Ethylene glycol dinitrate / 2-nitrooxyethyl nitrate

MAK Value Documentation

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DOI: 10.1002/3527600418.mb62896e6318

Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated the maximum concentration at the workplace (MAK value) of ethylene glycol dinitrate [628-96-6] of 0.05 ml/m³, considering all toxicity endpoints. A detailed description of the underlying studies is given.

The critical effect in volunteers after a 25-minute exposure to 0.05 ml/m³ of a mixture of ethylene glycol dinitrate and nitroglycerin was vasodilation, as indicated by the development of headaches or decreases in blood pressure. The effects were very slight. In occupational situations it is very difficult to assess the levels of exposure to ethylene glycol dinitrate 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 ethylene glycol dinitrate vapours. In workers, headaches were reported at nitroglycerin concentrations of 0.03 to 0.11 ml/m³ with a NOAEC below 0.01 ml/m³ nitroglycerin. Based on this data, the MAK value for nitroglycerin was established at 0.01 ml/m³. Because of the same mode of action and the similar LOAEC of the two substances, the MAK value for ethylene glycol dinitrate has been lowered to 0.01 ml/m³. The MAK value also applies to the sum of the concentrations of the two substances in the air. As systemic effects are critical, the assignment to Peak Limitation Category I and the excursion factor of 1, due to the short half-life, are retained. Although there are no studies on developmental toxicity, ethylene glycol dinitrate is assigned to Pregnancy Risk Group C in analogy to nitroglycerin. No data are available for genotoxicity or carcinogenicity. Skin contact may contribute significantly to systemic toxicity and ethylene glycol dinitrate continues to be designated with an "H". Sensitization is not expected from the limited data.

Keywords

ethylene glycol dinitrate; dinitroglycol; glycol dinitrate; nitroglycol; 2-nitrooxyethyl nitrate; mechanism of action; toxicokinetics; metabolism; (sub)acute toxicity; (sub)chronic toxicity; irritation; allergenic effects; reproductive toxicity; carcinogenicity; peak limitation; prenatal toxicity; germ cell mutagenicity; absorption through the skin; sensitization; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

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Ethylene glycol dinitrate[1),2)]

[628-96-6]

Supplement 2017

MAK value (2016)	**0.01 ml/m³ (ppm) ≙ 0.063 mg/m³**
Peak limitation (2001)	**Category II, excursion factor 1**
Absorption through the skin (1980)	**H**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (2016)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value (1996)	**0.3 µg/l blood**
Synonyms	dinitroglycol glycol dinitrate nitroglycol
Chemical name	2-nitrooxyethyl nitrate
Structural formula	$O_2N–O–(CH_2)_2–O–NO_2$
Molecular formula	$C_2H_4N_2O_6$
Molar mass	152.06 g/mol
Melting point	–22.3 °C (ECHA 2016)
Boiling point at 1013 hPa	197.5 °C (ECHA 2016)
Vapour pressure at 25 °C	0.096 hPa (SRC 2016)
log K_{OW}[3)]	1.16 (ECHA 2016)
Solubility at 20 °C	6800 mg/l water (SRC 2016)
1 ml/m³ (ppm) ≙ 6.31 mg/m³	**1 mg/m³ ≙ 0.158 ml/m³ (ppm)**

1) MAK value applies for the sum of the concentrations of ethylene glycol dinitrate, nitroglycerin and propylene glycol dinitrate in the air.

2) The substance can occur simultaneously as vapour and aerosol.

3) octanol/water partition coefficient.

Ethylene glycol dinitrate is used commercially as an explosive in different formulations, generally as a mixture of nitroglycerin and ethylene glycol dinitrate (at least 50% of the latter).

Documentation for a MAK value was published in 1982 (documentation "Ethylenglykoldinitrat" 1982, available in German only) and documentation for a BAT value in 1996 (documentation "Ethylene glycol dinitrate" 1998). The MAK value for nitroglycerin (supplement "Glycerintrinitrat" 2011, available in German only) was lowered in 2011, which has made a re-evaluation of the MAK value for ethylene glycol dinitrate necessary.

