toxicity studies were conducted in dogs, rats, and mice. In dogs, the NOAEL was 25 mg/kg bw in a 12-month oral study. The only notable effect was methaemoglobinaemia. In rats, dietary exposure to 6 mg/kg bw for 5 weeks followed by 25 mg/kg bw for another 8 weeks did not induce adverse effects. In mice, no effects were seen in animals given doses of 1.3-100 mg/kg bw/day and higher for 3 weeks, but haematopoiesis in liver and/or spleen were induced at subsequent dosing with 6.5-580 mg/kg bw/day for 10 weeks. The LOAEL was 6.5 mg/kg bw/day.

Long-term oral exposure of mice fed doses up to 1058 mg/kg bw did not result in treatment-related increases in tumour incidences. A dose of 96 mg/kg caused hepatic, splenic, and renal pigmentation in some animals while no such effects were seen at 9.7 mg/kg bw. In male and female rats fed average daily doses of 400 mg/kg bw, increases in the incidences of hepatocellular neoplasms in male and female rats and of interstitial cell tumours of the testes in male rats were found, accompanied by severe toxicity such as bluish skin, methaemoglobinaemia, and, in the target organ, cholangiofibrosis, proliferation of the bile duct, and fibrous tissue. At the lowest dose tested, i.e., 3.5 mg/kg bw, an increased incidence of hepatic hyperplastic foci was observed. In view of this severe toxicity at the tumour-inducing dose in the target organ, the committee feels that the carcinogenicity is likely induced by cell damage and subsequent cell proliferation and not of relevance at low occupational exposures. This conclusion corroborates with the absence of a carcinogenic effect in mice. The

committee concludes that the data available on the potential mutagenicity/genotoxicity are inadequate for a proper evaluation because of lack of experimental details or adequate study design. Therefore, a genotoxic mechanism of the carcinogenic effects in rats cannot be excluded at present. However, GTN showed a weak mutagenic response in 2 out of 5 strains of *S. typhimurium* (TA 1535 and TA1537) tested only, with and without metabolic activation. The mutants found were similar to those induced by nitric oxide (NO). This is consistent with the mechanism of action of GTN *in vivo*, i.e., formation of NO in mammalian cells, resulting in induction of vascular smooth muscle dilation.

Apart from infertility observed in male rats at oral doses of ca. 400 mg/kg bw/day, no indications of reproduction toxicity effects were found.

From the data on Swedish gunpowder (Gje85) and US pharmaceutical workers (Han66), the committee considers 0.1 mg/m³ to be a NOAEL while complaints of irritation and headaches may occur at slightly higher levels of 0.3 mg/m³ and above. Because the groups studied and the margin between no-effect and effect levels were relatively small, the committee applies a factor of 2, which leads to a preferred value of 0.05 mg/m³. As with EGDN, these headaches may develop within a few minutes. Therefore, in order to prevent peak levels, 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 glycerol trinitrate of 0.05 mg/m³ (0.006 ppm), as 15-minute time-weighted average. In addition, the committee recommends addition of a skin notation, since absorption by skin may be of more importance than absorption via the lungs.

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Annex

Occupational exposure limits for glycerol trinitrate 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	0.5	8 h	administrative	S	SZW05
Germany - AGS	0.05	0.5	8 h		S, ^c	TRG04
- DFG MAK-Kommission	0.2	2.0	15 min			
	-	-	-		S, ^d	DFG05
	-	-	-			
Great-Britain - HSE	-	-				HSE03
Sweden	0.03	0.3	8 h		S	Swe00
	0.1	0.9	15 min			
Denmark	0.02	0.2	ceiling		S	Arb02
USA						
- ACGIH	0.05	-	8 h	TLV	S	ACG05
- OSHA	0.2	2	ceiling	PEL	S	ACG04
- NIOSH	-	0.1	15 min	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.

^d Classified in carcinogenicity category 3B, e.e., among substances for which *in vitro* or animal studies have yielded evidence of carcinogenic effects that is not sufficient for classification of the substances in one of the other categories. Further studies are required before a final decision can be made. A MAK or BAT value can be established provided no genotoxic effects have been detected.

