

(Ethylenedioxy)dimethanol

MAK Value Documentation – Translation of the German version from 2024

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carcinogenicity; germ cell
mutagenicity; developmental
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Abstract

The German Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission) summarized and evaluated the data for (ethylenedioxy)dimethanol [3586-55-8] to derive an occupational exposure limit value (maximum concentration at the workplace, MAK value) considering all toxicological end points. Relevant studies were identified from a literature search and also unpublished study reports were used. (Ethylenedioxy)dimethanol is used as a biocide. It releases formaldehyde in aqueous solution. (Ethylenedioxy)dimethanol is not expected to occur in aerosol form because of its high vapour pressure. The substance is irritating to the skin and corrosive to the eyes of rabbits. At a pH of 7.0 and 20 °C, a 1% (ethylenedioxy)dimethanol solution has a hydrolysis half-life of 6 minutes. It can therefore be assumed that (ethylenedioxy)dimethanol hydrolyses to formaldehyde upon impaction in the respiratory tract. Based on the worst-case, the release of two formaldehyde molecules per molecule of (ethylenedioxy)dimethanol in the respiratory tract, a MAK value of 0.15 ml/m³ has been derived for (ethylenedioxy)dimethanol in analogy to the MAK value of formaldehyde of 0.3 ml/m³. Peak Limitation Category I has been assigned with an excursion factor of 2 in analogy to the classifications made for formaldehyde. Formaldehyde is classified in Carcinogen Category 4 because it causes nasal tumours at concentrations that exceed the detoxification capacity of that tissue. Studies investigating the carcinogenicity and germ cell mutagenicity of (ethylenedioxy)dimethanol are not available. Thus, in analogy to the classifications made for formaldehyde, the substance has been assigned to Carcinogen Category 4 and Germ Cell Mutagenicity Category 5. In rats, the NOAEC for the developmental toxicity of formaldehyde is 10 mg/m³ and the NOAEL of ethylene glycol, a hydrolysis product of (ethylenedioxy)dimethanol, is 200 mg/kg body weight. As no teratogenicity was observed and the margins between the NOAELs and the MAK value are sufficiently large, (ethylenedioxy)dimethanol has been assigned to Pregnancy Risk Group C. Skin contact is expected to make a relatively minor contribution to systemic toxicity. The available data show no evidence of sensitization.

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MAK value (2023)	0.15 ml/m³ (ppm) $\approx$ 0.76 mg/m³
Peak limitation (2023)	Category I, excursion factor 2
Absorption through the skin	–
Sensitization	–
Carcinogenicity (2023)	Category 4
Prenatal toxicity (2023)	Pregnancy Risk Group C
Germ cell mutagenicity (2023)	Category 5
BAT value	–
Synonyms	[2-(hydroxymethoxy)ethoxy]methanol 1,6-dihydroxy-2,5-dioxahexane dimethylol glycol (1,2-ethanediylbis(oxy))bismethanol ethyleneglycol bis(hydroxymethyl ether) reaction products of ethylene glycol with paraformaldehyde
Chemical name (IUPAC)	[1,2-ethanediylbis(oxy)]dimethanol
CAS number	3586-55-8
Structural formula	HO–CH ₂ –O–CH ₂ –CH ₂ –O–CH ₂ –OH
Molecular formula	C ₄ H ₁₀ O ₄
Molar mass	122.12 g/mol
Melting point	–76.5 °C (ECHA 2022)
Boiling point at 1013.25 hPa	158.8 °C according to OECD Test Guideline 103 (ECHA 2022)
Density at 20 °C	1.197 g/cm ³ (ECHA 2022)
Vapour pressure at 20 °C	13.2 hPa (calculated) (US EPA 2022)
log K_{OW}	–1.36 (ECHA 2022)
Solubility	studies have not been carried out as the substance is hydrolytically unstable at pH 4, 7 and 9 (ECHA 2022)
1 ml/m³ (ppm) $\approx$ 5.067 mg/m³	1 mg/m³ $\approx$ 0.197 ml/m³ (ppm)
Hydrolytic stability	half-life 1 hour in the acidic pH range, half-life 6 minutes in the neutral range at 20 °C, very rapid hydrolysis at and above pH 7 (20 °C) (ITEM 2007)
Production	reaction product of ethylene glycol and paraformaldehyde in the ratio 1:1 (CCR 2000), the formaldehyde content is 46.2% (ITEM 2002 b)
Purity	90%–100% (ITEM 2009)
Impurities	0.002% methanol (ITEM 2009)
Uses	biocide, preservation of pigment slurries, filler suspensions, polymer dispersions, solutions and dispersions of glues and thickeners, concrete additives,

Concentrations used

cleaning agents, oil emulsions, polishes and other chemical/technical water-based preparations (Trigon Chemie GmbH 2023), preservation of metal-working fluids, paints, coatings, printing inks, fountain water and plasters (CTGB 2012) one commercial product contains 14.3% (ethylenedioxy)dimethanol and 1.4% isothiazoles; this is dosed in such a way that a 0.10% (w/w) solution is produced with the metal-working fluid (CTGB 2012), another commercial product contains 14.1% (ethylenedioxy)dimethanol (w/w), 5% glutaral (w/w), 8% didecyldimethylammonium chloride (w/w); a 2% solution is used as a disinfectant for surface treatment against fungal spores (Horejsh and Kampf 2011)

Note: releases formaldehyde.

