The MAK Collection for Occupational Health and Safety

Dipropylene glycol

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

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Keywords: dipropylene glycol; liver; inflammation; olfactory epithelium; MAK value; peak limitation; developmental toxicity; irritation; skin absorption; substance in the work area

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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) for dipropylene glycol has been set at 100 mg/m^3 for the inhalable fraction, considering the endpoints respiratory tract irritation and systemic toxicity as well as absorption through the skin. A 2-year drinking water study with rats shows a NOAEL for focal inflammation of the liver in males of 115 mg/kg body weight and day and a NOAEL for olfactory epithelium degeneration in males and females of 470 and 530 mg/kg body weight and day, respectively. This raises the question, whether the olfactory epithelium could also be a local target tissue after inhalation. Inhalation studies with dipropylene glycol are not available. The substance shows very slight irritation of skin and eyes, if any. Thus, there are no indications of a potential local irritative effect to the upper airways. Therefore, the MAK value of 100 mg/m^3 derived from systemic effects is validated. As systemic effects are critical, the assignment to Peak Limitation Category II and the excursion factor of 2 are retained. A recent in-vitro study with human skin shows that skin contact does not contribute significantly to systemic toxicity and the former designation with an "H" notation is withdrawn.

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Keywords

dipropylene glycol; toxicokinetics; metabolism; (sub)acute toxicity; (sub)chronic toxicity; irritation; peak limitation; prenatal toxicity; absorption through the skin; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

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Dipropylene glycol[1)]

[25265-71-8]

Supplement 2016

MAK value (2011)	**100 mg/m³ I (inhalable fraction)**
Peak limitation (2006)	**Category II, excursion factor 2**
Absorption through the skin	**–**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (2006)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value	**–**
log K_{OW}[2)]	–1.486 (calculated); –0.69 (calculated) (OECD 2001)
Solubility	1 000 000 mg/l water (SRC 2014)
pKa value	no data

In 2014, the Commission started using a physiologically and empirically-based method for deriving MAK values for substances that have an effect on the upper respiratory tract and eyes; it also describes criteria for classification as a sensory irritant (Brüning et al. 2014). The critical effect of dipropylene glycol, focal inflammation in the liver of male rats, is systemic (documentation "Dipropylenglykol" 2007, available in German only). The MAK value has been reviewed because the substance also induced degeneration of the nasal epithelium when given with the drinking water for 90 days and 2 years.

Documentation for dipropylene glycol was published in 2007 (documentation "Dipropylenglykol" 2007, available in German only), followed by a supplement in 2012 (supplement "Dipropylenglykol" 2012, available in German only).

A review by Fowles et al. (2013) was published after the supplement. A study of dermal absorption in dermatomed human skin (CEFIC 2007) is also new and has

1) The substance can occur simultaneously as a vapour and aerosol.

2) Octanol/water partition coefficient.

made a re-evaluation of absorption through the skin necessary. Some data described in this supplement were taken from ECHA's registration dossiers that are publicly available on the Internet (ECHA 2014 a).

The technical product with CAS number 25265-71-8 is a mixture of the isomers 2-hydroxypropyl-2′-hydroxyisopropylether, 2,2′-dihydroxydiisopropylether and 2,2′-dihydroxydipropylether. This mixture was used in the studies.

Toxicokinetics and Metabolism

Absorption, distribution and elimination

A dermal absorption study according to OECD Test Guideline 428 investigated undiluted dipropylene glycol (purity: 99.9%) in dermatomed human skin. The 7 samples originated from 4 donors, and the mean thickness of the skin was 389 ± 54 µm. The nominal dose was 1200 µl/cm^2 at a volume of 768 µl (OECD Test Guideline 428 recommends the application of liquid amounts of up to 10 µl/cm^2). After application, the skin was occluded on the side facing the donor chamber. Serial samples of the receptor fluid were taken during the first 8 hours after application and then every hour up to 24 hours after application. The occlusive conditions did not impair the integrity of the human skin. After 24 hours, only a very small amount of dipropylene glycol penetrated into the receptor fluid through the skin (912.6 ± 219.0 µg/cm^2; 0.075%). Dipropylene glycol was detected in the receptor fluid within 1 hour on average; the steady state penetration rate was 39.3 ± 10.7 µg/cm^2 and hour. A permeability coefficient of $3.85 \times 10^{-5} \pm 1.05 \times 10^{-5}$ cm and hour was calculated from this steady state flux, the dipropylene glycol concentration of the solution and the density of 1.02 g/cm^3 (CEFIC 2007). Taking into account the penetration rate of 39.3 ± 10.7 µg/cm^2 and hour determined experimentally in the steady state, the exposure of both hands and forearms (area: 2000 cm^2) to undiluted dipropylene glycol for 1 hour would lead as a result of dermal absorption to a systemically available dose of 79 mg.

