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4-Methyl-1,3-dioxolan-2-one

MAK Value Documentation – Translation of the German version from 2019

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Keywords

4-methyl-1,3-dioxolan-2-one; eye irritation; developmental toxicity; toxicity; maximum workplace concentration; MAK value

Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has evaluated 4-methyl-1,3-dioxolan-2-one [108-32-7; 51260-39-0; 16606-55-6] considering all toxicological endpoints. Available publications and unpublished study reports are described in detail.

The critical effect of 4-methyl-1,3-dioxolan-2-one is eye irritation. Rats did not show systemic effects in a 13-week inhalation study with whole-body exposure to aerosols of 4-methyl-1,3-dioxolan-2-one up to the highest concentration tested of 1000 mg/m^3. At 100 mg/m^3, swollen periocular tissue is observed in male animals. This finding is substantiated by the results of the acute eye irritation studies. Due to the weak effects, a NAEC (no adverse effect concentration) of 50 mg/m^3 (12 ml/m^3) is extrapolated. At this concentration, the substance can occur as a vapour; the maximum concentration at the workplace (MAK value) is therefore set in ml/m^3. By applying the usual extrapolation steps, a MAK value of 2 ml/m^3 is derived.

Since the critical effect of 4-methyl-1,3-dioxolan-2-one is local, Peak Limitation Category I is designated. An excursion factor of 1 is set as the critical effect concentration is twice as high as the extrapolated NAEC.

There is an adequate margin between the NOAEC for developmental toxicity and the MAK value. Therefore, damage to the embryo or foetus is unlikely when the MAK value is not exceeded and 4-methyl-1,3-dioxolan-2-one is assigned to Pregnancy Risk Group C.

4-Methyl-1,3-dioxolan-2-one is not genotoxic and the local tumour incidence was not increased in a chronic dermal study in male mice.

Skin contact is not expected to contribute significantly to systemic toxicity. Limited data show no sensitization.

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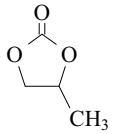
MAK value (2018)	**2 ml/m³ (ppm) ≙ 8.5 mg/m³**
Peak limitation (2018)	**Category I, excursion factor 1**
Absorption through the skin	–
Sensitization	–
Carcinogenicity	–
Prenatal toxicity (2018)	**Pregnancy Risk Group C**
Germ cell mutagenicity	–
BAT value	–
Synonyms	1-methylethylene carbonate 1,2-propanediol carbonate 1,2-propylene carbonate propylene carbonate cyclic 1,2-propylene carbonate
Chemical name (IUPAC name)	(R,S)-4-methyl-1,3-dioxolan-2-one
CAS number	racemate: 108-32-7 enantiomers: (S)-4-methyl-1,3-dioxolan-2-one: 51260-39-0 (R)-4-methyl-1,3-dioxolan-2-one: 16606-55-6
Structural formula	
Molecular formula	$C_4H_6O_3$
Molar mass	102.09 g/mol
Melting point	−48.8 to −49.5 °C (ECHA 2017)
Boiling point at 1013 hPa	241.8 to 243 °C (ECHA 2017)
Density at 20 °C	1.2 to 1.21 g/cm³ (ECHA 2017)
Vapour pressure at 20 °C	0.04 hPa (ECHA 2017)
log K_{OW} at 25 °C	0.48 (ECHA 2017)
Solubility in water	175 g/l at 25 °C; 240 g/l at 20 °C (ECHA 2017)
pKa value at 20 °C	3.92 (ECHA 2017)
1 ml/m³ (ppm) ≙ 4.236 mg/m³	**1 mg/m³ ≙ 0.236 ml/m³ (ppm)**
Stability	hydrolyses in phosphate buffer at 37 °C with a half-life of 47.2 hours (ECHA 2017)
Production	from propylene oxide and CO_2 (NCBI 2017)

Purity	no data (ECHA 2017)
Impurities	no data (ECHA 2017)
Uses	in lubricants and greases, coating products, plant protection products, polymers, detergents and cleaning products, cosmetics and personal care products (ECHA 2017) There are no data available for application concentrations

Note: 4-Methyl-1,3-dioxolan-2-one can occur simultaneously as vapour and aerosol.

The documentation is based mainly on the publicly available registration data under REACH (ECHA 2017).

4-Methyl-1,3-dioxolan-2-one has a stereogenic centre. Consequently, there are two stereoisomers, (R)-4-methyl-1,3-dioxolan-2-one and (S)-4-methyl-1,3-dioxolan-2-one. However, 4-methyl-1,3-dioxolan-2-one is usually used as a racemate. The studies cited here were conducted with the racemate (108-32-7).