Cited unpublished toxicological studies from companies have been made available to the Commission.

1 Toxic Effects and Mode of Action

(Ethylenedioxy)dimethanol releases formaldehyde. Hydrolysis takes place with a half-life of 6 minutes in the neutral range at 20 °C. After inhalation exposure, formaldehyde is carcinogenic to the nasal cavity of rats. Nasal carcinogenicity is therefore to be expected from (ethylenedioxy)dimethanol after exposure by inhalation, even if there are no studies available that demonstrate this effect.

(Ethylenedioxy)dimethanol is irritating to the skin and corrosive to the eyes.

The administration of gavage doses of 90 mg/kg body weight and day for 90 days led to piloerection, increased salivation and strong inflammatory reactions in the stomach of rats.

In a bacterial mutagenicity test, (ethylenedioxy)dimethanol was mutagenic in the *Salmonella typhimurium* strain TA98 after metabolic activation. Clastogenicity occurred in a chromosomal aberration test in the cytotoxic range.

There are no data available for the developmental toxicity of (ethylenedioxy)dimethanol.

Evidence that (ethylenedioxy)dimethanol itself has sensitizing potential in humans is not available. The hydrolysis product formaldehyde causes skin sensitization.

2 Mechanism of Action

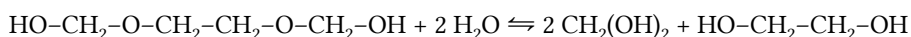
(Ethylenedioxy)dimethanol hydrolyses to form ethylene glycol and two molecules of formaldehyde. The formaldehyde (MAK value of 0.3 ml/m³) released after rapid hydrolysis is irritating to the upper respiratory tract. Concentrations above the MAK value can exceed the detoxification capacity of the nasal tissue, in which case formaldehyde can lead to tumours in this tissue. It has therefore been assigned to Carcinogen Category 4 (ECHA 2023; Greim 2002).

The other hydrolysis product, ethylene glycol, also has an irritant effect in humans, but below the MAK value of 10 ml/m³ this does not occur (Henschler 1992).

The mutagenicity of (ethylenedioxy)dimethanol in the *Salmonella typhimurium* strain TA98 is probably due solely to formaldehyde (Greim 2002), as ethylene glycol is neither mutagenic nor clastogenic in vitro (Henschler 1992).

3 Toxicokinetics and Metabolism

In aqueous solutions, the substance hydrolyses rapidly to formaldehyde hydrate and ethylene glycol:



Water shifts the equilibrium to the right so that a greater amount of formaldehyde hydrate is released (CCR 2000).

In technical products, a concentration-dependent equilibrium is established due to the closed system in the packaging. By contrast, complete hydrolysis to formaldehyde hydrate and ethylene glycol is expected in open systems (ECHA 2022).

The extent to which the hydrolysis of a 1% aqueous (ethylenedioxy)dimethanol solution is dependent on the pH was investigated using ^{13}C -NMR spectroscopy at 20 °C in accordance with OECD Test Guideline 111. The hydrolysis of (ethylenedioxy)dimethanol was too fast to determine the initial concentrations. The half-lives were therefore estimated from the curves. While the half-life in the strongly acidic pH range was about 1 hour and reached its maximum at pH 3.5, very rapid hydrolysis was observed at pH 7 and above. Table 1 shows the half-lives at the various pH values (ITEM 2007).

Tab. 1 Estimated half-lives of the hydrolytic release of formaldehyde from a 1% solution of (ethylenedioxy)dimethanol at different pH values and 20 °C (calculated from the amount of formaldehyde released) (ITEM 2007)

pH	Half-life [hours]
2.0	0.48
4.0	0.91
5.4	0.33
7.1	0.10
8.9	0.08

The complete hydrolysis of a 0.315% (ethylenedioxy)dimethanol solution in 0.1 M borate buffer (pH 8.5) at 25 °C to formaldehyde and ethylene glycol was demonstrated using ^{13}C -NMR spectroscopy. Methanol at a concentration of 0.002% was identified as an impurity (ITEM 2009).

The determination of the individual components of (ethylenedioxy)dimethanol solutions of different dilutions using ^{13}C -NMR spectroscopy showed that with the increasing dilution of the medium the substance is hydrolysed in increasing amounts to formaldehyde and ethylene glycol (Table 2). Other components were monomethylolethylene glycol, dimethylolethylene glycol, trimethylolethylene glycol, dimeric and trimeric formaldehyde hydrate and longer-chain reaction products of ethylene glycol and formaldehyde (ITEM 2006). The study was carried out in a closed system (NMR tube with external decoy capillary). By contrast, in the organism (as an open system), the metabolism of formaldehyde causes a shift in the equilibrium towards increased hydrolysis, that is the formation of formaldehyde and ethylene glycol.