Effects in Humans

A cumulative 14-day skin irritation test was carried out with dipropylene glycol in 26 male and female test persons aged between 18 and 70 years, who described themselves as having "sensitive skin". About 0.2 ml undiluted test substance (purity: fragrance grade; no other details) or a 50% solution of the test substance in water was applied occlusively to the upper part of the back of the test persons. The test material was applied from Monday to Friday, and test patches that were applied on Friday were not removed before Monday, until the skin had been in continuous contact with the substance for 14 days. Positive controls were not included in the study. One test person discontinued treatment before the end of the study (no other details). During the first 4 days of exposure, undiluted dipropylene glycol caused mild erythema (weak, but clearly pink discoloration) in one test person. Further exposure did not induce symptoms of irritation in this test person. Signs of skin irritation were not observed in any other test person at any time (ECHA 2014 a).

Animal Experiments and in vitro Studies

Subacute, subchronic and chronic toxicity

In 2012, the MAK value was lowered to 100 mg/m³ I (inhalable fraction) after the species-specific toxicokinetic method developed in 2010 was applied (supplement "Dipropylenglykol" 2012, available in German only). The MAK value was derived from systemic effects that were observed in the 2-year drinking water studies in rats and mice (NTP 2004); they are described again below.

Groups of 50 male and 50 female F344/N rats were given dipropylene glycol concentrations of 0, 2500, 10 000 or 40 000 mg/l drinking water (0, 115, 470 and 3040 mg/kg body weight for males or 140, 530 and 2330 mg/kg body weight for females) for 2 years. In male rats, the NOAEL (no observed adverse effect level) for focal inflammation in the liver and nephropathy was 115 mg/kg body weight and day and the LOAEL (lowest observed adverse effect level) was 470 mg/kg body weight and day. In the females, effects on the kidneys were not observed up to the high dose. Bile duct hyperplasia occurred in the females at the high dose of 2330 mg/kg body weight. Effects on the nose in the form of degeneration of the olfactory epithelium were found only at the high dose of 3040 mg/kg body weight and day in the males and of 2330 mg/kg body weight and day in the females. Atrophy and thrombosis were additionally observed in this tissue in male rats (see Table 1). The NOAEL for effects on the olfactory epithelium was thus 470 mg/kg body weight and day for the males and 530 mg/kg body weight and day for the females. In the 90-day study carried out as a range-finding study for the long-term study with drinking water, degeneration in the olfactory epithelium was found at the high dose of 12 800 mg/kg body weight and day in the males and 8950 mg/kg body weight and day in the females. The histological changes in the nose that were observed in the 2-year study at the same dose level were not found after 90 days (see Table 1). The study did not investigate the mechanism for the formation of lesions in the olfactory epithelium. The authors suggested that the lesions in the nose might be related to the metabolism of dipropylene glycol in the olfactory epithelium of rats. The olfactory epithelium of rats has a well-developed enzyme system that includes CYP450 enzymes (NTP 2004). However, studies of the metabolism of dipropylene glycol are not available.

Groups of 50 male and 50 female B6C3F1 mice were given dipropylene glycol concentrations of 0, 10 000, 20 000 or 40 000 mg/l drinking water (0, 735, 1220 and 2390 mg/kg body weight for males or 0, 575, 1040 and 1950 mg/kg body weight for females) for 2 years. In mice, the NOAEL for reduced body weights was 1220 mg/kg body weight and day for the males or 1040 mg/kg body weight and day for the females and the LOAEL was 2390 mg/kg body weight and day for the males or 1950 mg/kg body weight and day for the females. In the males, drinking water consumption was reduced at the high dose. No other treatment-related effects were observed in mice (NTP 2004).

