The MAK Collection for Occupational Health and Safety

Nitroglycerin

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

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Keywords: nitroglycerin; glycerol trinitrate; MAK value; maximum workplace concentration; developmental toxicity; respiratory volume; skin absorption

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The commission established rules and measures to avoid conflicts of interest.

Nitroglycerin / 1,3-dinitrooxypropan-2-yl nitrate

MAK Value Documentation

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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 work place (MAK value) and the Pregnancy Risk Group of nitroglycerin [55-63-0].

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. 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. As the MAK value is derived from experiences in workers, the increased respiratory volume at the work place is considered.

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.

In rats, the NOAEL for developmental toxicity after oral application is 86 mg/kg body weight and day. After toxicokinetic scaling this dose corresponds to a concentration of 16 ml/m³ at the work place. The difference of this concentration to the MAK value is sufficient, therefore, nitroglycerin remains assigned to Pregnancy Risk Group C.

Skin contact may contribute significantly to systemic toxicity and nitroglycerin continues to be designated with an "H". Sensitization is not expected from the limited data.

Keywords

nitroglycerin; 1,3-dinitrooxypropan-2-yl nitrate; reproductive toxicity; prenatal toxicity; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

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1984

Nitroglycerin[1),2)]

[55-63-0]

Supplement 2018

MAK value (2010)	**0.01 ml/m³ (ppm) ≙ 0.094 mg/m³**
Peak limitation (2010)	**Category II, excursion factor 1**
Absorption through the skin (1978)	**H**
Sensitization	**–**
Carcinogenicity (2005)	**Category 3B**
Prenatal toxicity (2010)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value	**–**
Vapour pressure at 25 °C	0.0024 hPa (ECHA 2016)
log K_{OW}[3)] at 21°C	1.62 (documentation "Glycerintrinitrat" 2006, available in German only)
1 ml/m³ (ppm) ≙ 9.423 mg/m³	**1 mg/m³ ≙ 0.106 ml/m³ (ppm)**

Documentation for nitroglycerin was published in 2006 (documentation "Glycerintrinitrat" 2006, available in German only), followed by a supplement in 2011 (supplement "Glycerintrinitrat" 2011, available in German only).

In 2016, the Commission began using a revised approach for assessing substances with a MAK value based on systemic effects and derived from inhalation studies in animals or studies with volunteers at rest; this new approach takes into account that the respiratory volume at the workplace is higher than under experimental conditions. However, this does not apply to gases or vapour with a blood:air partition coefficient < 5 (see the List of MAK and BAT Values, Sections I b and I c). The blood:air partition coefficient of 41 400 that was calculated according to the formu-

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.

la of Buist et al. (2012) is significantly higher than 5. This supplement evaluates whether the MAK value and the pregnancy risk group of nitroglycerin need to be re-assessed as a result of the higher respiratory volume at the workplace.

Reproductive and Developmental Toxicity

The following developmental toxicity study was already included in the 2011 supplement (supplement "Glycerintrinitrat" 2011, available in German only). However, the dosage per body weight has been recalculated according to EFSA (2012) from the feed data, taking into consideration the body weight and food consumption during gestation.

Following a 3-generation study, a study of the toxic effects on prenatal development was carried out, presumably using the animals that had already been mated during the 3-generation 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. The body weight doses were recalculated based on the nitroglycerin concentrations in the feed and were about 0, 9, 86 or 792 mg/kg body weight and day (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 (US Army Medical Bioengineering Research and Command 1978).

Manifesto (MAK value/classification)

The most sensitive end point of exposure to nitroglycerin is the development of headaches, which are probably associated with cerebral vasodilation.

MAK value. In a number of studies that investigated the effects of exposure to mixtures of nitroglycerin and ethylene glycol dinitrate or to nitroglycerin alone, test persons reported headaches at concentrations in the range of 0.01 to 0.05 ml/m^3 and changes to the pulse rate were observed. As dermal absorption cannot be ruled out, the body burden of nitroglycerin is probably significantly higher than if exposure were by inhalation only. A slight decrease in blood pressure and headaches were observed in a study in test persons exposed for 25 minutes to 0.05 ml/m^3; all but 1 person described these effects as very slight to slight (Trainor and Jones 1966). In view of 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 Frederick (1966), who reported headaches in workers exposed 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. A MAK value of 0.01 ml/m^3 has therefore been established. However, it is important that contact with the skin

is ruled out. As the MAK value is based also 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 nitroglycerin, ethylene glycol dinitrate and propylene glycol dinitrate. Ethylene glycol dinitrate and nitroglycerin 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 (Breuer and Heinrich 2003). No method of analysis has been described yet for propylene glycol dinitrate.

Prenatal toxicity. In a study of the toxic effects on prenatal development 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. 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 this NOAEL to a concentration in the air: the corresponding species-specific correction value for the rat of 1:4, oral absorption of 100%, the body weight of 70 kg, the respiratory volume of 10 m³ and 100% absorption by inhalation in the human. The nitroglycerin concentration calculated from this is 150.5 mg/m³ (16 ml/m³). As the margin between this value and the MAK value of 0.01 ml/m³ is sufficiently large, nitroglycerin is classified in Pregnancy Risk Group C.

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