1 Toxic Effects and Mode of Action

The primary acute effect of ethylene glycol dinitrate is a reduction in the muscle tone of the smooth muscles of arteries and arterioles, which causes vasodilation with a decrease in blood pressure and reduced venous reflux to the heart as well as tachycardia. Headaches and orthostatic hypotension are known to be the first symptoms of the acute effect. Although ethylene glycol dinitrate and nitroglycerin cause the same acute effects, ethylene glycol dinitrate appears to have more pronounced cumulative and long-term effects. The long-term effect is manifest as a compensatory reaction in the form of vasoconstriction, which very probably increases over the course of intoxication. It gradually leads to an increase in diastolic blood pressure without a corresponding increase in systolic blood pressure, and thus to a smaller amplitude of blood pressure (pulse pressure), increased pulse rate and at the same time less intense headaches and a lessening of the other symptoms of short-term exposure. The diastolic pressure increases to 90 mm Hg and above and remains high for some time even after the end of exposure. The pulse rate increases to 90 beats a minute and above, while the pulse pressure can simultaneously fall below 30 mm Hg. Other observed effects were bradycardia, impaired circulation in the form of a reduction of the blood flow to the heart (coronary ischemia) and the fingers (Raynaud's syndrome) without arteriosclerotic changes and without cerebrovascular diseases. The long-term effects of ethylene glycol dinitrate are often disguised by the acute symptoms that are present at the same time (a decrease in systolic and diastolic blood pressure). If exposure continues for a prolonged period of time, stronger acute "nitro effects" are necessary to compensate for the increase in diastolic pressure caused by the long-term effects of ethylene glycol dinitrate. After exposure is interrupted for several days (absence from work), the acute effects disappear and the long-term effects predominate (documentation "Ethylenglykoldinitrat" 1982, available in German only).

Slight decreases in blood pressure and headaches were observed in test persons at concentrations of 0.05 ml/m^3 and above.

There is only one case report on the effects of ethylene glycol dinitrate as a contact allergen; no animal studies are available.

Information is not available for the genotoxicity, reproductive toxicity and carcinogenicity of the substance.

2 Mechanism of Action

Vasodilatory effect

Headaches and a decrease in blood pressure are assumed to be the result of a vasodilatory effect caused by the release of nitrogen monoxide. The mechanism of action is similar to that of nitroglycerin.

The previously described metabolism of ethylene glycol dinitrate (Section 3.2) does not explain the formation of nitrogen monoxide, which plays a considerable role in physiological vascular regulation. The nitrogen monoxide released causes the concentration-dependent activation of the soluble guanylate cyclase of the cells of vascular smooth muscle. This promotes the formation of c-GMP, which causes vasodilation, in particular of the coronary vessels and the venous vascular system. As is the case with other organic nitrates, the release of nitrogen monoxide in vivo is conceivable via various metabolic pathways:

- enzymatic denitration by cytosolic glutathione *S*-transferase, whereby primarily inorganic nitrite is formed
- enzymatic reduction to thionitrite esters via a nitrosothiol intermediate, catalysed by NADPH-dependent microsomal monooxygenases
- reductive denitration via NADPH in the presence of cytochrome P450
- non-enzymatic transformation in the presence of cysteine

(see the BAT value documentation from 1996 (documentation "Ethylene glycol dinitrate" 1998)).

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

After exposure to ethylene glycol dinitrate concentrations of 133 to 428 mg/m^3, intubated tracheotomized rats absorbed 20% of the radioactively labelled substance by inhalation (documentation "Ethylenglykoldinitrat" 1982, available in German only).

Ethylene glycol dinitrate is absorbed by rats from blasting gelatine (93% ethylene glycol dinitrate) and from a mixture of explosives (22% ethylene glycol dinitrate) through the lateral abdominal skin at a rate of 10 and 6.5 mg/cm^2 and hour, respectively (Gross et al. 1960). About 100 mg of a simulated explosive, which contained an ethylene glycol dinitrate concentration of 22%, was applied occlusively for 7 hours to 1 cm^2 of skin on the forearms of 6 test persons; the amount absorbed was determined by measuring the remaining amount of ethylene glycol dinitrate. About 13% of the ethylene glycol dinitrate and thus 3 mg/cm^2 skin was absorbed during this time. The rate of absorption of ethylene glycol dinitrate through the skin of humans is thus about 0.4 mg per cm^2 and hour (Gross et al. 1960).

