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Propylene glycol dinitrate

MAK Value Documentation, supplement – Translation of the German version from 2018

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Keywords

propylene glycol dinitrate; hypotension; central nervous system; headache; visual evoked potentials; MAK value; maximum workplace concentration; peak limitation; developmental toxicity; skin absorption

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 propylene glycol dinitrate [6423-43-4], considering all toxicological end points. A detailed description of the underlying studies is given. The critical effect in volunteers after an 8-hour exposure to 0.1 ml/m^3 of propylene glycol dinitrate was vasodilation, as indicated by the development of headaches. The effects were very slight. After 4-hour exposure to 0.2 ml/m^3 most of the volunteers developed headaches and changes in visual evoked responses. At 0.03 ml/m^3 no effects were observed. In occupational situations it is difficult to assess the levels of exposure to propylene glycol dinitrate that induce symptoms and effects, because of both respiratory tract and skin absorption of vapours. The MAK value for propylene glycol dinitrate has been lowered to 0.01 ml/m^3 by analogy with nitroglycerin and ethylene glycol dinitrate because of the same mode of action and the similar NOAEC and LOAEC. The MAK value also applies to the sum of the concentrations of the three nitrate esters nitroglycerin, ethylene glycol dinitrate and propylene glycol dinitrate in the air. As systemic effects are critical, the assignment to Peak Limitation Category II and the excursion factor of 1, due to the short half-life, are retained. Although there are no studies on developmental toxicity, propylene glycol dinitrate is assigned to Pregnancy Risk Group C by analogy with nitroglycerin and ethylene glycol dinitrate. No data are available for genotoxicity or carcinogenicity. Skin contact may contribute significantly to systemic toxicity and propylene glycol dinitrate continues to be designated with an "H". Sensitization is not expected from the limited data.

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MAK value (2017)	**0.01 ml/m³ (ppm) ≙ 0.069 mg/m³**
Peak limitation (2002)	**Category II, excursion factor 1**
Absorption through the skin (1981)	**H**
Sensitization	–
Carcinogenicity	–
Prenatal toxicity (2017)	**Pregnancy Risk Group C**
Germ cell mutagenicity	–
BAT value	–
Synonyms	isopropylene nitrate methylnitroglycol 1,2-propanediol dinitrate propane-1,2-diyl dinitrate
CAS number	6423-43-4
Chemical name	1-nitrooxypropan-2-yl nitrate
Structural formula	
Molecular formula	$C_3H_6N_2O_6$
Molar mass	166.09 g/mol
Melting point	–7.7 °C (IFA 2017)
Boiling point at 1.3 hPa	92 °C (Forman 1988)
Density at 20 °C	1.4 g/cm³ (Forman 1988)
Vapour pressure at 25 °C	1.5 hPa (Fischer and Ballschmiter 1998), 0.5 hPa (NLM 2016)
log K_{OW}	1.83 (Fischer and Ballschmiter 1998)
Solubility in water	1.3 g/l (Forman 1988), 7.8 g/l (Fischer and Ballschmiter 1998)
1 ml/m³ (ppm) ≙ 6.892 mg/m³	**1 mg/m³ ≙ 0.145 ml/m³ (ppm)**

Note: MAK value for the sum of the concentrations of propylene glycol dinitrate, ethylene glycol dinitrate and nitroglycerin in the air. Propylene glycol dinitrate can occur simultaneously as vapour and aerosol.

Propylene glycol dinitrate is the main component of Otto fuel II (75% propylene glycol dinitrate, 20% di-*n*-butyl sebacate (sebacic acid dibutyl ester), 2% to 5% 2-nitrodiphenylamine), which is used in several modern types of torpedoes.

Documentation from 1981 (Henschler 1981, available in German only) and a supplement on peak limitation from 2002 are available (Greim 2002, available in German only). The MAK value of 0.05 ml/m³ was established in analogy to that for ethylene glycol dinitrate, which has a similar mode of action. As the MAK value for ethylene glycol dinitrate (Hartwig and MAK Commission 2018) was lowered in 2016, a re-evaluation of the MAK value for propylene glycol dinitrate became necessary.