Tab. 2 Content of individual components in (ethylenedioxy)dimethanol and in (ethylenedioxy)dimethanol/D₂O mixtures (ITEM 2006)

Substance	Content [% of initial weight of (ethylenedioxy)dimethanol]		
	(Ethylenedioxy)dimethanol/D ₂ O		
	100/0	50/50	20/80
ethylene glycol	5.6	9.7	18.9
formaldehyde hydrate (formaldehyde)	0.5	10.9	32.3

3.1 Toxicokinetics

There are no toxicokinetic studies available. The hydrolysis products ethylene glycol and formaldehyde are readily absorbed both orally and by inhalation (Greim 2002; Henschler 1992).

Model calculations according to IH SkinPerm v2.04 (Tibaldi et al. 2014) and Fiserova-Bergerova et al. (1990) yield a transdermal flux of 5–20 µg/cm² and hour or a total absorbed amount of 10–40 mg (exposure for 60 minutes, 2000 cm² of exposed skin) for a 5% aqueous solution under standard conditions. A 5% solution of a substance of skin irritation Category 2 is not classified as an irritant according to the CLP Regulation (European Parliament and European Council 2008). The presumed rapid hydrolysis of the substance in the acidic environment of the skin surface, which counteracts the absorption of the undecomposed compound, was not taken into account.

3.2 Metabolism

There are no studies available for the metabolism of (ethylenedioxy)dimethanol.

Data for the metabolism of the hydrolysis products can be found in Greim (2002) and Henschler (1992).

4 Effects in Humans

Data in humans are available only for allergenic effects.

Allergenic effects

Sensitizing effects on the skin

In an evaluation by the Information Network of Departments of Dermatology (Informationsverbund Dermatologischer Kliniken, IVDK), (ethylenedioxy)dimethanol (1% in petrolatum) was tested epicutaneously on 273 people in 5 centres (May 2000 and May 2003). The results of 201 persons employed in the metal industry were published (Geier et al. 2003). Of the 273 persons, 1 person produced a positive reaction (+) and another person a questionable reaction on day 3, all the others did not react. Both individuals reacted weakly (+) also to formaldehyde (1% in water) (Geier 2023).

There is a report about a lathe operator who produced a strong reaction to an occupationally used metal-working fluid which, according to the safety data sheet, contained also (ethylenedioxy)dimethanol. However, this substance was not tested separately. The person reacted to formaldehyde and other substances (Geier et al. 2011). No conclusions can be drawn from the data obtained as to whether (ethylenedioxy)dimethanol has a sensitizing effect.

Other studies investigating (ethylenedioxy)dimethanol are not available.

There are isolated reports of skin sensitization caused by the hydrolysis product ethylene glycol, but in view of its widespread use as an antifreeze, among other applications, there was not sufficient evidence for designating the substance with an “S” (Henschler 1992). However, there is no doubt about the sensitization potential of the hydrolysis product formaldehyde (Hartwig 2014).

Sensitizing effects on the airways

There are no findings available.

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

There are no data available.

5.1.2 Oral administration

In a study carried out according to OECD Test Guideline 423, single gavage doses of (ethylenedioxy)dimethanol in distilled water were given to 3 Wistar rats per dose group. The doses were 200 or 2000 mg (ethylenedioxy)dimethanol/kg body weight for the females and 200 mg/kg body weight for the males. At 2000 mg/kg body weight all animals died, at 200 mg/kg body weight none died. The animals in the high dose group exhibited sedation and ventral recumbency before they died (no other details; ECHA 2022). The LD₅₀ for rats was therefore between 200 and 2000 mg/kg body weight.

Gavage doses of 750 or 850 mg (ethylenedioxy)dimethanol/kg body weight administered to 5 female Wistar rats and of 1000 mg/kg body weight to 5 female and 5 male Wistar rats resulted in redness and swelling of the mucous membranes of the gastrointestinal tract in the animals that died. There were no unusual findings in the surviving animals. An LD₅₀ for female rats of 760 mg/kg body weight was derived from this study. The LD₅₀ for the males was less than 1000 mg/kg body weight (ECHA 2022).

In a range-finding study for an in vivo micronucleus test, 2 male and 2 female Crl:NMRI BR mice per group were given gavage doses of (ethylenedioxy)dimethanol of 250, 500, 1000 or 2000 mg/kg body weight. Reduced motility, ataxia and dyspnoea were observed even in the low dose group. The effects were more pronounced at 500 mg/kg body weight. The dose levels of 1000 and 2000 mg/kg body weight were lethal after 60 minutes (LPT 2002 b). The LD₅₀ in mice was therefore between 500 and 1000 mg/kg body weight.

In a study, single doses of (ethylenedioxy)dimethanol of 30, 100 or 300 mg/kg body weight in corn oil were administered by gavage to groups of 5 male and 5 female NMRI mice. In the animals of the dose groups given 30 and 100 mg/kg no signs of toxicity were found 24 and 48 hours after administration. Reduced motility, ataxia and dyspnoea occurred in the animals of the high dose group as early as 30–60 minutes after administration (LPT 2002 b).