Comparing absorption through the skin and via the lungs led to the conclusion that contamination of the skin leads to greater exposure to the effects of ethylene glycol dinitrate in exposed persons than inhalation from the air (documentation "Ethylenglykoldinitrat" 1982, available in German only). The substance is not eliminated (unchanged) with the exhaled air. Both studies in vitro in erythrocytes and in

whole blood as well as studies in vivo established that the first step to ethylene glycol mononitrate takes place relatively rapidly (maximum concentration after 3 hours), while the second metabolic step, which yields ethylene glycol, proceeds much more slowly (4% within 4 hours). The intermediate inorganic nitrite is oxidized mainly to nitrate and eliminated as such unchanged in the urine. In rats, up to about 60% of the nitrate fraction of an ethylene glycol dinitrate dose (subcutaneous injection) was recovered as inorganic nitrate in the urine within 24 hours. Only a small percentage of ethylene glycol mononitrate is eliminated unchanged. About 1.5% of a subcutaneous dose was recovered as ethylene glycol mononitrate in the urine of rats. After subcutaneous administration to rats, ethylene glycol dinitrate could no longer be determined in the blood after only 8 hours; likewise, the three main degradation products were no longer detected after 12 hours. Inorganic nitrate, which is formed by both ethylene glycol dinitrate and ethylene glycol mononitrate, is completely eliminated with the urine within 24 hours (documentation "Ethylenglykoldinitrat" 1982, available in German only; BAT value documentation 1996 (documentation "Ethylene glycol dinitrate" 1998)).

In rabbits given subcutaneous injections of ethylene glycol dinitrate, the maximum concentration in the blood was reached after 1 to 2 hours; in the case of nitrate, the maximum concentration in the blood was reached after 4 to 5 hours (Hasegawa and Sato 1963).

The degradation process appears to be similarly rapid in humans. In 5 workers with ethylene glycol dinitrate concentrations of 0.01 to 0.07 ppm (0.01 to 0.07 μg/ml) in the blood and corresponding concentrations of 0.02 to 0.08 ppm (0.02 to 0.08 μg/ml) in the urine, no ethylene glycol dinitrate could be determined in either media 16 hours after the end of exposure. The biological half-life of ethylene glycol dinitrate in erythrocytes (in vitro 37 °C) was 0.4 to 1.3 hours in the blood samples of female exposed persons (> 2-year exposure period) and 0.4 to 1.4 hours in the blood samples of male exposed persons (> 2-year exposure period) (documentation "Ethylenglykoldinitrat" 1982, available in German only; BAT value documentation 1996 (documentation "Ethylene glycol dinitrate" 1998)).

3.2 Metabolism

During and after distribution, ethylene glycol dinitrate is metabolized rapidly, primarily in the liver, but also in other organs as well as in the erythrocytes. Ethylene glycol dinitrate is denitrated in two steps; reduced glutathione is very probably involved. Ethylene glycol mononitrate and nitrite are formed as intermediates. Ethylene glycol mononitrate is metabolized to form ethylene glycol via reductive hydrolysis. To a lesser extent, ethylene glycol mononitrate is also hydrolysed directly to ethylene glycol and nitrate is formed. Ethylene glycol is transformed mainly to glycolic acid and oxalate. In addition, glycolaldehyde, glyoxylic acid, glycine, glyoxal and carbon dioxide are formed. The degradation of ethylene glycol mononitrate in rat blood was markedly slower (4% within 4 hours) than that of ethylene glycol dinitrate. Glycolic acid can either be eliminated with the urine or broken down further to carbon dioxide. The metabolic pathway described above does not explain the formation of nitrogen monoxide, which is very important for physiological vascular regulation (BAT value documentation 1996 (documentation "Ethylene glycol dinitrate" 1998)).

4 Effects in Humans

Information is not available for the end points genotoxicity, reproductive toxicity and carcinogenicity.

Ethylene glycol dinitrate is used primarily in the form of a mixture with nitroglycerin or other nitrate esters in the explosives and gunpowder industry. The mixing ratios used until 1981 are discussed in detail in the 1982 documentation (documentation "Ethylenglykoldinitrat" 1982, available in German only). The mixtures most commonly used today contain at least 50% ethylene glycol dinitrate (ACGIH 2001). There are no documented cases of exposure to pure ethylene glycol dinitrate.