1 Toxic Effects and Mode of Action

Propylene glycol-1,2-dinitrate causes reduced blood pressure, accompanied by "nitrate headache". In a study with subjects, headaches occurred at concentrations of 0.1 ml/m^3 and above. Elevated diastolic blood pressure values and smaller blood pressure amplitudes were also observed. In addition, dizziness and a disturbed sense of balance similar to the effects following alcohol consumption were found. Ethylene glycol nitrate produces similar effects in humans and animals. Eye irritation without conjunctivitis and visual disturbances were described after local exposure. In animal experiments, propylene glycol dinitrate, like ethylene glycol dinitrate, was found to be a potent methaemoglobin former. Data for the reproductive toxicity, genotoxicity, carcinogenicity and sensitizing effects of the substance are not available.

2 Mechanism of Action

Data for the mechanism of action of the substance are not available. Headaches and reduced blood pressure are probably due to vasodilation caused by released nitric oxide. The mechanism of action is similar to that of ethylene glycol dinitrate and nitroglycerin. Depending on the concentration, released nitric oxide activates the soluble guanylate cyclase in the cells of the smooth vascular muscles. This causes the increased formation of c-GMP, which triggers vasodilation, especially of the coronary vessels and the venous vascular system. The release of nitric oxide in vivo is conceivable via various metabolic pathways, as is the case with other organic nitrates (see Hartwig and MAK Commission 2018):

- enzymatic denitration by the cytosolic glutathione *S*-transferase, producing mainly inorganic nitrite
- 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 reaction in the presence of cysteine.

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

Two male rhesus monkeys were exposed 23 hours a day for 125 days to increasing propylene glycol dinitrate concentrations of 0.3 to 4.2 ml/m^3. Between days 91 and 111 of exposure, the propylene glycol dinitrate concentrations in blood were 35 µg/ml after exposure to 1.6 ml/m^3 and 170 µg/l after exposure to 4.2 ml/m^3 (Mattsson et al. 1981).

A comparative study of the elimination or degradation rate of propylene glycol dinitrate, ethylene glycol dinitrate and nitroglycerin in vivo (rabbits) and in vitro (blood, homogenized liver, reduced glutathione) demonstrated that propylene glycol dinitrate and ethylene glycol dinitrate have similar degradation and excretion patterns; unlike nitroglycerin, neither dinitrate reacts with glutathione in vitro (see Henschler 1981).

The application of a 10% solution of propylene glycol dinitrate in corn oil to 4 cm^2 of shaved skin on the flanks of rats at a dose level of 50 mg/kg body weight led to a decrease in blood pressure within 30 minutes. The extent of the decrease was the same as that produced by 5 mg/kg body weight administered subcutaneously, so that the authors concluded that 10% of the applied dose is absorbed dermally (Clark and Litchfield 1969). The body weights of the rats were between 200 and 250 g. Thus, about 10 mg per animal was applied. Taking an area of 4 cm^2 and 10% absorption as a basis, the flux is 0.5 mg/cm^2 and hour. Assuming the exposure of 2000 cm^2 of skin for 1 hour, this would correspond to an absorbed amount of 1000 mg.

Otto fuel II dissolved in corn oil was applied occlusively to 1 cm^2 of shaved skin on the backs of 4 F344 rats per group (propylene glycol dinitrate doses of 0, 5, 10, 20, 40, 80, 160, 300 or 450 mg/kg body weight). From the difference between the amount applied, the content of the exposed skin and the aluminium foil used as a cover, conclusions were drawn about the amount absorbed. The highest proportion of the applied dose (75%) was absorbed at the lowest dose of 5 mg/kg body weight; the proportion absorbed decreased in non-linear fashion with the increasing dose (10 mg: 60%; 20 mg: 63.3%; 40 mg: 48.9%; 80 mg: 32.5%; 160 mg: 19.4%; 300 mg: 15.9%; 450 mg: 20.2%) (Godin et al. 1993).