1 Toxic Effects and Mode of Action

Single applications of 4-methyl-1,3-dioxolan-2-one are only slightly irritating to the skin and moderately irritating to the eyes of rabbits.

It may be assumed that 4-methyl-1,3-dioxolan-2-one, like ethylene carbonate (1,3-dioxolan-2-one) and other alkyl carbonates, hydrolyses very rapidly both in vitro and in vivo to CO_2 and the corresponding alcohol, in this case propylene glycol.

The systemic toxicity after inhalation and oral or dermal absorption is low. In a 13-week inhalation study with whole-body exposure of male and female F344 rats to 4-methyl-1,3-dioxolan-2-one aerosol, no systemic effects occurred up to the highest concentration tested of 1000 mg/m^3. At concentrations of 100 mg/m^3 and above, the periocular tissue was swollen. Systemic effects in the form of statistically significant changes in clinico-chemical and haematological parameters were observed in male and female Sprague Dawley rats only at the high dose level of 5000 mg/kg body weight and day after oral administration for 90 days. In addition, the relative testis weights were increased at this dose.

There is no evidence of skin or respiratory sensitization caused by 4-methyl-1,3-dioxolan-2-one.

Developmental toxicity studies in rats with gavage administration did not reveal substance-related embryotoxic or teratogenic effects up to 5000 mg/kg body weight and day; maternal toxicity was observed in the form of reduced body weight gains and mortality.

4-Methyl-1,3-dioxolan-2-one is not genotoxic and did not induce local tumours after the application of 50 µl to the skin of male C3H/HeJ mice twice weekly for 2 years.

2 Mechanism of Action

There are no specific studies available.

The critical effect is the swelling of periocular tissue after inhalation. This reaction was observed also in the eye irritation test in the form of thickened eyelids and eyelid oedema. The effect does not occur after oral application, so it can be assumed to be local and not systemic. The mechanism of action of 4-methyl-1,3-dioxolan-2-one which could be responsible for this effect is unknown.

3 Toxicokinetics and Metabolism

There are no in vivo studies available that show whether 4-methyl-1,3-dioxolan-2-one is absorbed in any significant amount. In 13-week studies in rats, no systemic toxicity was observed up to the highest concentration tested of 1000 mg/m^3 and only low systemic toxicity was found after oral administration of 5000 mg/kg body weight and day. Dermal exposure of rabbits up to 1000 mg/kg body weight and day for 2 weeks likewise did not lead to systemic effects.

In an in vitro study with human skin, a penetration rate of 0.7 g/(m^2 × h) (70 µg/cm^2 and hour) was determined for undiluted 4-methyl-1,3-dioxolan-2-one (Ursin et al. 1995). Assuming the exposure of 2000 cm^2 of skin for 1 hour, this penetration rate would correspond to the absorption of 140 mg.

A study from 2015 investigated the in vitro degradation of 4-methyl-1,3-dioxolan-2-one in the blood of Wistar rats. 1,3-Dioxolan-2-one was used in parallel as a reference substance. Both substances hydrolysed rapidly in the blood. The maximum degradation rate was 0.68 µmol/(ml × min) for 4-methyl-1,3-dioxolan-2-one and 0.14 µmol/(ml × min) for 1,3-dioxolan-2-one. Complete hydrolysis of 4-methyl-1,3-dioxolan-2-one to propylene glycol was attained within 5 minutes and of 1,3-dioxolan-2-one to ethylene glycol within 30 minutes. The half-lives were 0.7 and 3.5 minutes, respectively. Since 4-methyl-1,3-dioxolan-2-one was largely stable in the phosphate buffer for 2 hours and only 30% had hydrolysed after 24 hours, it can be assumed that hydrolysis of the substance is catalysed enzymatically in the blood (ECHA 2017).

Since 4-methyl-1,3-dioxolan-2-one hydrolyses faster in the blood of rats than 1,3-dioxolan-2-one, which has been demonstrated to hydrolyse in vivo in rats, it can be assumed that 4-methyl-1,3-dioxolan-2-one also hydrolyses in vivo to CO_2 and propylene glycol (ECHA 2017).

4 Effects in Humans

Only data for skin effects and sensitization are available.