Single doses of (ethylenedioxy)dimethanol of 100, 200, 504, 635, 790 or 1000 mg/kg body weight in NaCl solution were administered by gavage to groups of 10 male and 10 female NMRI mice. Slight sedation and ataxia occurred at 200 mg/kg body weight and above, which increased with the increasing dose. Mortality was first observed at the dose of 635 mg/kg body weight (2 males and 2 females) and increased at the higher doses (760 mg/kg body weight, 6 males and 6 females, and 1000 mg/kg body weight, 10 males and 10 females). An LD₅₀ for mice of 740 mg/kg body weight was derived from this study (ECHA 2022).

5.1.3 Dermal application

In a study carried out according to OECD Test Guideline 402, undiluted (ethylenedioxy)dimethanol (purity 95%) at a dose of 2.0 ml/kg body weight (about 2384 mg/kg body weight) was applied semi-occlusively to 5 male and 5 female HanBrl:Wist (SPF) rats for 24 hours. Slight, moderate, and marked erythema maculata, slight and moderate scales, slight and marked scabs, and yellow skin were evident in males and females between day 2 and day 15. There were no clinical signs, and body weight development remained unaffected during the study (ECHA 2022). In this study, the acute dermal LD₅₀ of the tested substance in rats was more than 2000 mg/kg body weight.

In another study carried out according to OECD Test Guideline 402, 2000 mg of the undiluted test substance/kg body weight was applied semi-occlusively to the skin of 5 male and 6 female Wistar rats for 24 hours, followed by a 14-day observation period. Apart from yellow discoloration of the skin and fur, no local effects were observed. Two female

animals showed transient severe signs of intoxication. In addition, a haemorrhagic nasal discharge occurred in the female animals. Piloerection was observed in the males, which lasted 1 to 2 days. Body weight development was unaffected by the treatment. Gross pathology revealed no other findings (ECHA 2022). The acute dermal median lethal dose (LD₅₀) of (ethylenedioxy)dimethanol in this study for rats was greater than 2000 mg/kg body weight.

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

There are no data available for the inhalation of (ethylenedioxy)dimethanol.

5.2.2 Oral administration

In a 90-day gavage study carried out in accordance with OECD Test Guideline 408, groups of 10 male and 10 female Sprague Dawley rats were given (ethylenedioxy)dimethanol doses of 0, 30, 90 or 270 mg/kg body weight and day in corn oil on 7 days a week. The substance contained 46.8% readily cleavable formaldehyde, no impurities, and as a 1% aqueous solution had a pH of 7.5. Histopathological examination of all organs was carried out only in the animals of the high dose and control groups and those that died before the end of the 90-day exposure period. In the animals of the low and middle dose groups, only the stomach and bone marrow were examined histopathologically due to gross-pathological substance-related changes. In the low dose group, no effects were observed except for chronic multifocal ulcerative gastritis and peritonitis in 1 male rat. This one case was considered by the authors to be of spontaneous nature. At 90 mg/kg body weight, chronic ulcerative gastritis and peritonitis and/or hyperplastic-hyperkeratotic epithelial reactions with bacterial infection, particularly of the proventricular part of the stomach, occurred in all male (10/10) and 5 female (5/10) animals. As a physiological response to the inflammatory reaction in the stomach, most of these animals displayed increased granulocytopenia in the bone marrow. Gross-pathological examination revealed greenish or blackish discoloured indurations/nodules in the stomach of the male (7/10) and female (2/10) animals. An ulcer of the stomach was observed in 1 male animal and haemorrhagic indurations in 3 of 10 females. Further changes in other organs of the low and middle dose group occurred only sporadically and were not considered by the authors to be treatment-related. Therefore, histopathological examination of these organs was not performed. All animals in the high dose group exhibited chronic ulcerative gastritis and peritonitis and/or hyperplastic-hyperkeratotic epithelial reactions with bacterial infection and with increased granulocytopenia in the bone marrow. The liver (4/10 and 3/10, male and female animals, respectively) and spleen (2/10 and 1/10) were adhered to the stomach. In the stomach, also discoloured foci, nodules or deposits (10/10 and 9/10), ulcers (1 male and 1 female) and haemorrhagic indurations (1 female) were observed. The body weight gains of the male animals were reduced in a statistically significant manner. The increased relative organ weights of the brain, adrenal glands and gonads were attributed by the authors to the reduced body weights. The clinico-chemical data revealed only in the animals in the high dose group a reduction in glucose in the males and in plasma albumin and total protein in the females. Neurological tests ("Functional Observation Battery" (FOB)) revealed reduced pupil sizes in males (7/9 and 7/10, respectively) and females (8/9 and 4/9, respectively) in the middle and high dose groups and a lack of pupil responses in males (5/9 and 4/9, respectively). Reduced active locomotion was observed in the high dose group. Long-lasting piloerection was seen in all animals in the middle dose group from day 16 and increased salivation occurred in all male animals from day 64. The animals in the high dose group displayed piloerection from day 14 and increased salivation from day 27. One male animal in the middle dose group died on day 81 and 1 male and 2 females in the high dose group died before the end of the study. No effects were found in the ophthalmological examination, or as regards drinking water intake, other clinico-chemical and urine data, and immune status. According to the authors, the NOEL (no observed effect level) in this study was 30 mg/kg body weight and day (LPT 2002 a). It is unusual that the effects started in all animals on the same day of the study (ECHA 2022). However, the finding "chronic multifocal ulcerative gastritis/peritonitis" in 1 animal in the low dose group of 30 mg/kg body weight and day indicates an incipient effect, as this occurred in almost all animals in the middle dose group.