3.2 Metabolism

After subcutaneous injection of a propylene glycol dinitrate dose of 65 mg/kg body weight, the 24-hour urine of 6 rats contained mainly inorganic nitrate (55–57%), hardly any propylene glycol dinitrate < 0.01%) and inorganic nitrite (< 0.1%) and the 2 mononitrates propylene glycol 1-mononitrate and propylene glycol 2-mononitrate; propylene glycol 2-mononitrate was predominant (0.23–0.29%). Excretion was complete within 24 hours (Henschler 1981).

In vitro experiments with rat blood showed that propylene glycol dinitrate degrades rapidly, within 2 to 3 hours, almost exclusively in the erythrocytes. 50% of the dose is metabolized to propylene glycol 2-mononitrate and inorganic nitrate in the first hour and about 50% in the second hour. Smaller amounts of propylene glycol 1-mononitrate and inorganic nitrite are also formed. Propylene glycol 2-mononitrate is likewise found in vivo as the main metabolite in rats. The two mononitrates are not converted in vitro, but further degradation takes place in vivo, and only small amounts of the mononitrates are excreted. The degradation rate of propylene glycol dinitrate is slower in vitro (erythrocytes) than that of ethylene glycol dinitrate; also less inorganic nitrite is produced. According to other reports, however, there is no difference in the degradation rate of the two substances. It is generally agreed that the degradation mechanisms of propylene glycol nitrate and ethylene glycol dinitrate are qualitatively comparable and differ only in that one mononitrate can be formed during the degradation of ethylene glycol dinitrate, while two mononitrates can be formed in the case of propylene glycol dinitrate. In animal studies, the levels of propylene glycol dinitrate in the blood reached a maximum 20 to 30 minutes after subcutaneous injection. Nitrite reached the maximum level after 2 hours, nitrate after about 4 hours; both were no longer detectable after 12 hours. The curves of the propylene glycol 1-mononitrate and propylene glycol 2-mononitrate levels were similar; they culminated after about 2.5 hours and were detectable only in traces after 12 hours. The maximum levels in blood and the reduction in blood pressure correlated well (see Henschler 1981).

Groups of 3 to 4 male F344 rats were given intravenous injections of propylene glycol dinitrate at dose levels of 0.3, 3 and 30 mg/kg body weight. The concentrations of propylene glycol dinitrate and its metabolites were determined after 0.5, 1, 2, 5, 10 and 20 minutes after the injection. The maximum blood concentrations of propylene glycol dinitrate were 0.71 ± 0.057, 8.41 ± 2.0 and 64.84 ± 12.1 µg/ml, respectively. The half-lives were determined at 8.8 ± 1.5, 13.1 ± 1.3 and 17.4 ± 4.5 hours for each of the three doses. However, the illustrations in the publication show that the initial half-lives are in the minute range. The areas under the concentration–time curve were 4.69 ± 1.51, 55.65 ± 5.4 and 629.45 ± 70.35 µg/ml × hour, respectively. The maximum concentrations of propylene glycol 2-mononitrate and propylene glycol 1-mononitrate were reached 10 minutes after the injection. The blood concentrations of propylene glycol 1-mononitrate were 0.07 ± 0.02, 1.04 ± 0.051 and 9.65 ± 3.22 µg/ml and the AUC 2.34 ± 0.33, 44.59 ± 6.81 and 414.80 ± 15.86 µg/ml × hour, whereas the blood concentrations of propylene glycol 2-mononitrate were 1.21 ± 0.23, 8.14 ± 0.91 and 64.09 ± 21.90 µg/ml and the AUC 45.09 ± 6.99, 375.35 ± 77.33 and 2670.32 ± 1053.10 µg/ml × hour, respectively (Godin et al. 1995).

4 Effects in Humans

Only studies of acute and chronic toxicity are available. There is no information on other end points.