4.1 Local effects on skin and mucous membranes

In a patch test, 100 µl undiluted 4-methyl-1,3-dioxolan-2-one was applied daily to the scarified skin of 5 male and 5 female volunteers for 3 days. The mean irritation scores at the 72-hour reading were between 1.5 and 2.4 (on a scale with a maximum of 4.0) in the subjects, which was regarded as moderately irritating (no other details; ECHA 2017).

Also, 0.2 ml of a 20% 4-methyl-1,3-dioxolan-2-one solution in ethanol was applied five days per week, 21 times to the skin of volunteers (n = 26). Prior to application, the solution was placed on the patches for 30 minutes so that volatile material could evaporate. There were skin reactions in 12 of the volunteers, 11 of them produced minimal erythema, one of them bright red erythema; hyperpigmentation and dryness were observed at the affected areas of skin in some of the volunteers (no other details; ECHA 2017).

In clinical studies with 50 volunteers, a 5% or 10% solution of 4-methyl-1,3-dioxolan-2-one (solvents not specified) did not cause irritation in occlusive patch tests (no other details; ECHA 2017).

4.2 Allergenic effects

4.2.1 Sensitizing effects on the skin

There are no clinical findings available.

Repeated insult patch tests with 15 applications of 5% or 10 % aqueous preparations of 4-methyl-1,3-dioxolan-2-one did not result in sensitization or irritant reactions in 50 volunteers (CIR 1987; ECHA 2017).

Other negative results in repeated insult patch tests with a deodorant stick containing 20% 4-methyl-1,3-dioxolan-2-one and with a total of 13 cosmetic products containing 0.54% to 3.5% 4-methyl-1,3-dioxolan-2-one, as well as studies of photocontact sensitization with the deodorant stick (CIR 1987; ECHA 2017) are not suitable for inclusion in the evaluation due to the very low substance concentrations in some cases and exposure to undefined mixtures of substances.

4.2.2 Sensitizing effects on the airways

There are no data available.

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

Exposure of 6 rats to an atmosphere saturated with 4-methyl-1,3-dioxolan-2-one at 20 °C for 8 hours was not lethal to any of the animals within the 7-day recovery period. During the first days, a slight reduction in body weights was observed, followed by body weight gains thereafter (no other details; ECB 2000; ECHA 2017).

5.1.2 Oral administration

A study from 1985 yielded an LD_{50} of more than 5000 mg/kg body weight. Groups of 5 male and 5 female Sprague Dawley rats were given an oral dose of 4-methyl-1,3-dioxolan-2-one of 5000 mg/kg body weight, and the animals were observed for 14 days. The dose was not lethal to any of the animals. Salivation was observed immediately after administration of the substance. The gross-pathological examination at necropsy did not reveal any unusual findings (ECHA 2017).

In an earlier study from 1960, male and female Schmitt Fischer and Hannover rats were given 4-methyl-1,3-dioxolan-2-one doses of 16, 25 or 29.1 ml/kg body weight, and the animals were observed for one week. Ten animals were used for the low and high dose groups, and 4 animals for the medium dose group. None of the animals in the low or medium dose group died, the high dose was lethal to all 10 animals within 48 hours. Gross-pathological findings were seen only in the latter animals. They included red-spotted lungs, anaemic liver and reddened small intestine, partly filled with a reddish-black content. Clinical signs in the two low dose groups comprised unsteady or staggering gait, prone position and inactivity on the first day and ruffled fur on the following day (ECHA 2017). The LD_{50} is therefore between 25 and 29 ml/kg body weight (about 30 000 to 35 000 mg/kg body weight).

In addition, there are other studies mentioned in secondary citations in the registration dossier which report an LD_{50} of 29 100 mg/kg body weight in Carworth Wistar rats (no other details) and of 20 700 mg/kg body weight in male albino mice (no other details) (ECHA 2017).

5.1.3 Dermal application

In a limit test according to OECD Test Guideline 402 in 5 male and 5 female New Zealand White rabbits, occlusive dermal exposure to 2000 mg/kg body weight for 24 hours was not lethal to any of the animals. The recovery period was 14 days. All animals had slight erythema at the application site 2 and 4 hours and 2 days after the exposure period. After 3 days the effects had regressed. Gross-pathological examination did not reveal any unusual findings (ECHA 2017).

In another limit test carried out according to OECD Test Guideline 402 in 5 male and 5 female New Zealand White rabbits, the occlusive dermal exposure to 3000 mg/kg body weight for 24 hours was not lethal to any of the animals.

The recovery period was 14 days. The gross-pathological examination at necropsy did not reveal any unusual findings (ECHA 2017). Skin effects were not reported.