5.2.3 Dermal application

There are no data available for dermal application.

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

In a study carried out according to OECD Test Guideline 404, 0.5 ml of the undiluted substance (pH 3.32) was applied semi-occlusively to the shaved skin of 3 New Zealand White rabbits for 4 hours. Readings were performed after 0–60 minutes, 24 hours, 48 hours, 72 hours and daily up to day 15. Erythema with a score of 1.2 (0, 1, 2, 3 on a scale with a maximum of 4) and oedema with a score of 1.3 (0, 2, 2 on a scale with a maximum of 4) were observed after 24, 48 and 72 hours. Erythema was no longer visible after 12 days, while oedema was not completely reversible within 15 days. The substance is classified as a Category 2 skin irritant according to GHS criteria (IBR Forschungs GmbH 1992). Only the trade name is mentioned in the study report. The density of the substance was determined to be 1.21 g/ml; this suggests that it was (ethylenedioxy)dimethanol. In the registration dossier (ECHA 2022), (ethylenedioxy)dimethanol is stated as the substance used.

To determine the dermal LD₅₀ in 5 male and 5 female HanBrl:Wist (SPF) rats, 2.0 ml/kg body weight (about 2.384 g/kg body weight) of undiluted (ethylenedioxy)dimethanol containing 95% active substance was applied semi-occlusively for 24 hours. Slight to marked erythema, scabs and yellow skin were observed in the animals from day 2 onwards (Section 5.1.3; ECHA 2022).

5.3.2 Eyes

In a study carried out according to OECD Test Guideline 405, 0.1 ml of undiluted (ethylenedioxy)dimethanol was instilled into the conjunctival sac of 1 eye of a female Little Russian rabbit. The untreated eye of the animal served as a control. After 24 hours, the eye was rinsed with 20 ml of a 0.9% sodium chloride solution. After 1 hour, 24, 48 and 72 hours, the animal exhibited severe damage to the cornea of score 1 (on a scale with a maximum of 4), which was not reversible after 15 days, severely reddened conjunctivae of score 3 (maximum 3) combined with severe chemosis of score 3.67 (maximum 4), iris lesions of score 1 (maximum 2) and persistent heavy discharge for at least 15 days (Frey-Tox GmbH 2002). The substance is classified as a strong eye irritant of Category 1 according to GHS criteria (ECHA 2022). The substance has therefore corrosive properties.

5.4 Allergenic effects

5.4.1 Sensitizing effects on the skin

In a maximization test according to OECD Test Guideline 406 in 20 female Dunkin/Hartley guinea pigs, a 0.25% (v/v) test preparation in a triglyceride mixture (Alembicol D) was injected intradermally. For topical induction a 10% test preparation was used. All animals produced a reaction after challenge treatment with a 1% and a 0.5% preparation (Huntington Life Sciences Ltd. 2001).

In a maximization test conducted in 10 female Himalayan spotted guinea pigs based on OECD Test Guideline 406, intradermal induction was performed with a 5% test preparation of (ethylenedioxy)dimethanol in water and topical induction with a 50% (v/v) test preparation. None of the animals reacted after challenge treatment with the 25% aqueous test preparation after 24 and 48 hours; the result is therefore negative (ECHA 2022). In the preliminary study, no irritation was observed with the undiluted test substance. It is therefore unclear why only a 50% test preparation was used for dermal induction and only a 25% test preparation for challenge treatment.

Studies with “new approach methods” are not available.

5.4.2 Sensitizing effects on the airways

There are no data available.

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

There are no data available.

5.5.2 Developmental toxicity

There are no data available.

Data are available for the prenatal developmental toxicity of the 2 main hydrolysis products formaldehyde and ethylene glycol (Henschler 1991, available in German only; Henschler 1992).

Formaldehyde was not found to be teratogenic in prenatal developmental toxicity studies in rats (up to the highest concentration tested of 40 ml/m³), mice (up to the highest oral dose tested of 185 mg/kg body weight and day), dogs (up to the highest oral dose tested of 9.4 mg/kg and day) and golden hamsters (up to the highest dermal concentration tested of a formaldehyde solution of 37%). The lowest effect concentration in rats after inhalation was 20 ml/m³ at which decreased foetal weights were observed. The NOAEC (no observed adverse effect concentration) for developmental toxicity was 10 ml/m³. Maternal toxicity did not occur at this concentration (Henschler 1991).