Symptoms following accidental exposure include headaches, nasal congestion, eye irritation, dizziness, vasomotor collapse and unconsciousness (Henschler 1981).

In a study with volunteers, 17 healthy men (non-smokers, 22 to 25 years), 2 research assistants (45 and 51 years) and 1 female member of the research group (24 years) took part. The volunteers were exposed once to propylene glycol dinitrate for 1 hour or for up to 8 hours to 0, 0.03, 0.1, 0.2, 0.35, 0.5 or 1.5 ml/m^3, or on up to 5 consecutive days to 0.2 to 0.3 ml/m^3 for 8 hours per day in ambient air. During the exposure, each subject had to fill in a questionnaire regarding subjective symptoms. Blood parameters, blood pressure, heart rate, VER (visual evoked response = visual evoked potentials, VEP) and lung function parameters were determined and cognitive coordination tests were performed. VEP are very sensitive parameters, but not very specific for neurotoxic effects. The blood pressure, heart rate and cardiac rhythm were not affected. No signs of pulmonary dysfunction were observed. After exposure to 0.1 ml/m^3, 2 participants complained of headaches after 4 and 8 hours respectively. The majority, 11 of 12 subjects exposed for 8 hours to a propylene glycol dinitrate concentration of 0.2 ml/m^3, reported headaches after 4 hours at the latest, and changes in the VEP were observed. At concentrations of 0.3 ml/m^3 and above, headaches set in more rapidly and intensified, changes in the VEP increased and one subject experienced slight eye irritation after 5 minutes, which was reversible 5 minutes after the end of exposure. After exposure to a propylene glycol dinitrate concentration of 0.5 ml/m^3, the results of the balancing test (heel-to-toe test) and a modified coordination test (Rhomberg's test) were significantly altered in 2 subjects after 6.25 hours and in 3 subjects after 8 hours, respectively. In the group exposed to the highest concentration, 2 subjects developed eye irritation without conjunctivitis or excessive lacrimation after 1 hour and 6 subjects after 3.2 hours. The eye irritation persisted throughout the experiment and ceased 5 to 8 minutes after the end of exposure. In addition, at the concentration of 1.5 ml/m^3 the "nitrate headache" increased in all test persons to such an extent that the test had to be terminated after 3 hours. In 4 subjects, the performance in Flanagan's coordination test was reduced. Repeated exposure to 0.2 ml/m^3 led to tolerance, also known from other nitrate esters. The headaches did not recur, but there was a progressive increase in changes in the VEP. Sensitive persons may therefore experience headaches at concentrations as low as 0.1 ml/m^3. The concentrations in the blood were below the detection limit of 5 µg/l. In the exhaled air, concentrations of 20 to 35 µl/m^3 were determined 1 hour after the exposure to 1.5 ml/m^3. Increased nitrate levels in the blood or increasing methaemoglobin formation were not observed. The odour threshold for propylene glycol dinitrate is about 0.2 ml/m^3 (Henschler 1981; Stewart et al. 1974). From this study, a NOAEC (no observed adverse effect concentration) of 0.03 ml/m^3 can be derived.

In a torpedo production facility, 87 workers were exposed to propylene glycol dinitrate concentrations of up to 0.22 ml/m^3 for an average of 47.4 months (1 to 132 months); 88% of the values determined were equal to or below 0.1 ml/m^3 and 50% equal to or below 0.05 ml/m^3. Twenty-eight of the workers were exposed for 60 months or more (average 91.8 months) and 58 workers for less than 5 years. As controls, 21 persons without exposure, matched for age, sex and ethnicity were used. The employees were asked about the occurrence and frequency of subjective symptoms such as headaches, dizziness and nausea. The following parameters were used to examine the oculomotor system: visual acuity, visual field, pupillary reaction, nystagmus, and extraocular muscle movement. Furthermore, tests for ataxia were performed. The workers drank on average twice as much alcohol (191 ml) per week as the control persons (94 ml). A subgroup of 28 workers who were exposed to propylene glycol dinitrate for 60 months and longer, were, on average, 10 years older than the controls. Of the workers, 65% complained of frequent or occasional headaches, 31% of nasal congestion, 26% of eye irritation, 13% of nausea, 10% of tachycardia, 6% of dyspnoea, 4% of thoracic pain and 1% of balance disorders. No significant changes were observed in workers exposed to propylene glycol dinitrate for 5 years or less, or in workers exposed to propylene glycol dinitrate for more than 5 years, with respect to the parameters studied (oculomotor parameters and ataxia). The saccade maximum velocity correlated with the duration of exposure, even after adjustment for age and alcohol consumption. The saccade delay time correlated significantly with the age of the exposed workers, but not in the control group (Horvath et al. 1981).