Table 1 Histological findings in the nose of rats in drinking water studies with dipropylene glycol (NTP 2004)

F344/N rats, 90 days							
mg/l drinking water		0	5000	10 000	20 000	40 000	80 000
mg/kg body weight and day	♂	0	425	890	1840	3890	12 800
	♀	0	460	920	1690	3340	8950
olfactory epithelium, focal degeneration (average severity)	♂	0/10	0/0	0/0	0/0	0/10	10/10** (3.1)
	♀	0/10	0/0	0/0	0/0	0/10	10/10** (3.1)

significantly different from the control group; ** $p \leq 0.01$ (poly-3 test);
severity of histological changes: 1 = minimal, 2 = mild, 3 = moderate, 4 = severe

F344/N rats, 2 years					
mg/l drinking water		0	2500	10 000	40 000
mg/kg body weight and day	♂	0	115	470	3040
	♀	0	140	530	2330
olfactory epithelium, degeneration (average severity)	♂	0/46	0/50	0/50	7/49** (2.4)
	♀	0/48	0/48	0/46	9/49** (2.4)
olfactory epithelium, atrophy (average severity)	♂	4/46 (1.3)	3/50 (1.3)	3/50 (1.0)	34/49** (1.0)
	♀	0/48	0/48	0/46	0/49
thrombosis (average severity)	♂	2/46 (3.0)	5/50 (2.4)	4/50 (2.0)	9/49** (2.9)
	♀	0/48	0/48	0/46	0/49

significantly different from the control group; ** $p \leq 0.01$ (poly-3 test);
severity of histological changes: 1 = minimal, 2 = mild, 3 = moderate, 4 = severe

Local effects on skin and mucous membranes

Dipropylene glycol causes slight to very slight irritation of the skin and eyes of rabbits (documentation "Dipropylenglykol" 2007, available in German only).

Skin

An amount of 0.5 ml undiluted dipropylene glycol (purity: 100%) was applied occlusively for 4 hours to the shaved dorsal skin of 3 male and 3 female New Zealand White rabbits according to EPA Test Guideline OPP 81-5. After removal of the test patch and cleansing of the application site, the reactions were scored after 30 to 60 minutes and after 4, 24, 48 and 72 hours. Mean irritation scores of 0 were obtained for erythema and oedema according to the method of Draize (maximum values of 4 in each case). The very mild erythema observed in 1 animal after 45 minutes was no longer observed after 24 hours (ECHA 2014 a).

Eyes

An amount of 0.1 ml undiluted dipropylene glycol (purity: 100%) was instilled into the conjunctival sac of 3 male and 3 female New Zealand White rabbits according to EPA Test Guideline OPP 81-4. The untreated eye served as the control. The test substance was not washed out following instillation into the eyes unless debris or discharge interfered with the examination. The state of the eyes was evaluated after 1 hour and after 24, 48 and 72 hours according to the method of Draize. The mean irritation scores recorded after 24, 48 and 72 hours were 0 for the cornea, iris, conjunctivae and chemosis (maximum irritation values of 4 for the cornea, 4 for chemosis, 2 for the iris and 3 for the conjunctivae). One hour after application, redness of the conjunctivae (grade 1) was observed in all treated eyes, and chemosis (grade 1) was detected in the eyes of 2 rabbits. These changes had subsided after 24 hours. There were no effects on the cornea at any time (ECHA 2014 a).

Conclusions

In rabbits, dipropylene glycol causes only slight irritation of the skin and eyes, if at all.

Manifesto (MAK value/classification)

Focal inflammation in the liver of male rats is the critical effect of dipropylene glycol.

MAK value.
Dipropylene glycol causes only slight irritation of the skin and eyes of rabbits, if at all. Inhalation studies in animals or human data suitable for deriving a MAK value are not available. A NOAEL for focal inflammation in the liver of 115 mg/kg body weight and day for males (LOAEL: 470 mg/kg body weight and day) and a NOAEL for degeneration of the olfactory epithelium of 470 mg/kg body weight and day (LOAEL: 2330 mg/kg body weight and day) for male and female animals were obtained from the 2-year drinking water study in rats (NTP 2004). The study did not

investigate the mechanism for the formation of lesions in the olfactory epithelium. The authors suggested that the lesions in the nose might be related to the metabolism of dipropylene glycol in the olfactory epithelium of rats. The olfactory epithelium of rats has a well-developed enzyme system that includes CYP450 enzymes (NTP 2004). However, studies of the metabolism of dipropylene glycol are not available. A metabolism study of tripropylene glycol showed that it may lead to the formation of dipropylene glycol and monopropylene glycol, the latter of which may ultimately enter the citric acid cycle (Fowles et al. 2013).