Mortality, alcohol intolerance, low blood pressure, bradycardia and headaches were reported after exposure to mixtures of ethylene glycol dinitrate and nitroglycerin at the workplace. The threshold for these effects has yet to be established conclusively. It is significantly lower than 0.08 ml ethylene glycol dinitrate/m^3. An early observation was that workers develop a tolerance to the pharmacological effects of nitrate esters after a certain period of exposure, which, however, is lost quickly, for example after absence from the workplace for 36 to 48 hours, and may then lead to a "withdrawal syndrome" that many authors have described in detail. The withdrawal symptoms are usually not accompanied by changes in routine laboratory values and the electrocardiographic findings of persons exposed to ethylene glycol dinitrate/nitroglycerin (documentation "Ethylenglykoldinitrat" 1982, available in German only).

4.1 Single exposures

There are no new data available.

4.2 Repeated exposure

There are no new studies available with repeated exposure to ethylene glycol dinitrate in humans. Workers in the explosives industry who handled mixtures of nitroglycerin and ethylene glycol dinitrate (mixing ratio: 2:8 or 1:9) developed headaches after being exposed to concentrations at the workplace in the range of 0.1 to 0.5 mg/m^3 (mean: 0.36 mg/m^3), which are the lowest concentrations determined to date (Trainor and Jones 1966). The concentrations given in air represent the total exposure to nitroglycerin and ethylene glycol dinitrate. However, as the vapour pressure of ethylene glycol dinitrate is higher than that of nitroglycerin, it is assumed that exposure was mainly to ethylene glycol dinitrate. In a letter to the editor of the journal, Hanlon and Fredrick (1966) provided further information to that published in the report of Trainor and Jones (1966); workers involved in the manufacture of nitroglycerin tablets developed headaches after exposure to 0.03 to 0.11 ml/m^3 (0.3 to 1.04 mg/m^3), but not after exposure to concentrations below 0.01 ml/m^3. They cited a comprehensive study carried out by the Detroit Bureau of Industrial Hygiene from 1961. However, the letter does not include any other details, for example as regards the number of workers questioned, the period of exposure or the type of questioning and when this was carried out.

A total of 7 test persons were exposed to 0.5 mg/m³ of a mixture of nitroglycerin and ethylene glycol dinitrate (0.4 to 0.67 mg/m³) in explosives magazines for 25 minutes. The concentrations given in air represent the total exposure to nitroglycerin and ethylene glycol dinitrate, expressed as nitroglycerin. The systolic or diastolic blood pressure or both were decreased in all test persons. Very slight to moderate headaches were reported by 3 test persons; 3 test persons described very slight to slight weariness. The symptoms were more marked after exposure to 0.7 mg/m³ (0.65 to 0.74 mg/m³). The data for the end point headache are difficult to quantify (Trainor and Jones 1966). The individual findings are listed in Table 1 below (documentation "Ethylenglykoldinitrat" 1982, available in German only).

The nitroglycerin concentration of 0.5 mg/m³ is equivalent to an ethylene glycol dinitrate concentration of 0.35 mg/m³ or 0.05 ml/m³ (the primary component of the mixture).

An attempt was made to verify the findings of Trainor and Jones (1966) in persons exposed at the workplace. Over a period of 3 months, 72 short-term analyses were carried out in the breathing zones of test persons occupationally exposed to ethylene glycol dinitrate. The concentrations of ethylene glycol dinitrate were in the range of 0.06 to 1.64 mg/m³ (0.009 to 0.26 ml/m³). Prior to the beginning of the analysis, 78% (n = 63) of the workers did not have headaches. A total of 35 of these workers were exposed to concentrations lower than 0.4 mg/m³ (0.063 ml/m³), 17 of them to concentrations in the range of 0.4 to 0.74 mg/m³ (0.063 to 0.12 ml/m³) and 11 to concentrations of 0.75 to 1.64 mg/m³ (0.12 to 0.26 ml/m³). One worker who was exposed to less than 0.4 mg/m³ developed a headache during the analysis, the other exposed persons did not develop headaches. The authors reported that, based on the results of Trainor and Jones (1966), 5 cases of headache would have been expected in the group of workers exposed to ethylene glycol dinitrate in the range of 0.4 and 0.74 mg/m³, but not one was recorded. The authors concluded from this that headaches do not develop in workers at the incidence calculated by Trainor and Jones (1966). The findings were published only in the form of an abstract (Lamm et al. 1993). Since no information was provided as to which day of the week the analyses took place, the absence of headaches in the exposed persons may have been caused by the tolerance that is known to develop over the course of the working week.

