

Diethylene glycol monobutyl ether acetate

MAK value (2007)	10 ml/m³ \triangleq 84 mg/m³
Peak limitation (2007)	Category I, excursion factor 1.5
Absorption through the skin	–
Sensitization	–
Carcinogenicity	–
Prenatal toxicity (2007)	Pregnancy Risk Group C
Germ cell mutagenicity	–
BAT value	–
Synonyms	2-(2-butoxyethoxy)ethyl acetate butyl carbitol acetate butyl diethylene glycol acetate
Chemical name (CAS)	2-(2-butoxyethoxy)ethyl acetate
CAS number	124-17-4
Structural formula	<chem>CH3COO(CH2CH2O)2CH2CH2CH2CH3</chem>
Molecular formula	C ₁₀ H ₂₀ O ₄
Molecular weight	204.27
Melting point	–32°C (OECD 2005)
Boiling point at 1013 hPa	245°C (OECD 2005)
Density at 25°C	0.981 g/cm ³ (OECD 2005)
Vapour pressure at 25°C	<0.01 hPa (OECD 2005)
Solubility in water at 20°C	65 g/l (OECD 2005)
log K _{OW} ¹⁾	1.3 (calculated; OECD 2005)
1 ml/m³ (ppm) \triangleq 8.476 mg/m³	1 mg/m³ \triangleq 0.118 ml/m³ (ppm)

1) octanol/water partition coefficient

This documentation is based mainly on a review of the data for diethylene glycol monobutyl ether acetate carried out under the OECD-ICCA programme (OECD 2005).

1 Toxic Effects and Mode of Action

Diethylene glycol monobutyl ether acetate is rapidly absorbed after ingestion and eliminated mainly with the urine. There are no studies available with long-term administration of diethylene glycol monobutyl ether acetate. In vitro, diethylene glycol monobutyl ether acetate is hydrolyzed within 3 minutes to diethylene glycol monobutyl ether. Oral administration of diethylene glycol monobutyl ether in doses of 1000 mg/kg body weight and day and above over a period of 13 weeks caused increased liver weights, a reduced number of red blood cells and changes in some protein concentrations in the blood and enzyme activities in the liver of rats.

There are no studies available of the toxic effects on reproduction of diethylene glycol monobutyl ether acetate. Studies carried out with diethylene glycol monobutyl ether in rats did not lead to substance-induced findings in the offspring after dermal application of up to 2000 mg/kg body weight and day or oral administration of up to 633 mg/kg body weight and day.

Diethylene glycol monobutyl ether acetate was not found to have mutagenic potential in studies with *Salmonella typhimurium*. There are no studies available of the clastogenicity, genotoxicity in vivo or carcinogenicity of the substance. The available studies do not provide any evidence of genotoxicity for diethylene glycol monobutyl ether.

Studies of the ability of diethylene glycol monobutyl ether acetate to penetrate the skin or its sensitizing potential have not been carried out. Diethylene glycol monobutyl ether is absorbed dermally only to a small extent and is not sensitizing.

2 Mechanism of Action

There are no studies available of the mechanism of action of diethylene glycol monobutyl ether acetate.

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution and elimination

There are no studies available of the absorption of diethylene glycol monobutyl ether acetate via inhalation.

