The MAK Collection for Occupational Health and Safety

Glycerin

MAK Value Documentation, addendum – Translation of the German version from 2016

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Glycerin / Propane-1,2,3-triol

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) of glycerol [56-81-5], considering the endpoints irritation of the respiratory tract and developmental toxicity.

Since 2014, the Commission uses an empirical approach to set MAK values for substances with critical effects on the upper respiratory tract or the eyes. However, examination of the study results showed that this approach does not apply for glycerol, because glycerol is not an eye irritant and the minimal to slight metaplasia of the squamous epithelium of the larynx seen in rats at 662 mg/m^3 with glycerol aerosol is not interpreted as adverse. The response does not increase with the exposure duration. Therefore, the MAK value is raised to 200 mg glycerol/m^3 for the inhalable fraction.

Peak Limitation Category I for local effects with an excursion factor of 2 is retained, as the effect is hardly concentration-dependent, a sensory irritation is not known, and glycerol is, if at all, only slightly irritating to the eye.

After scaling the oral NOAELs for developmental toxicity of 1310, 1280 and 1180 mg/kg body weight and day for rats, mice, and rabbits, respectively, to a concentration at the work place (2293, 1280, and 3442 mg/m^3), the differences to the MAK value are considered so large, that there is no reason to fear damage to the embryo or foetus when the MAK value is observed. The classification in Pregnancy Risk Group C is therefore retained.

Keywords

glycerin; glycerol; 1,2,3-trihydroxypropane; 1,2,3-propanetriol; (sub)acute toxicity; (sub)chronic toxicity; irritation; reproductive toxicity; peak limitation; prenatal toxicity; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

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Glycerin

[56-81-5]

Supplement 2016

MAK value (2015)	**200 mg/m³ I (inhalable fraction)**
Peak limitation (2006)	**Category I, excursion factor 2**
Absorption through the skin	**–**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (2006)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value	**–**

Since 2014, the Commission has been using a procedure based on physiological and empirical aspects to extrapolate animal data for local irritants to humans (Brüning et al. 2014; see Section I of the List of MAK and BAT Values). This procedure has been used to review the MAK value on the basis of the criteria for sensory irritants.

The re-examination has shown that the procedure of Brüning et al. (2014) cannot be used for glycerin, however, as the substance did not cause any specific local irritation in the inhalation study, but induced minimal to slight squamous metaplasia in the larynx (epiglottis) of rats, which, at this level of severity, is not regarded as adverse (Kaufmann et al. 2009). The squamous metaplasia is most likely a non-specific effect of the aerosol.

Documentation is available for glycerin from 2007 (documentation "Glycerin" 2007, in German only). Since then, no new studies of the effects of glycerin after inhalation have been published, apart from a re-assessment of the squamous metaplasia in the larynx by Kaufmann et al. (2009).

Subacute, subchronic and chronic toxicity

Inhalation

Compared with the OECD Test Guidelines 412 and 413, the two studies with rats (Renne et al.1992) described below have methodological shortcomings, as only a reduced number of haematological and clinico-chemical examinations were car-

ried out and not all of the organs named in the guidelines were microscopically examined. The following parameters were investigated: blood cell count, serum urea, creatinine, glucose, protein, albumin, albumin/globulin ratio, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, γ-glutamyl transferase, cholesterol, triglycerides, phospholipids; the histopathological examination included the respiratory tract and accompanying lymph nodes, the liver, kidneys, heart and organs with gross pathological findings. Organ weights were determined for the lungs, liver, kidneys, brain and heart. Groups of 10 female and 10 male Sprague Dawley rats were exposed nose only to glycerin aerosol concentrations of 0, 1000, 1930 or 3910 mg/m^3 for 6 hours a day, on 5 days a week, for 14 days. The MMAD (mass median aerodynamic diameter) was less than 1.5 µm. The body weight gains of all exposed animals were reduced, but not in a concentration-dependent manner. In all exposed female animals, the glucose level was significantly reduced in a manner inversely proportional to the glycerin concentration. No other systemic effects were found. Histopathological examination revealed minimal to slight squamous metaplasia of the epiglottis of the treated animals: 1/10, 13/18, 16/19 and 13/14 at 0, 1000, 1930 and 3910 mg/m^3, respectively (see Table 1; Renne et al. 1992).