As regards the studies in occupationally exposed persons (see Table 1 of the 1996 BAT documentation (documentation "Ethylene glycol dinitrate" 1998), it should be kept in mind that dermal exposure very probably resulted in additional exposure, which makes it difficult to assign the effects to concentrations in the air.

Mortality data were recorded for 16 years in a cohort of 4061 male workers who were younger than 65 years and employed in an explosives factory on 1st January 1965. As only very few women were exposed, they were not included in the cohort. The population living in the direct vicinity of the explosives factory was used for the external control group. The workers were divided into exposure categories: blasting workers with low or high exposure to nitroglycerin and ethylene glycol dinitrate (mixing ratio: 4:1) and fuel workers with low or high exposure to nitroglycerin only. Persons not exposed were used for the internal control group. The workers were further divided into two groups according to their age on 1st January 1965; the first included workers from 15 to 49 years of age and the second workers from 50 to

Table 1 Symptoms after exposure to different ethylene glycol dinitrate/nitroglycerin concentrations in air (Trainor and Jones 1966)

Persons	EGDN/GTN conc.[1)] [mg/m³]	Exposure period [min]	Blood pressure before exposure [mm Hg]	Blood pressure after exposure [mm Hg]	Symptoms[2)]
1st	2.0	no data	105/70	90/60	headache after 2 minutes
2nd	2.0	no data	100/68	90/60	headache after 2 minutes
3rd	2.0	no data	120/80	120/90	no headache
4th	2.0	no data	150/90	120/70	headache after 3 minutes
5th	2.0	no data	130/55	120/75	headache after 1 minute
6th	2.0	no data	120/70	110/70	headache after 2 minutes
1st	0.7	25	105/72	80/60	headache
2nd	0.7	25	125/100	100/85	slight headache
3rd	0.7	25	120/90	120/90	slight headache
4th	0.7	25	130/90	120/90	dullness
5th	0.7	25	120/75	90/70	throbbing in head
6th	0.7	25	120/85	120/82	slight dullness
7th	0.7	25	120/75	105/75	headache
8th	0.7	25	125/90	100/80	dullness
9th	0.7	25	130/100	100/75	dullness
10th	0.7	25	115/85	95/65	dullness
1st	0.5	25	105/70	90/55	slight dullness
2nd	0.5	25	135/100	115/85	headache
3rd	0.5	25	125/90	120/90	slight dullness

Table 1 (continued)

Persons	EGDN/GTN conc.[1)] [mg/m³]	Exposure period [min]	Blood pressure before exposure [mm Hg]	Blood pressure after exposure [mm Hg]	Symptoms[2)]
4th	0.5	25	120/70	110/70	very slight dullness
5th	0.5	25	160/100	150/90	no headache
6th	0.5	25	130/80	105/80	transitory headache
7th	0.5	25	100/75	108/70	very slight headache

[1)] Air analyses were carried out in 6 magazines; the concentrations appeared to be dependent on the amount of explosives stored and the length of time the rooms were ventilated.
[2)] Headache is understood to be the typical throbbing "nitrate headache".

64 years of age. There was no information provided for the exposure period or level. The increase in mortality caused by acute myocardial infarction was statistically significant in blasting workers of the younger age group compared with the incidence in both the internal and external control groups; in the age group of 50 to 64 year olds, however, this was only the case when the low exposure group was compared with the internal control group, but not with the external control group. The incidence of death from ischaemic heart disease was not increased in the groups of fuel workers. Mortality caused by cerebrovascular diseases was twice as high in older fuel workers of the high exposure group than in the external control group; this was not the case in comparison with the internal control group (Craig et al. 1985).