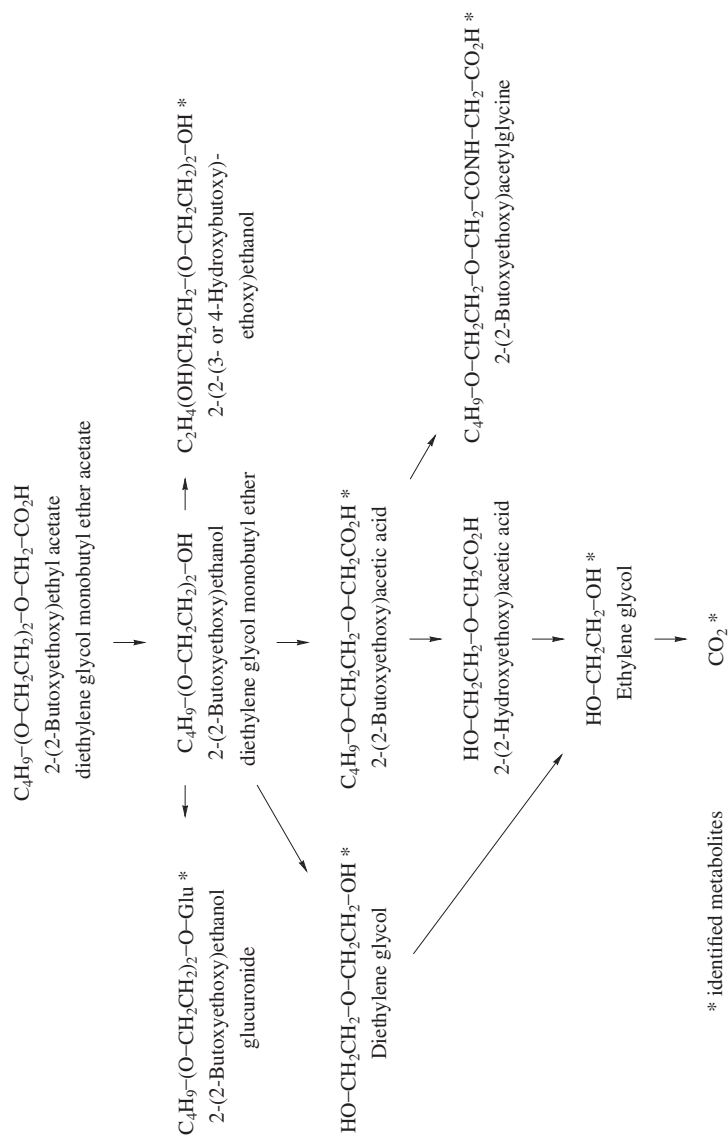


Figure 1 Metabolites of diethylene glycol monobutyl ether acetate

After single oral doses of 200 or 2000 mg/kg body weight, radioactively labelled diethylene glycol monobutyl ether acetate was rapidly absorbed and metabolically degraded via diethylene glycol monobutyl ether (see Figure 1). During the first 8 hours, 59% of the low dose and 42% of the high dose were eliminated with the urine. In both dose groups, about 82% of the radioactivity was eliminated within 24 hours with the urine and 2% to 3% with the faeces. Around 5% of the radioactivity was exhaled as CO₂. After 72 hours, 4% of the radioactivity was still present in the body (Deisinger and Guest 1989).

After 24-hour occlusive application of radioactively labelled diethylene glycol monobutyl ether acetate in doses of 2000 mg/kg body weight or of a 10% aqueous solution of 200 mg/kg body weight to the dorsal skin of 4 male or 4 female Sprague Dawley rats, up to 88% of the radioactivity was recovered within 24 hours in the urine and faeces and when the animals and cages were washed. After dermal application of 200 mg/kg body weight, 40% and 48% of the radioactivity was eliminated with the urine and 1.45% and 3.15% with the faeces by the males and females, respectively. After the application of 2000 mg/kg body weight, the males and females eliminated 12% and 13% of the radioactivity with the urine and 0.4% and 1.4% with the faeces, respectively. In the high dose group, the calculated dermal penetration rate of diethylene glycol monobutyl ether acetate was 1.58 and 1.28 mg/cm² and hour in male and female rats, respectively. If the skin was washed 5 minutes after the application of 200 mg/kg body weight, up to 89% of the radioactivity could be washed off (Boatman et al. 1993).

In vitro studies yielded a mean permeability constant of 1.38×10^{-3} cm rat skin per hour for diethylene glycol monobutyl ether acetate. This corresponds to a mean absorption rate of 1.36 mg/cm² and hour. In another study, an absorption rate of 0.035 mg/cm² and hour was determined for human skin (OECD 2005). In diffusion cell experiments with excised human skin, a flux of 59 ± 36.2 µg/cm² and hour was calculated for undiluted diethylene glycol monobutyl ether acetate. With a rate of 162 ± 43.3 µg/cm² and hour, the flux of a saturated aqueous solution (6.65%) was higher than that of the undiluted substance (Venier et al. 2004).