The occlusive exposure of 4 male New Zealand White rabbits to 20 ml/kg body weight for 24 hours was not lethal within the 14-day recovery period (ECHA 2017). The LD_{50} is therefore greater than 24 000 mg/kg body weight. Skin effects were likewise not reported.

In a study reported only in summary form, the abraded skin of 5 male and 5 female albino rabbits was exposed occlusively to 2 mg/kg body weight for 24 hours and observed for 14 days. The exposure was not lethal to any of the animals. Erythema was found in all animals at the exposure site on day 2, which was reversible on day 3. The gross-pathological examination at necropsy did not reveal any unusual findings (ECHA 2017).

5.1.4 Subcutaneous and intraperitoneal injection

Ten male dd mice and 10 Wistar rats per dose group were treated subcutaneously with 4-methyl-1,3-dioxolan-2-one. The LD_{50} was 15.8 ml/kg body weight for mice and 11.1 ml/kg body weight for rats (ECHA 2017), corresponding to about 19 000 and 13 000 mg/kg body weight, respectively.

The intraperitoneal LD_{50} in Tübingen mice was reported to be 1.8 ml/kg body weight (ECHA 2017), corresponding to about 2100 mg/kg body weight.

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

In a well-documented 11-day GLP study from 1989, groups of 5 male and 5 female F344/CDF rats were exposed whole-body for 6 hours daily, on 5 days a week (a total of 9 exposures) to 4-methyl-1,3-dioxolan-2-one aerosol (purity 99%) concentrations of 0, 1000, 2500 or 5000 mg/m^3 (analysed concentrations: 0, 996, 2489 or 5092 mg/m^3; mass median aerodynamic diameter (MMAD) 7.20, 8.19 and 9.20 µm; geometric standard deviation (GSD) 3.27, 3.44 and 3.47, respectively). All animals in the high concentration group had an unkempt appearance at least once during the study due to a lack of grooming or the inability to groom the substance residues from their fur. This effect was also observed in all females and 3 males in the middle concentration group. At the concentration of 5000 mg/m^3, also irritation of the eyes and upper respiratory tract occurred (reddened eyes, swollen periocular tissue, perinasal encrustation). Furthermore, urogenital wetness, ataxia and emaciation were observed. At the concentration of 2500 mg/m^3 reddened eyes, irritation of the upper respiratory tract and urogenital wetness were found only in the female animals. At the low concentration, the only finding was urogenital wetness in females. The clinical observations, apart from ocular irritation, were transient and no longer present in the second week of exposure. The body weight gains of all exposed animals were significantly decreased; at the end of the study they amounted to only 81% and 64% of those in the control animals in the male and female animals of the 1000 mg/m^3 group, respectively. Organ weights were determined only for the liver, lungs, kidneys and testes. The absolute and relative liver weights and the relative kidney weights were significantly increased in the female animals of the high concentration group compared with the values in the controls. The increase in relative kidney weights was probably due to the parallel decrease in body weights. The fact that the absolute liver weight of males exposed to 5000 mg/m^3 was the same as that of the controls, despite the reduced body weight gains of these animals, may indicate an exposure-related response. A gross-pathological examination was performed on the liver, kidneys, stomach, lungs, nose, larynx, trachea, spleen, ovaries, testes, brain, adrenal glands, heart, thymus and eyes and did not reveal any substance-related findings in the male animals. In the female animals, slight swelling of the eyelids and periocular tissue occurred. A histopathological examination was performed only on the liver, kidneys, lungs, testes and on organs with gross-pathological findings. Histopathologically, the swollen eyelids were found to be due to mild subcutaneous oedema. At the concentration of 5000 mg/m^3, squamous metaplasia of the maxillary or nasal turbinates in 2 of the 5 female animals, and respiratory epithelial necrosis in 1 female animal were found. In 1 male

animal, bilateral keratitis with unilateral superficial corneal ulcer was observed in the eye, and squamous metaplasia of the arytenoid cartilages in the larynx. Likewise, in 1 female and 1 male control animal, squamous metaplasia of the maxillary or nasal turbinates was observed (Texaco Inc 1989 a). The LOAEC (lowest observed adverse effect concentration) was 1000 mg/m³ based on the reduced body weight gains in male and female animals. At concentrations of 2500 mg/m³ and above, reddened eyes and irritation of the upper respiratory tract were found in the female animals.