In another study of employees (1352 persons) from the same production facility, the incidences of heart attack, angina pectoris and cardiac arrhythmia were investigated. Employees not exposed to propylene glycol dinitrate and fire safety technicians served as two control groups. Risk factors such as smoking or obesity were considered. The risk of myocardial infarction (4 cases), angina pectoris (2 cases) and cardiac arrhythmia (one case) was 2 to 3 times as high among those exposed (Forman et al. 1987). Since the number of cases was very small and the concentrations they were exposed to (see above) were not given, this study cannot be used to evaluate the cardiac effects of propylene glycol dinitrate.

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

More recent studies are available for short-term inhalation, dermal, intravenous and subcutaneous exposure, which are described below.

5.1.1 Inhalation

Two male rhesus monkeys were exposed to propylene glycol dinitrate concentrations of 2, 3, 7, 10, 20 or 33 ml/m^3 for 2 or 4 hours once a week per concentration. As an electrophysiological end point, VEP were investigated; these were significantly affected at all times and concentrations (Mattsson et al. 1981). The results found with the two rhesus monkeys during acute exposure confirm in principle the findings in humans in the study by Stewart et al. (1974) and should be considered as adverse. However, they are relativized by other psychological events that may lead to or counteract similar effects on this electrophysiological end point. Nevertheless, due to the experimental variation, the observed effect on the VEP is clearly attributable to propylene glycol dinitrate. In the long-term experiment (see Section 5.2) VEP were not investigated, so that no statement can be made regarding adaptation effects.

5.1.2 Oral administration

There are no new data available.

5.1.3 Dermal application

Otto fuel II dissolved in corn oil (propylene glycol dinitrate doses of 0, 5, 10, 20, 40, 80, 160, 300 or 450 mg/kg body weight) was applied occlusively to the shaved skin of the backs of 4 F344 rats per group. The abdominal vessels were not dilated and no changes in blood pressure were observed during narcosis (using a mixture of ketamine and xylazine), which lasted for 30 to 45 minutes (Godin et al. 1993).

5.1.4 Intravenous and subcutaneous injection

Groups of 3 to 4 male F344 rats were given intravenous injections of propylene glycol dinitrate at dose levels of 0, 0.1, 0.3, 1, 3 or 30 mg/kg body weight. Blood pressure and brain perfusion were determined 0.5, 1, 2, 5, 10 and 20 minutes after the injection. The maximum fall in blood pressure occurred during the first minute and was most pronounced after the injection of 0.3 to 30 mg/kg body weight. Cerebral blood flow reached its maximum in all animals after only 2 minutes (Godin et al. 1995).

Groups of 3 F344 rats received subcutaneous injections of Otto fuel II dissolved in corn oil (propylene glycol dinitrate doses of 0, 5, 10, 20, 40, 80, 160, 300 or 450 mg/kg body weight). Heart rate and blood pressure were determined during the narcosis period of 30 to 45 minutes and every 5 minutes after the exposure. The maximum fall in blood pressure occurred after 15 to 30 minutes in the dose range of 5 to 20 mg/kg. In the highest dose group, the results varied so much that no statement was possible. At dose levels of 160 mg/kg body weight and above, dilation of the abdominal vessels and cyanosis occurred (Godin et al. 1993).