3.2 Metabolism

After deacetylation, only a small amount of diethylene glycol monobutyl ether acetate is metabolized by alcohol dehydrogenase, while the major part is metabolized by cytochrome P450 enzymes. After single oral doses of radioactively labelled diethylene glycol monobutyl ether acetate of 200 or 2000 mg/kg body weight, male Sprague Dawley rats exhaled about 5% of the administered radioactive dose as ¹⁴CO₂. The metabolites were determined in the urine. 2-(2-Butoxyethoxy)acetic acid was the major urinary metabolite with about 53% to 60% of the radioactivity. In addition, diethylene glycol accounted for 12% of the radioactivity, a non-quantified fraction was ethylene glycol and 32% was detected in 2-(2-(3- or 4-hydroxy-

butoxy)ethoxy)ethanol. Traces of 2-butoxyethanol, 2-butoxy acetic acid and 2-(2-butoxyethoxy)acetylglycine were found, although it could not be determined whether these substances were metabolites of diethylene glycol monobutyl ether acetate or impurities of the parent compound (Deisinger and Guest 1989). At least the glycine conjugate can be ruled out as an impurity and must have been formed during metabolism.

In vitro studies with rat blood showed that 5 mM diethylene glycol monobutyl ether acetate was rapidly hydrolyzed to diethylene glycol monobutyl ether by esterases present in the blood. The half-life was less than 3 minutes. After 10-minute incubation, a plateau concentration of about 6% of the initial concentration was reached, which remained constant for about 14 minutes (OECD 2005).

In a study with male and female Sprague-Dawley rats with dermal application of radioactively labelled diethylene glycol monobutyl ether in doses of 200 or 2000 mg/kg body weight or as a 10% aqueous solution, 2-(2-butoxyethoxy)acetic acid was the major urinary metabolite with 60% to 80% of the radioactivity. Traces of 2-butoxy acetic acid were detected. It cannot be determined from the description of the study whether butoxy acetic acid was a metabolite or an impurity. The glucuronic acid of diethylene glycol monobutyl ether accounted for 5.2% to 8.2% of the urinary radioactivity. Further unidentified metabolites were found (Boatman et al. 1993).

4 Effects in Humans

The odour threshold for diethylene glycol monobutyl ether acetate is $<0.1 \text{ ml/m}^3$ (Lundberg 1995). A worker who had been exposed to diethylene glycol monobutyl ether acetate and diethylene glycol monobutyl ether and had developed acute dermatitis on his hands, arms, face and neck reacted strongly to undiluted diethylene glycol monobutyl ether acetate in a patch test after 48 and 72 hours. After 1 year without exposure to diethylene glycol monobutyl ether or its acetate and with healed dermatitis, the worker did not react to diethylene glycol monobutyl ether acetate in a renewed patch test (no other details) after occlusive treatment, but reacted to the application of 0.1 ml diethylene glycol monobutyl ether acetate or diethylene glycol monobutyl ether in a test after 20 minutes of non-occlusive treatment (Dawson et al. 1989). The authors did not explain this conflicting result.

In Alaska, frequent treatment of a 3-year-old child with an insect repellent containing 50% diethylene glycol monobutyl ether acetate, 15% diethylene glycol ethyl ether and 28% ethanol during one summer led to nephrosis (Lundberg 1995).

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

The LC_{50} after the exposure of rats (no other details) to diethylene glycol monobutyl ether acetate for 4 hours was 8696 ml/m³. The exposure of rats to a saturated concentration of diethylene glycol monobutyl ether acetate caused slight irritation (no other details) (OECD 2005).

5.1.2 Ingestion

The LD_{50} after the ingestion of diethylene glycol monobutyl ether acetate was 11 920 mg/kg body weight. Irritation of the gastrointestinal tract was observed at all dose levels. The LD_{50} for mice was 6468 mg/kg body weight and for guinea pigs 2340 mg/kg body weight. Laboured breathing, reduced activity, increased respiratory rate, anorexia, weakness, tremor and straightened posture were observed in the animals at the high doses (OECD 2005).

5.1.3 Dermal absorption

The dermal LD_{50} in rabbits was 5500 mg/kg body weight (OECD 2005).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

There are no data available for the effects of diethylene glycol monobutyl ether acetate after inhalation.