Ethylene glycol was teratogenic in prenatal developmental toxicity studies in rats and mice; the substance induced external, skeletal and visceral malformations. The NOAEL (no observed adverse effect level) and NOAEC for developmental toxicity in rats are 200 mg/kg body weight/day after oral administration (diet, LOAEL (lowest observed adverse effect level) 1000 mg/kg body weight/day) and 150 mg/m³ (whole-body exposure, LOAEC (lowest observed adverse effect concentration) 1000 mg/m³, corresponding to a total dose by licking the fur of 278–403 mg/kg body weight/day, calculated on the basis of the amount of ethylene glycol determined in the fur at 2500 mg/m³; Bushy Run Research Center 1985), respectively. After gavage administration a LOAEL of 1250 mg/kg body weight and day for developmental toxicity was obtained in rats, the lowest dose tested. In mice, the NOAEC for developmental toxicity is 150 mg/m³ (whole-body exposure, LOAEC 1000 mg/m³, corresponding to a total dose by licking the fur of 410–606 mg/kg body weight and day, calculated on the basis of the amount of ethylene glycol determined in the fur at 2500 mg/m³; Bushy Run Research Center 1985) and 1000 mg/m³ (nose-only exposure, LOAEC 2500 mg/m³). For the mouse, there is a LOAEL of 750 mg/kg body weight and day, the lowest dose tested, after gavage administration. After dermal application (occlusive), a NOAEL for developmental toxicity of 1775 mg/kg body weight and day was derived for the mouse. The study with nose-only exposure was conducted in order to limit oral and dermal uptake as far as possible (Henschler 1992). Taking into account the additional oral uptake after whole-body inhalation exposure, the observed effects and the NOAEC/LOAEC agree well with those following oral administration.

5.6 Genotoxicity

5.6.1 In vitro

The details of the in vitro genotoxicity tests are listed in [Table 3](#).

Tab. 3 In vitro genotoxicity of (ethylenedioxy)dimethanol

End point	Test system	Concentration ^{a)}	Effective concentration ^{a)}	Cytotoxicity ^{a)}	Results		References
					–m. a.	+m. a.	
gene mutation	Salmonella typhimurium TA1535	1–333	–	333	–	–	ECHA 2022 (not apparent whether preincubation was performed)
	Salmonella typhimurium TA1537	1–333	–	–m. a.: 33 +m. a.: 333	–	–	
	Salmonella typhimurium TA98	1–333	33	–m. a.: 100 +m. a.: 333	–	+	
		1–333	33	–m. a.: 100 +m. a.: 333	–	(+)	
	Salmonella typhimurium TA100	1–333	33	333	–	(+)	
		1–333	100	333	–	(+)	
	Escherichia coli WP2 uvr A	0.5–333	–	333	–	–	
CA	V79 cells	5–20 µg/ml	–m. a.: 15 µg/ml +m. a.: 20 µg/ml	–m. a.: 15 µg/ml +m. a.: 20 µg/ml	+	+	ECHA 2022
gene mutation HPRT	V79 cells	3 hours incubation: –m. a.: 2–25 µg/ml +m. a.: 1–40 µg/ml	–m. a.: 20 µg/ml +m. a.: –	–m. a.: 15 µg/ml +m. a.: 40 µg/ml	+	–	ITEM 2002 a
gene mutation HPRT	V79 cells	6 hours incubation: –m. a.: 1–10 µg/ml +m. a.: 0.25–40 µg/ml	–m. a.: – +m. a.: 5 µg/ml	–m. a.: 7.5 µg/ml +m. a.: 20 µg/ml	–	+ ^{b)}	ITEM 2002 a

^{a)} unless otherwise specified, details cited refer to µg/plate

^{b)} concentration-dependency not given

(+) less than double the control value; CA: chromosomal aberrations; m. a.: metabolic activation

In a bacterial reverse mutation assay according to OECD Test Guideline 471, (ethylenedioxy)dimethanol, dissolved in dimethyl sulfoxide, was not mutagenic in the *Salmonella* strains TA1535 and TA1537 and in *Escherichia coli* WP2 uvr A without and with the addition of metabolic activation systems up to 333 µg/plate. Under the same conditions, an increased number of revertants occurred in the strains TA98 and TA100 under non-cytotoxic concentrations after metabolic activation at and above 33 µg/plate (TA98) and at 100 µg/plate (TA100), which was less than twofold in TA100, however. Although this could not be confirmed in a second test, a possible mutagenic potential cannot be entirely excluded (ECHA 2022). The exact numbers of revertants are not given. Therefore, no statement can be made on the concentration-dependency of the mutagenic effect in the *Salmonella* strain TA98.

A chromosomal aberration test in V79 cells according to OECD Test Guideline 473, with and without the addition of a metabolic activation system, was performed with (ethylenedioxy)dimethanol concentrations of 5–20 µg/ml. Incubation was carried out for 3 hours. A statistically significant and dose-dependent increase in chromosomal aberrations occurred without metabolic activation at 15 and 20 µg/ml and at 20 µg/ml with metabolic activation. Cytotoxicity was observed also at 15 and 20 µg/ml in the presence and absence of metabolic activation (no other details; ECHA 2022). (Ethylenedioxy)dimethanol is therefore clastogenic only at cytotoxic concentrations.