Evaluation of the pharmacological data after the administration of nitroglycerin

Ethylene glycol dinitrate is not used as a medicine. The 2011 supplement (supplement "Glycerintrinitrat" 2011, available in German only) included studies of the therapeutic effect threshold of nitroglycerin after dermal, sublingual, intravenous and oral exposure that investigated and described effects in test persons. On the basis of this information, an attempt was made to determine the lowest concentration of nitroglycerin to cause effects after inhalation. Overall, the studies were not conclusive with regard to the nitroglycerin concentration in the blood at which effects are no longer detectable. Furthermore, in the case of long-term administration, the effect of habituation must be taken into account. As the pharmacokinetic and pharmacodynamic effects vary quite greatly from individual to individual, the data for a therapeutic effect threshold are not suitable for deriving a limit value.

4.3 Local effects on skin and mucous membranes

There are no data available for local effects.

4.4 Allergenic effects

Since the 1982 documentation (documentation "Ethylenglykoldinitrat" 1982, available in German only) was published, only one case of what is assumed to be an allergic reaction to ethylene glycol dinitrate caused by occupational exposure to an explosive has become available in the literature. Patch testing with 0.1% to 2% ethylene glycol dinitrate in water yielded 2+ reactions in 1 of 2 tested persons. A 0.01% formulation still yielded a 1+ reaction. The worker also produced a 2+ reaction to 0.02% to 2% nitroglycerin as well as to 0.1% to 2% dinitrotoluene. It is unclear whether the worker was also exposed to ethylene glycol dinitrate and dinitrotoluene. The test formulation did not produce a reaction in 20 control persons (Kanerva et al. 1991).

An article on the effects of ethylene glycol dinitrate (and nitroglycerin) absorbed by inhalation or percutaneously in workers of a plant that manufactured explosives (Einert et al. 1963) did not provide any information about irritation or the sensitizing effects of ethylene glycol dinitrate.

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

There are no data available for inhalation.

5.1.2 Oral administration

The oral LD_{50} was 540 mg/kg body weight for mice and 460 to 616 mg/kg body weight for rats (ECHA 2016).

5.1.3 Dermal application

In animal studies, absorption through the skin may easily lead to ethylene glycol dinitrate poisoning. Compared with nitroglycerin, ethylene glycol dinitrate is absorbed much more rapidly through the skin of test animals and quickly reaches fatal doses. In most cases, the animals die after only a few days. In cats, undiluted ethylene glycol dinitrate that was applied under an occlusive dressing (4×6 cm^2) to the shaved skin of the back caused severe methaemoglobinaemia after widely varying periods of exposure; only a few animals survived. One animal died after only 4 hours and 20 minutes, another did not die until 7 days after the 7-hour test had been concluded. The application of the occlusive dressing did not cause mortality in rabbits (documentation "Ethylenglykoldinitrat" 1982, available in German only).

5.1.4 Subcutaneous injection

The toxicity of ethylene glycol dinitrate is less pronounced in cats than in rabbits and is determined primarily through changes in the blood, such as the formation of Heinz bodies and methaemoglobin as well as haemolytic anaemia. The death of the animals was caused mainly by disturbances in respiratory function resulting from the formation of methaemoglobin and in some cases also by a decrease in blood pressure. The most marked symptoms of toxicity were weakness, dyspnoea, vomiting, salivation and discoloration caused by methaemoglobin, but no convulsions. Animals that died days or several weeks after being given moderate doses of 40 mg/kg body weight and above were found to have more or less severe fatty degeneration of the organs (liver, kidneys and heart), haemorrhages of internal organs (liver and spleen), marked pigment deposits (spleen, liver and kidneys), and in some cases also bone marrow hyperplasia or ulceration of the mucous membranes of the stomach. Changes in the electrocardiographic findings were recorded in the rabbit heart after subcutaneous injection; these could still be detected even when no traces of ethylene glycol dinitrate could be determined in the rabbit blood. The subcutaneous LD_{100} was 400 mg/kg body weight in rabbits and 100 mg/kg body weight in cats (documentation "Ethylenglykoldinitrat" 1982, available in German only).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

Exposure of cats by inhalation (8 hours/day; 5 days/week) to 2 to 26 ml/m^3 over a period of 97 to 1000 days caused fatty degeneration of the heart muscle, liver and kidneys, pigment deposits, haemosiderosis of the liver and spleen, and methaemoglobinemia and its secondary effects. At 2 ml/m^3, no adverse effects were observed. Similar studies with up to 3-month exposure to 47 to 79 ml/m^3 revealed Heinz bodies in the blood of mice, rats and guinea pigs as well as drowsiness, and in some cases convulsions. A NOAEC (no observed adverse effect concentration) was not determined (documentation "Ethylenglykoldinitrat" 1982, available in German only).