5.2.2 Ingestion

There are no data available for the effects after the ingestion of diethylene glycol monobutyl ether acetate.

5.2.3 Dermal absorption

In an inadequately documented study from 1944, diethylene glycol monobutyl ether acetate was applied to the skin of rabbits (no other details) in doses of 489,

978, 1956 or 3912 mg/kg body weight and day once a day for 90 days. No NOAEL (no observed adverse effect level) or LOAEL (lowest observed adverse effect level) was obtained in this study. An LD₅₀ of 1956 mg/kg body weight and day was reported. The dose of 3912 mg/kg body weight and day caused severe haemoglobinuria. Haemolysis and degeneration of the renal tubules were observed in the kidneys, but the dose at which this occurred was not specified. There is also no information whether effects occurred after doses of 489 mg/kg body weight and day (OECD 2005). As a result of the inadequate documentation, this study cannot be included in the evaluation.

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

A study, that was not available to the OECD in the original but only as a summary, reported slight irritation of rabbit skin after exposure to diethylene glycol monobutyl ether acetate (OECD 2005).

5.3.2 Eyes

Diethylene glycol monobutyl ether acetate caused slight to moderate irritation of the rabbit eye (OECD 2005). The application of 0.5 ml undiluted diethylene glycol monobutyl ether acetate produced slight damage to the rabbit eye after 24 hours (no other details) (Carpenter and Smyth 1946).

5.4 Allergenic effects

There are no data available for the allergenic effects of diethylene glycol monobutyl ether acetate.

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

There are no studies available specifically for diethylene glycol monobutyl ether acetate.

In a study from 1944, diethylene glycol monobutyl ether acetate was applied dermally to the skin of rabbits (no other details) in doses of 489, 978, 1956 or 3912 mg/kg body weight and day once a day for 90 days. No histological changes

were observed in the reproductive organs (OECD 2005). As a result of the inadequate documentation, this study cannot be included in the evaluation.

Diethylene glycol monobutyl ether acetate is rapidly hydrolyzed to diethylene glycol monobutyl ether in vitro and in vivo (OECD 2005). Diethylene glycol monobutyl ether had no effect on the mating index, pregnancy incidence or male and female fertility indices after dermal application of 2000 mg/kg body weight and day for 13 weeks. In a 13-week study in which diethylene glycol monobutyl ether was administered to rats with the drinking water, no histopathological changes to the sexual organs were detected up to the highest dose used of 1000 mg/kg body weight and day (see “Diethylene glycol monobutyl ether” 2008).

5.5.2 Developmental toxicity

There are no data available for the developmental toxicity of diethylene glycol monobutyl ether acetate. Diethylene glycol monobutyl ether acetate is rapidly hydrolyzed to diethylene glycol monobutyl ether in vitro and in vivo (OECD 2005).

Several studies were carried out to investigate the effects of diethylene glycol monobutyl ether on offspring after ingestion and dermal application, but no evidence of prenatal or postnatal toxicity was found up to the highest doses tested: in rats, after the administration of diethylene glycol monobutyl ether with the diet on days 1 to 21 of gestation in doses of up to 633 mg/kg body weight and day with prenatal and postnatal examinations and after 13-week dermal application of 2000 mg/kg body weight and day; in mice, after the oral administration of up to 2050 mg/kg body weight and day on days 6 to 13 of gestation, and in rabbits after the dermal application of up to 1000 mg/kg body weight and day on days 7 to 18 of gestation and prenatal examination (see “Diethylene glycol monobutyl ether” 2008).

5.6 Genotoxicity

5.6.1 In vitro

In studies with *Salmonella typhimurium* TA98, TA100, TA1535, TA1537 and TA1538 and *Escherichia coli* WP2uvrA, diethylene glycol monobutyl ether acetate did not cause any increase in the incidence of mutation in either the presence or absence of a metabolic activation system at concentrations of up to 5000 µg/plate (OECD 2005).

5.6.2 In vivo

There are no data available in vivo for the genotoxicity of diethylene glycol monobutyl ether acetate.