5.2 Subacute, subchronic and chronic toxicity

Long-term inhalation experiments have been carried out with rats, guinea pigs, squirrel monkeys and beagle dogs. All animal species were found to have elevated methaemoglobin levels; the differences between the species were marked. The pathological findings were mainly haemosiderin deposits in the liver and, depending on the concentration, also in the kidneys as a consequence of the increasing erythrocyte breakdown (see Henschler 1981). More recent studies are presented below.

Two male rhesus monkeys were exposed 23 hours per day for 125 days to increasing propylene glycol dinitrate concentrations of 0.3 to 4.2 ml/m^3. Two animals served as controls. No behavioural changes (avoidance performance test = shock avoidance) or changes in food consumption, and no signs of toxicity or histopathological changes were observed up to the highest concentration tested (Mattsson et al. 1981). These behavioural tests are very insensitive. Severe effects must be induced in the CNS to counteract the motivation for shock avoidance. Data for VEP, as determined after short-term exposure, were not collected.

Groups of 10 to 15 male and female F344 rats and C57/BL6 mice were exposed by inhalation to 1.43 mg/m^3 and 241 mg/m^3 for 6 hours daily, on 5 days per week, for 1 year. A group of 3 male and 3 female beagle dogs were likewise exposed to 1.43 mg/m^3 for an additional 60 days. The vapour concentrations were generated from Otto fuel II, which consisted of 75% propylene glycol dinitrate, 2% 2-nitrodiphenylamine and 23% di-*n*-butyl sebacate. In the **dogs**, the haemoglobin and haematocrit values decreased significantly after 2 to 4 weeks, but did not change further until the end of the 1-year exposure period. Within the subsequent 60-day exposure period, the values increased slightly. All other haematological and chemical parameters were unchanged. A slight, but statistically significant increase in methaemoglobin and reduced relative liver weights were observed. Microscopic examinations of all organs and the bone marrow did not yield any unusual findings. No substance-related effects were observed in the **mice**. After a 1-year recovery period, splenic lymphoid hyperplasia occurred significantly more frequently in the male mice of the high concentration group. A statistically significant increase in the incidence of atrophy and focal hyperplasia of the adrenal cortex was observed in the male mice of the low concentration group, but not of the high concentration group. It is therefore unlikely that this was a substance-related effect. The body weights were reduced in the male and female **rats** of both concentration groups. There was no consistent concentration-dependent or time-dependent decrease in the erythrocyte count, haemoglobin content and haematocrit value. As in the dogs, a slight but statistically significant increase in methaemoglobin and reduced relative liver weights were found. In the female animals, significantly reduced absolute spleen weights were observed in the 241 mg/m^3 group. In both concentration groups, mild hyaline degeneration of the nasal epithelium and an increased incidence of very slight inflammatory changes in the lungs occurred. In the female animals of the high concentration group, a statistically significant greater number of animals developed osteosclerosis and haemosiderosis after a 1-year recovery period. A slight increase in endometrial polyps was observed (US Air Force Aerospace Medical Research Laboratory 1985). As the exposure was not carried out with pure propylene glycol dinitrate, but with Otto fuel II, this study can provide only an indication of the effects of propylene glycol dinitrate.

Since the various animal species react much less sensitively to nitrate esters than humans, the animal studies are only of minor importance.

5.3 Local effects on skin and mucous membranes

There is no information available.

5.4 Allergenic effects

There is no information available.

5.5 Reproductive and developmental toxicity

There are no data available for the reproductive toxicity of propylene glycol dinitrate.

The following developmental toxicity study is reported in the 2011 supplement to the structurally related nitroglycerin (Hartwig 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 days 6 to 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; 300 g body weight of the rats 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 (US Army Medical Bioengineering Research and Command 1978).