In an HPRT gene mutation test according to OECD Guideline 476 in V79 cells, (ethylenedioxy)dimethanol was investigated at concentrations of 0.25–40 µg/ml with and without metabolic activation after 3 or 6 hours of exposure. Mutagenic effects were observed after 3 hours without metabolic activation only near cytotoxic concentrations. With metabolic activation, a mutagenic effect was observed even below cytotoxic concentrations after incubation for 6 hours, but this was not concentration-dependent. The substance contained 46.8% readily cleavable formaldehyde, no impurities, and as a 1% aqueous solution had a pH of 7.5. Ethyl methanesulfonate was used as a positive control in the experiments without metabolic activation and dimethylbenz[a]anthracene was used as a positive control in the experiments with metabolic activation (ITEM 2002 a). The positive findings with metabolic activation are highly variable, for which reason they cannot be interpreted with any clarity.

5.6.2 In vivo

In a micronucleus test according to OECD Test Guideline 474, single gavage doses of (ethylenedioxy)dimethanol of 0, 30, 100 or 300 mg/kg body weight in corn oil were administered to groups of 5 male and 5 female NMRI mice. The induction of micronuclei in the polychromatic erythrocytes (PCE) in the bone marrow was investigated after 24 hours. In the high dose group, an additional examination was carried out after 48 hours. An increase in the frequency of micronuclei was not observed. Treatment with (ethylenedioxy)dimethanol did not cause a statistically significant change in the PCE/NCE (normochromatic erythrocyte) ratio compared with that in the vehicle controls. The ratios were within the range of the historical vehicle control data from the same laboratory. The substance contained 46.8% readily cleavable formaldehyde, no impurities, and as a 1% aqueous solution had a pH of 7.5. Cyclophosphamide was administered as a positive control (Section 5.2.2; LPT 2002 b). From the data obtained, it cannot be concluded whether the bone marrow was reached or not.

5.7 Carcinogenicity

There are no data available for carcinogenicity. However, since (ethylenedioxy)dimethanol in aqueous solution spontaneously releases formaldehyde, which was found to be a local carcinogen in rodents (Greim 2002), (ethylenedioxy)dimethanol can likewise be expected to be locally carcinogenic.

Ethylene glycol, the other product of hydrolysis, did not cause increased tumour incidences in rats and mice in 2-year feeding studies (Henschler 1992).

6 Manifesto (MAK value/classification)

The critical effect is expected nasal carcinogenicity due to the hydrolysis product formaldehyde. In addition, the strong irritant effect on the skin, the corrosive effect on the eye as well as the inflammatory reactions in the stomach and the skin sensitizing effect of formaldehyde must be regarded as critical effects. In the case of ethylene glycol, a further hydrolysis product, irritation is likewise the decisive effect.

MAK value. (Ethylenedioxy)dimethanol is highly irritating to the skin and corrosive to the eyes. These effects can assumedly be attributed to the release of formaldehyde.

At a pH of 7.0 and 20 °C, a 1% (ethylenedioxy)dimethanol solution has a hydrolysis half-life of 6 minutes. It can therefore be assumed that (ethylenedioxy)dimethanol hydrolyses to formaldehyde on reaching the respiratory tract. The hydrolysis product ethylene glycol is not carcinogenic and has a MAK value of 10 ml/m³, which was derived from the irritating effect on the mucous membranes of test persons (Henschler 1992).

The calculated vapour pressure of (ethylenedioxy)dimethanol is 13.2 hPa at 20 °C. (Ethylenedioxy)dimethanol, like formaldehyde (about 5180 hPa at 25 °C, ECHA 2023), is thus present in vapour form, and no additional effects from aerosols are to be expected. On the basis of the MAK value for formaldehyde, it is thus possible to convert the formaldehyde released from (ethylenedioxy)dimethanol and derive a limit value for (ethylenedioxy)dimethanol in air.

Based on the worst-case, the complete release of two formaldehyde molecules per molecule of (ethylenedioxy)dimethanol in the respiratory tract, a MAK value of 0.15 ml/m³ or 0.76 mg/m³ has been derived for (ethylenedioxy)dimethanol in analogy to the MAK value of formaldehyde of 0.3 ml/m³ or 0.37 mg/m³.

When used in diluted aqueous solutions, complete hydrolysis is to be expected and therefore the MAK value for formaldehyde (Greim 2002; Hartwig 2014) should be observed.

Peak limitation. Peak Limitation Category I has been assigned with an excursion factor of 2 in analogy to the classifications made for formaldehyde.

Carcinogenicity. In bacterial mutagenicity tests, (ethylenedioxy)dimethanol was mutagenic after metabolic activation. With beginning cytotoxicity, (ethylenedioxy)dimethanol was found to be clastogenic in a chromosomal aberration test. It can be assumed that the positive results in the in vitro genotoxicity tests with (ethylenedioxy)dimethanol are due to the release of formaldehyde.