5.7 Carcinogenicity

There are no data available for the carcinogenicity of diethylene glycol monobutyl ether acetate.

6 Manifesto (MAK value/classification)

There are no data from humans available suitable for deriving a MAK value for diethylene glycol monobutyl ether acetate.

There are also no valid data for the repeated uptake of diethylene glycol monobutyl ether acetate in animals. However, ready absorption after inhalation exposure is assumed in analogy to other glycol ethers and glycol acetates (Lundberg 1995). Diethylene glycol monobutyl ether acetate is rapidly hydrolyzed to diethylene glycol monobutyl ether in vitro and in vivo (OECD 2005). Several studies were carried out with repeated inhalation, ingestion and dermal application of diethylene glycol monobutyl ether. In 13-week studies with rats exposed to diethylene glycol monobutyl ether, a NOAEL of 50 mg/kg body weight and day was obtained after oral administration and a NOAEL of 2000 mg/kg body weight and day after dermal application. A no adverse effect concentration of 14 ml/m³ (about 100 mg/m³) was obtained from the inhalation studies with rats. A MAK value of 10 ml/m³ was established for diethylene glycol monobutyl ether. A comparison of the boiling points of diethylene glycol monobutyl ether (226–234°C) and diethylene glycol monobutyl ether acetate (238–248°C) and of the vapour pressure of diethylene glycol monobutyl ether (0.027 hPa) with that of diethylene glycol monobutyl ether acetate (0.013–0.05 hPa) shows that the two substances are of similar volatility. Up to concentrations of 15 ml/m³, diethylene glycol monobutyl ether acetate, like diethylene glycol monobutyl ether, is therefore probably present as a vapour. In analogy to diethylene glycol monobutyl ether, a MAK value of 10 ml/m³ has provisionally been established also for diethylene glycol monobutyl ether acetate. Also Peak Limitation Category I with an excursion factor of 1.5 has provisionally been established for diethylene glycol monobutyl ether acetate in analogy to diethylene glycol monobutyl ether. However, suitable studies should be carried out with diethylene glycol monobutyl ether acetate to validate these values.

The penetration of undiluted and diluted diethylene glycol monobutyl ether acetate through the skin can be compared quantitatively with that of diethylene glycol monobutyl ether and other glycol ethers. On the basis of the available data and by analogy with diethylene glycol monobutyl ether, dermal exposure is assumed to pose no additional risk. Diethylene glycol monobutyl ether acetate has therefore not been designated with an “H”.

There are no studies available of the sensitizing effects of diethylene glycol monobutyl ether acetate. Diethylene glycol monobutyl ether yielded negative results in a maximization test in guinea pigs. In analogy to diethylene glycol monobutyl ether,

diethylene glycol monobutyl ether acetate has not been designated with “Sa” or “Sh”.

Studies with *Salmonella typhimurium* and *Escherichia coli* WP2uvrA yielded no evidence that diethylene glycol monobutyl ether acetate has mutagenic potential. Nor was diethylene glycol monobutyl ether found to have any mutagenic effects in the available studies (see “Diethylene glycol monobutyl ether” 2008). Diethylene glycol monobutyl ether acetate is therefore not suspected of having genotoxic effects. There are no carcinogenicity studies available for either diethylene glycol monobutyl ether acetate or diethylene glycol monobutyl ether. In analogy to diethylene glycol monobutyl ether, diethylene glycol monobutyl ether acetate is not classified in any of the categories for carcinogens or germ cell mutagens.

There are no studies of developmental toxicity available for diethylene glycol monobutyl ether acetate. Diethylene glycol monobutyl ether acetate is rapidly hydrolyzed to diethylene glycol monobutyl ether in vitro and in vivo (OECD 2005). Diethylene glycol monobutyl ether had no effect on the offspring of rats given oral doses of up to 633 mg/kg body weight and day, or of rats treated dermally with up to 2000 mg/kg body weight and day, or of rabbits given up to 1000 mg/kg body weight and day (see “Diethylene glycol monobutyl ether” 2008). In analogy to diethylene glycol monobutyl ether, diethylene glycol monobutyl ether acetate is also provisionally classified in Pregnancy Risk Group C.

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