5.2.2 Oral administration

There are no data available for oral administration.

5.2.3 Dermal application

There are no data available for dermal application.

5.2.4 Subcutaneous injection

A total of 19 male Wistar rats were given subcutaneous injections of 0.5 ml of a 10% ethylene glycol dinitrate and olive oil solution once a day for 9 weeks. A control group was given only olive oil (14 days) and another control group (15 animals) was not treated. Body weight gains were very irregular during the 9 weeks and had reached 20 to 30 g at the end of exposure, which was below the control values of 40 to 50 g. The relative organ weights of the heart, lungs, liver, kidneys and spleen increased compared with those in the two control groups. An increase in the methaemoglobin concentration was not observed. The activity of aspartate aminotransferase and acetylcholinesterase was slightly increased compared with that in the control groups. The oxalate levels in the kidneys remained unchanged. Other parameters were not investigated, and a histopathological examination was not carried out (Furuno and Sugawara 1976).

5.3 Local effects on skin and mucous membranes

There are no data available for irritation of the skin and eyes caused by ethylene glycol dinitrate. Nitroglycerin caused mild irritation of the skin and did not induce irritation of the rabbit eye in the Draize test (documentation "Glycerintrinitrat" 2006, available in German only).

5.4 Allergenic effects

There are no data available for allergenic effects.

5.5 Reproductive and developmental toxicity

There are no data available for the developmental toxicity of ethylene glycol dinitrate.

The following developmental toxicity study was described in the 2011 supplement to nitroglycerin (supplement "Glycerintrinitrat" 2011, available in German only).

A prenatal developmental toxicity study was carried out following a 3-generation study, presumably using the animals that had already been mated during this study (older than 5 months; 230 to 300 g body weight). Groups of 9 to 19 pregnant animals were given feed containing 0%, 0.01%, 0.1% or 1% nitroglycerin from gestation day 6 to day 15 (nitroglycerin doses of about 0, 9, 86 or 792 mg/kg body weight and day; calculated from the total amount of feed consumed during gestation in the generation study; 22 to 23 gestation days; body weights of the rats 300 g at dietary concentrations of 0%, 0.01% and 0.1% and 230 g at 1%). The adjusted body weight gains were decreased and the absolute and relative liver weights increased in the dams of the high dose group. The incidences of delayed or absent ossification of the hyoid bone and of diaphragmatic hernia were increased in the foetuses of this dose group. A NOAEL (no observed adverse effect level) of 86 mg/kg body weight and day can therefore be derived for maternal toxicity and developmental toxicity (U.S. Army Medical Bioengineering Research and Command 1978).

5.6 Genotoxicity

There are no data available for genotoxicity.

5.7 Carcinogenicity

There are no data available for carcinogenicity.

6 Manifesto (MAK value/classification)

The most sensitive end point of exposure to ethylene glycol dinitrate in humans is its hypotensive effect and the development of headaches, which are probably associated with cerebral vasodilation.

MAK value. A slight decrease in blood pressure and headaches were observed in a study in test persons exposed for 25 minutes to combined nitroglycerin and ethylene glycol dinitrate concentrations of 0.05 ml/m^3; all but 1 test person described these effects as very slight to slight (Trainor and Jones 1966). However, it is likely that exposure was mainly to ethylene glycol dinitrate. Based on the only mild effects at 0.05 ml/m^3, it can be assumed that no effects will occur at the concentration of 0.01 ml/m^3. This is in agreement with the data of Hanlon and Fredrick (1966), who reported headaches in workers exposed only to nitroglycerin at concentrations in the range of 0.03 to 0.11 ml/m^3. These symptoms were no longer described at exposure levels below 0.01 ml/m^3.