The further hydrolysis product ethylene glycol is not genotoxic and not carcinogenic (Henschler 1992).

The local carcinogenicity of the hydrolysis product formaldehyde has been extensively documented (Greim 2002). Formaldehyde has been classified in Carcinogen Category 4, as it has a carcinogenic effect at concentrations that exceed the detoxification capacity of the nasal tissue.

Studies of the carcinogenicity and effects in the nose after inhalation are not available for (ethylenedioxy)dimethanol. Due to the hydrolytic release of formaldehyde in the nasal tissue, the carcinogenic effects of formaldehyde are likewise to be expected after exposure to (ethylenedioxy)dimethanol.

In analogy to formaldehyde, (ethylenedioxy)dimethanol has been assigned to Carcinogen Category 4.

Prenatal toxicity. There are no data available for the prenatal toxicity of (ethylenedioxy)dimethanol.

Formaldehyde, with a MAK value of 0.3 ml/m³ (0.37 mg/m³), is assigned to Pregnancy Risk Group C. With a MAK value of 10 ml/m³ (26 mg/m³), ethylene glycol is classified in Pregnancy Risk Group C.

Formaldehyde has not been shown to be teratogenic in rats, mice, dogs and golden hamsters. The lowest concentration in rats to cause effects after inhalation exposure was 20 ml/m³, which resulted in reduced foetal weights; the NOAEC was 10 ml/m³ without maternal toxicity (Henschler 1991). Ethylene glycol was found to be teratogenic in prenatal developmental toxicity studies in rats and mice; it induces external, skeletal and visceral malformations. The NOAEL for developmental toxicity in rats was 200 mg/kg body weight/day after oral administration (diet, LOAEL 1000 mg/kg body weight/day) and the NOAEC was 150 mg/m³ (whole-body exposure, total dose by licking the fur of 278–403 mg/kg body weight/day) (Bushy Run Research Center 1985). In mice, the NOAEC for developmental toxicity was 1000 mg/m³ (390 ml/m³, nose-only exposure, LOAEL 2500 mg/m³) (Henschler 1992).

Taking into account the release of two molecules of formaldehyde and one molecule of ethylene glycol from one molecule of (ethylenedioxy)dimethanol, the margin between the MAK value of 0.15 ml/m³ (taking the increased respiratory volume into consideration) and the NOAEC for developmental toxicity of formaldehyde (10 ml/m³, 17-fold) and ethylene glycol (390 ml/m³, 1300-fold) is sufficiently large.

Therefore, (ethylenedioxy)dimethanol has been assigned to Pregnancy Risk Group C.

Germ cell mutagenicity. A micronucleus test in rats yielded a negative result; the accessibility of germ cells could not be demonstrated in this study. (Ethylenedioxy)dimethanol was mutagenic in the Salmonella strain TA98 after metabolic activation. With beginning cytotoxicity, (ethylenedioxy)dimethanol was found to have clastogenic effects in a chromosomal aberration test. It can be assumed that the positive in vitro results of (ethylenedioxy)dimethanol are due to the release of formaldehyde.

The hydrolysis product formaldehyde is classified in Category 5 for germ cell mutagens. The inhalation of formaldehyde at the MAK value of 0.3 ml/m³ can be expected to make only a very small contribution to the genetic risk for humans

(Greim 2002). By analogy, this applies also to (ethylenedioxy)dimethanol. The substance has therefore been classified in Category 5 for germ cell mutagens.

Absorption through the skin. No experimental studies are available for the dermal absorption of (ethylenedioxy)dimethanol. Estimates based on model calculations suggest that for a non-irritating concentration of 5% the amount absorbed within 1 hour is 10–40 mg. Assuming rapid complete hydrolysis, this results in the release of 5–20 mg formaldehyde. The physiological formaldehyde level in human blood is about 2–3 mg/l or 10–15 mg in 5 l of blood (AGS 2022; Heck et al. 1985). Since the half-life of formaldehyde in plasma of 1–1.5 minutes is very short (Kaden et al. 2010), the dermal uptake of 20 mg (ethylenedioxy)dimethanol per hour leads to an increase in the formaldehyde level in the blood of 0.9 mg at steady state. This quantity results from the assumption that a constant 0.33 mg formaldehyde per minute (20 mg/60 minutes) is absorbed and then degraded with a half-life of 1.5 minutes with first-order kinetics. The degradation that takes place during absorption is therefore not taken into consideration. This additional uptake is within the range of physiological variation. (Ethylenedioxy)dimethanol has therefore not been designated with an “H” (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. Despite its various applications, there is no evidence that (ethylenedioxy)dimethanol itself has skin-sensitizing potential in humans. Animal studies in guinea pigs yielded heterogeneous results and, in one case, a positive result. (Ethylenedioxy)dimethanol has therefore not been designated with “Sh” (for substances which cause sensitization of the skin). No data are available for sensitization of the airways. Therefore, the substance has not been designated with “Sa” (for substances which cause sensitization of the airways).

Notes

Competing interests

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

The views expressed in these publications are those of the individual authors acting in their personal capacity as experts and do not represent the positions of their respective institutions or employers.

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