5.6 Genotoxicity

Data for the administration of propylene glycol dinitrate alone are not available. Information on the genotoxicity of Otto fuel II is given in summary. Salmonella mutagenicity tests with and without the addition of metabolic activation, a $TK^{+/-}$ mutation test (positive results only at cytotoxic concentrations) and an SCE test with L5178Y mouse lymphoma cells yielded negative results. Likewise, the results of cytogenetic studies in mouse bone marrow and a dominant lethal assay were negative (Forman 1988). Since data for propylene glycol dinitrate alone are not available and the results for Otto fuel II can provide only an indication of the effects of propylene glycol dinitrate, the genotoxic potential of the substance cannot be assessed conclusively.

5.7 Carcinogenicity

There is no information available.

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. Healthy male subjects occasionally experienced headaches after exposure to a propylene glycol dinitrate concentration of 0.1 ml/m^3. The majority of the subjects developed headaches at the latest after 4 hours following exposure to a propylene glycol dinitrate concentration of 0.2 ml/m^3, and changes in VEPs were found. Both effects increased with increasing concentration. At 0.03 ml/m^3, no headaches occurred. According to the available data, propylene glycol dinitrate does not differ qualitatively or quantitatively from ethylene glycol dinitrate and nitroglycerin in its effect characteristics. By analogy, the MAK value of 0.01 ml/m^3 for ethylene glycol dinitrate and nitroglycerin has therefore been adopted as the MAK value for propylene glycol dinitrate. Since the MAK value for nitroglycerin is based also on experience at the workplace, the increased respiratory volume at the workplace has therefore already been taken into account. For simultaneous exposure to propylene glycol dinitrate, ethylene glycol dinitrate and nitroglycerin, a cumulative value of 0.01 ml/m^3 applies.

Peak limitation. Since the threshold for the systemic effect is presumably close to the MAK value, and as the effect occurs rapidly and the initial half-life is short (in the range of minutes), propylene glycol dinitrate has been assigned to Peak Limitation Category II with an excursion factor of 1 in analogy to the classification for ethylene glycol dinitrate.

Prenatal toxicity. There are no developmental toxicity data available for propylene glycol dinitrate. In the case of propylene glycol dinitrate, humans are more sensitive than rats with regard to reduced blood pressure and headaches. These effects are probably mediated by the same mechanism as in the case of nitroglycerin and ethylene glycol dinitrate. No other systemic effects occur. Therefore, the developmental toxicity data for nitroglycerin can be used for the evaluation (see Hartwig 2011).

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 tested, 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 for the rat (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 m^3) of the person, and the assumed 100% absorption by inhalation. The concentration calculated from this is 2.4 mg nitroglycerin/m^3 (0.24 ml/m^3), which is equivalent to a 24-fold difference to the MAK value of 0.01 ml/m^3 for nitroglycerin. As 1 mol ethylene glycol dinitrate is equivalent to 1 mol nitroglycerin, the difference to the MAK value of 0.01 ml/m^3 is also 24-fold for propylene glycol dinitrate and thus sufficiently large. For this reason, propylene glycol dinitrate, like nitroglycerin, has been classified in Pregnancy Risk Group C.

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

Absorption through the skin. The substance is already designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts). From an in vivo study with rats (Section 3.1), an absorbed amount of 1000 mg after exposure to a 10% solution under standard conditions (2000 cm^2 skin, exposure for 1 hour) can be estimated. This amount is much higher than the amount of 0.69 mg absorbed after exposure at the level of the MAK value at a respiratory volume of 10 m^3 and the assumed 100% absorption by inhalation. The fact that the substance is readily absorbed through the skin was confirmed in another study in rats (Godin et al. 1993). Designation with an "H" has therefore been retained.

Sensitization. There are no animal experiments from which a skin sensitizing effect of propylene glycol dinitrate could be derived. There are also no data for sensitizing effects on the airways. Propylene glycol dinitrate has therefore not been designated with "Sh" or "Sa" (for substances which cause sensitization of the skin or of the airways).

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (www.dfg.de/mak/conflicts_interest) ensure that the content and conclusions of the publication are strictly science-based.

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