As the severity of the squamous metaplasia observed was minimal to slight, the effect is not regarded as adverse (Kaufmann et al. 2009).

The no observed adverse effect concentration (NOAEC) in rats for local and systemic effects after 2-week exposure is 3910 mg/m^3.

Groups of 15 Sprague Dawley rats were exposed nose only to glycerin aerosol concentrations of 0, 33, 165 or 662 mg/m^3 for 6 hours a day, on 5 days a week, for 13 weeks. The MMAD was less than 2 µm. In the male animals the plasma triglyceride concentration was increased by 34% (significant), 22% (significant) and by 18% (not significant) at 33, 165 and 662 mg/m^3, respectively. As the effect was not dose-dependent, occurred only in the male animals and no corresponding systemic, gross pathological or microscopic effects were found, the authors regarded it as biologically not relevant. In the animals of the high concentration group, the incidence of minimal to slight squamous metaplasia in the epiglottis of the larynx was significantly increased: 2/25, 1/19, 4/20 and 11/21 ($p < 0.05$) at 0, 33, 165 and 662 mg/m^3 (see Table 2). Ultrastructural investigation of the Clara cells of 6 animals in the high dose group did not yield any evidence of proliferation of the smooth endoplasmic reticulum. No clinical symptoms were found (Renne et al. 1992).

The minimal to slight squamous metaplasia observed is not regarded as adverse (Kaufmann et al. 2009).

The NOAEC in rats for local and systemic effects after 13-week exposure is 662 mg/m^3.

No increase in the incidence and severity of the effects was found between the 2-week exposure (1000 mg/m^3, 13 of 18 animals affected (72%)) and the 13-week exposure (662 mg/m^3, 11 of 21 animals affected (52%)) (see bold print in Table 1 and Table 2). Even after longer periods of exposure, no squamous cell metaplasia of greater severity than minimal to slight (not adverse) is therefore to be expected.

Table 1 Incidence and severity of the effects in the larynx of rats after 2-week exposure to aerosolized glycerin (Renne et al. 1992)

	Concentration (mg/m³)			
	0	**1000**	1930	3910
Epiglottis				
number of investigated animals	10	**18**	19	14
Squamous metaplasia				
minimal	1	**10**	13	7
slight	0	**3**	3	6
total	1	**13**	16	13

Table 2 Incidence and severity of the effects in the larynx of rats after 13-week exposure to aerosolized glycerin (Renne et al. 1992)

	Concentration (mg/m³)			
	0	33	165	**662**
Epiglottis				
number of investigated animals	25	19	20	**21**
Squamous metaplasia				
minimal	2	1	4	**10**
slight	0	0	_	**1**
total	2	1	4	**11**

Local effects on skin and mucous membranes

Eyes

A study carried out according to OECD Test Guideline 405 reported slight to moderate eye irritation after one hour in all treated rabbits. The irritation had decreased after 24 hours and was reversible after 72 hours. In another study, the application of 0.1 ml glycerin did not cause irritation in 6 rabbits. The irritation index was 0 to 2 of a maximum 110. Slight irritation was found one hour after the application of 0.1 ml glycerin into the conjunctival sac of one eye of 4 rabbits. This was reversible after 24 hours (documentation "Glycerin" 2007, available in German only).

Glycerin is therefore regarded as not irritating or, at most, only very slightly irritating to the eye.

Developmental toxicity

In a study, similar to OECD Test Guideline 414, of the toxic effects on prenatal development in Wistar rats, CD-1 mice and Dutch Belted rabbits, groups of 25 to 29 female rats and mice were given gavage doses of glycerin from days 6 to 15 of gestation. The rats received 0, 13.1, 60.8, 282 or 1310 mg/kg body weight and day and the mice 0, 12.8, 59.6, 275 or 1280 mg/kg body weight and day. Groups of 15 to 20 female rabbits were given glycerin doses of 0, 11.8, 54.8, 254.5 or 1180 mg/kg body weight and day from gestation days 6 to 18. The animals given aspirin as positive controls demonstrated the sensitivity of the test system. Up to the highest glycerin doses tested of 1310, 1280 and 1180 mg/kg body weight and day, no embryotoxic, foetotoxic or teratogenic effects were found in rats, mice and rabbits (FDA 1974).