Based on these findings in test persons and workers, a MAK value of 0.01 ml/m³ has been established for nitroglycerin. As ethylene glycol dinitrate has the same mechanism of action as nitroglycerin and both substances have very similar potencies, a MAK value of 0.01 ml/m³ has likewise been established for ethylene glycol dinitrate. As the MAK value is also based on effects observed at the workplace, the increased respiratory volume at the workplace has already been taken into account. A cumulative value of 0.01 ml/m³ applies in cases of simultaneous exposure to both substances. Both substances occur as vapour in this concentration range; therefore, the concentration is given in ml/m³. Both substances can be quantified separately in the air by HPLC analysis (Kettrup et al. 2003).

Peak limitation. Irritation of the skin and mucous membranes has not been described. The primary effects are the rapid onset of pharmacological effects known from nitrate esters that are induced by nitrogen monoxide, such as a decrease in blood pressure and the associated headaches (most sensitive parameter), a general feeling of being unwell and dullness. Ethylene glycol dinitrate is therefore classified in Peak Limitation Category II. The effect threshold after 25-minute exposure is below 0.08 ml/m³. Exposure to 0.05 ml/m³ is in a range at which measurable changes in blood pressure occur. A half-life in erythrocytes of 0.4 to 1.4 hours was determined in persons who had been exposed for longer than 2 years (Götell 1976; Sundell et al. 1975). An excursion factor of 1 has been established because the effect threshold is close to the MAK value, the effect occurs rapidly and the half-life is very short.

Prenatal toxicity. There are no data available for the developmental toxicity of ethylene glycol dinitrate. Adult humans react more sensitively than the rat to ethylene glycol dinitrate as regards the decrease in blood pressure and headaches. It is very likely that these effects are caused by the same mechanism as in the case of nitroglycerin. There are no additional systemic effects. The data for the developmental toxicity of nitroglycerin can therefore be used for the evaluation (see supplement "Glycerintrinitrat" 2011, available in German only).

In a prenatal developmental toxicity study in rats, delayed or absent ossification of the hyoid bone and diaphragmatic hernias were observed only at the highest maternally toxic dose of 792 mg/kg body weight and day. A NOAEL of 86 mg/kg body weight and day can be derived from this study for developmental toxicity and maternal toxicity. The following toxicokinetic data are taken into consideration for the extrapolation of the NOAEL for developmental toxicity to a concentration in the workplace air: the corresponding species-specific correction value between rat and human (1:4), the bioavailability of 1.6% (worst case for first-pass effect: 1.6% at 3.5 mg/kg body weight or 20% at 50 mg/kg body weight, determined after gavage doses; Fung et al. 1984), the body weight (70 kg) and the respiratory volume (10 m³) of the person, and the assumed 100% absorption by inhalation. The concentration calculated from this is 2.4 mg nitroglycerin/m³ (0.24 ml/m³), which is equivalent to a 24-fold difference to the MAK value of 0.01 ml/m³ for nitroglycerin. As 1 mol ethylene glycol dinitrate is equivalent to 1 mol nitroglycerin, the difference to the MAK value of 0.01 ml/m³ is also 24-fold for ethylene glycol dinitrate and thus sufficiently large. For this reason, both ethylene glycol dinitrate and nitroglycerin are classified in Pregnancy Risk Group C.

Carcinogenicity and germ cell mutagenicity. As no data are available for genotoxic and carcinogenic effects, the substance is not classified in one of the categories for germ cell mutagens or carcinogens.

Absorption through the skin. Based on a study in vivo (Section 3.1), dermal absorption of 800 mg has been estimated for humans after exposure to ethylene glycol dinitrate, assuming the exposure of 2000 cm^2 of skin for 1 hour. The systemically tolerable dose calculated from the MAK value at a respiratory volume of 10 m^3 is 0.6 mg. Absorption through the skin is therefore markedly higher than the systemically tolerable dose and the substance retains its "H" designation (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. There is only one case report of ethylene glycol dinitrate as a contact allergen. In the case of nitroglycerin, which structurally is closely related to ethylene glycol dinitrate, it is assumed that allergic reactions usually develop only after prolonged or regular occlusive application, which is not relevant for exposure conditions at the workplace. There are no animal studies available from which ethylene glycol dinitrate could be shown to cause contact allergy. Likewise, there are no data available for sensitizing effects on the respiratory tract. Ethylene glycol dinitrate is therefore not designated with "Sh" or "Sa" (for substances which cause sensitization of the skin or airways).

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completed February 24, 2016