The difference between the NOAEL for inflammation of the liver and the NOAEL and LOAEL for degeneration of the olfactory epithelium derived from the above-mentioned 2-year drinking water study in rats was 4 and 16 times, respectively (NTP 2004). As dipropylene glycol causes only slight irritation of the skin and eyes of rabbits, if at all, it is assumed that the MAK value of 100 mg/m^3 derived in 2012 from the systemic effect also provides protection from local irritation after inhalation. This assumption is supported by the fact that the postulated metabolite propylene glycol (1,2-propanediol = monopropylene glycol) did not cause damage to the olfactory epithelium in a 90-day inhalation study in rats up to the high concentration of 2200 mg/m^3. However, in this study, propylene glycol induced nasal haemorrhage at 160 mg/m^3 and above (Suber et al. 1989) and a MAK value was not established (documentation "Propylenglykol" 2007, available in German only). The authors of the study of propylene glycol considered dehydration to be the cause of nasal haemorrhage (Suber et al. 1989). According to the 2007 documentation, dehydration of the nasal mucosa is not likely because the humidity determined in the study was 30% to 70% Suber et al. (1989). The fact that glycerin has roughly the same hygroscopic properties as propylene glycol (documentation "Propylenglykol" 2007, available in German only) but did not induce such effects at the same concentration, also speaks against dehydration. A comparison of the hygroscopic properties of dipropylene glycol and propylene glycol revealed the following: The dew point of a gas is reduced when water vapour is removed from the gas. At the same temperature of the solution (26.7 °C), a more highly concentrated solution of dipropylene glycol (93.5%) (weight/weight) than of propylene glycol (88%) is required to reduce the dew point of the gas to 10 °C (Dow 2003). Dipropylene glycol is thus less hygroscopic than propylene glycol.

The primary irritation index of propylene glycol is 1.3/110 (ECHA 2014 b); therefore, the substance is slightly more irritating than dipropylene glycol, which has a primary irritation index of 0/110 (ECHA 2014 a). The primary irritation index of tripropylene glycol is 0/110 (ECHA 2014 c).

The following conclusions can be drawn:

1. Dipropylene glycol causes only slight irritation of the skin and eyes of rabbits, if at all. There is thus no evidence of irritation of the mucous membranes of the upper respiratory tract.
2. The method of Brüning et al. (2014) for substances that have effects on the upper respiratory tract and eyes cannot be applied because the prime effects are systemic.

3. The NOAEL in rats decisive for the derivation of the MAK value is determined by the systemic effects on the liver; this NOAEL is lower than the NOAEL for effects on the olfactory epithelium.
4. The degeneration of the olfactory epithelium of rats caused by dipropylene glycol when given with the drinking water might be related to metabolism in this tissue. Studies of the metabolism of dipropylene glycol are, however, not available.
5. In mice, effects on the olfactory epithelium were not observed in the 2-year drinking water study up to doses of 2390 mg/kg body weight in males and 1950 mg/kg body weight in females.

Therefore, the MAK value of 100 mg/m^3 for the inhalable fraction of dipropylene glycol, which was derived from the systemic toxicity of the substance, has been retained.

Peak limitation.
In the absence of toxicokinetic data, and because of the primarily systemic effects, dipropylene glycol remains in Peak Limitation Category II with a default excursion factor of 2.

Absorption through the skin.
Recent data from in vitro tests with human skin have made a more valid estimate of the dermal penetration of dipropylene glycol possible. A systemically available dose of 79 mg can be calculated from the flux established experimentally with undiluted dipropylene glycol for dermal exposure under standard conditions (exposed area: 2000 cm^2; period of exposure: 1 hour). A dose of 1000 mg would be obtained for absorption by inhalation only if the exposure level remained at the MAK value of 100 mg/m^3 over the whole working day (8 hours; respiratory volume: 10 m^3). The contribution of absorption through the skin to the systemic toxicity of the compound is well below 25% and is thus considered to be low. Therefore, dipropylene glycol is not designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Prenatal toxicity.
There are no new data available for developmental toxicity. Because the MAK value has been retained, classification in Pregnancy Risk Group C has been reaffirmed.

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