Manifesto (MAK value/classification)

The local effects in the larynx are the critical effects after inhalation exposure in rats.

MAK value. There are no studies in humans available from which a MAK value can be derived. At most, glycerin has a weak irritating effect in the eyes. In high concentrations, glycerin is slightly irritating as a result of its hygroscopic properties (Renne et al. 1992). After repeated inhalation of a glycerin aerosol for 13 weeks, no clinical irritation was observed in rats, but at 662 mg/m^3 and above, a slight, but statistically significant increase in squamous metaplasia of the epiglottis was found. Between 2 and 13 weeks of exposure this did not increase in incidence or severity. It may therefore be assumed that this would also not increase in severity after longer exposure periods. This assumption is supported by the flat concentration–response relationship for this effect which was found in the 28-day inhalation study with di-*n*-butylphthalate (documentation "Di-n-butylphthalate" 2013) and in inhalation studies with butynediol (documentation"2-Butin-1.4-diol" 2012, available in German only). In the latter, the level of severity of between 1 and 2 for the squamous type metaplasia in the larynx likewise did not increase with the exposure period. Minimal to slight squamous metaplasia, such as occurred also in the inhalation studies with glycerin, is not regarded as adverse (Kaufmann et al. 2009). No systemic effects occurred after the 13-week inhalation of concentrations up to 662 mg/m^3. The NOAEC was therefore 662 mg/m^3. In humans, at about 1500 mg/kg body weight and day, an increase in plasma triglycerides was reported, and in earlier oral animal studies, a no observed adverse effect level (NOAEL) of more than 1000 mg/kg body weight is given (see documentation "Glycerin" 2007, available in German only). Based on the NOAEC of 662 mg/m^3 from the 13-week study, the MAK value, which is taken to be half this value, has been established at 200 mg glycerin/m^3 in line with the "preferred value approach". It must, however, be borne in mind that, at such high aerosol concentrations, annoyance and the formation of mists at the workplace could occur. For this reason, exposure should be minimized for reasons of workplace hygiene and maintaining safety at work, so that exposure levels should be below the MAK value of 200 mg glycerin/m^3.

Peak limitation. As a result of the local effects on the larynx, the substance is classified in Peak Limitation Category I. As the increase in effect size with increasing concentrations is slight, sensory irritation is not known, and the irritation to the eyes caused by glycerin is, at most, slight, the excursion factor of 2 has been retained for the substance at the now higher MAK value.

Prenatal toxicity. There are no new studies available for the developmental toxicity of glycerin. In a study with rats, mice and rabbits of the toxic effects on prenatal development, no embryotoxic, foetotoxic or teratogenic effects were found at 1310, 1280 and 1180 mg/kg body weight and day, the highest dose tested for each species, respectively (see also documentation "Glycerin" 2007, available in German only).

The NOAELs for developmental toxicity are therefore 1310, 1280 and 1180 mg/kg body weight and day for rats, mice and rabbits, respectively. The following toxicokinetic data are taken into consideration for the extrapolation of these NOAELs for rats, mice and rabbits after oral administration to concentrations in the workplace air: the species-specific correction values (1:4, 1:7 and 1:2.4), the assumed oral absorption (100%), the body weight (70 kg) and respiratory volume (10 m^3) of the person, and the assumed 100% absorption by inhalation. The concentrations calculated from this are 2293, 1280 and 3442 mg/m^3, respectively, which are higher than the MAK value of 200 mg/m^3 by factors of 11, 6 and 17, and, in the case of the mouse, would therefore not actually be sufficient for the substance to be classified in Pregnancy Risk Group C. However, all the doses are above the limit dose given in the OECD Test Guideline, and no effects occurred up to the highest dose tested in each case. As the true NOAEL for the mouse is probably higher, and the difference of 11 and 17 times between the calculated concentration for the NOAELs for developmental toxicity and the MAK value of 200 mg/m^3 is sufficiently large in the case of rats and rabbits, glycerin remains in Pregnancy Risk Group C.

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