A well-documented 13-week inhalation study from 1991 is available, in which 15 male and 15 female F344 rats per concentration group were exposed whole-body to 4-methyl-1,3-dioxolan-2-one aerosol (purity 99.9%). Ten additional animals per sex and concentration were included for acute neurotoxicity tests. The animals were exposed for 6 hours daily, on 5 days a week, for 93 days to 0, 100, 500 or 1000 mg/m³ (analysed concentrations: 0, 102, 500, 1010 mg/m³; MMAD 5.32, 4.62 and 4.72 µm; GSD 2.74, 2.52 and 2.32, respectively). No systemic effects were observed up to concentrations of 1000 mg/m³. The scope of the study included body weights, food and water intake, behaviour, haematology, clinical chemistry, urinalysis, organ weights, gross-pathology, histopathology and a neurotoxicity test (functional observation battery). The NOAEC (no observed adverse effect concentration) for systemic effects in this study is considered to be 1000 mg/m³ because of the longer exposure duration and the higher number of animals compared with in the 11-day study. Clinical observation revealed swollen periocular tissue in 2 males of the 100 mg/m³ group, in 3 of the 500 mg/m³ group and in 4 of the 1000 mg/m³ group. This effect was likewise observed in the female animals; however, it occurred with high frequency also in the control group (see Table 1), so that the significance of this observation for the exposed animals is questionable (Texaco Inc 1991).

Swelling of the periocular tissue (thickening of the eyelids, eyelid oedema) was found also in the eye irritation studies. This effect must therefore be regarded as substance-related, although it was observed also in many female control animals. However, there is no explanation for the difference between the sexes. Since female control animals were affected, only the results in the male animals are included in the evaluation. The LOAEC of this study is therefore 100 mg/m³.

Tab. 1 Number of affected animals with eye/nose findings after whole-body exposure of rats to 4-methyl-1,3-dioxolan-2-one aerosol for 13 weeks (Texaco Inc 1991)

Findings	Sex	Concentration (mg/m³)			
		0	100	500	1000
swollen periocular tissue in one of the eyes (both eyes affected)	♂	0	2	3	4 (1)
	♀	6 (2)	4 (2)	9 (1)	7 (4)
periocular incrustation in one eye	♂	0	1	1	0
	♀	1	1	1	0
perinasal incrustation	♂	0	3	1	0
	♀	2	1	3	6

In a 21-day inhalation study with 4-methyl-1,3-dioxolan-2-one aerosol, reported only as a secondary citation, rats, guinea pigs and dogs (number, sex and strain not specified) were exposed to 2800 mg/m³ for 6 hours daily, on 5 days a week. The rats developed rhinitis and diarrhoea. No other effects were reported (no other details; ECHA 2017).

5.2.2 Oral administration

In a 28-day range-finding study from 1988, groups of 5 male and 5 female Sprague Dawley rats were given gavage doses of the undiluted substance of 0, 500, 1000, 2000, 3000 or 5000 mg/kg body weight and day on 5 days a week. Food intake, body weights and body weight gains were not affected. Immediately after the administration, salivation was seen in some animals at dose levels of 500 mg/kg body weight and day and above. One male animal of the high dose group exhibited alopecia and scab formation from day 11 of the study. One female animal of the high dose group displayed decreased activity and lacrimation on day 9, another decreased activity on days 14 and 17. The liver, kidneys, adrenal glands, ovaries, testes, brain and heart were weighed and preserved for possible histopathological evaluation. Additionally, lungs and organs with gross-pathological findings were subjected to histopathological examination. A

statistically significant, dose-dependent increase in absolute and relative ovary weights was observed at 3000 and 5000 mg/kg body weight and day. At 5000 mg/kg body weight and day the relative testis weights were significantly increased (ECHA 2017). The observed salivation is probably due to the gavage administration, so that the NOAEL (no observed adverse effect level) is 2000 mg/kg body weight and day. At 3000 mg/kg body weight and day and above, the absolute and relative ovary weights were increased. However, the study did not include haematological and clinico-chemical parameters or urinalysis, and histopathological investigation was not done.

In a well-documented and valid 90-day study from 1989, 15 male and 15 female Sprague Dawley rats per dose group were given gavage doses of 4-methyl-1,3-dioxolan-2-one of 0, 1000, 3000 or 5000 mg/kg body weight and day on 5 days a week. Dose selection was based on the previously reported 28-day study. Both in the control group and in the treated animals, alopecia and scab formation occurred. Five animals in the high dose group died following administration of the test substance; mortality was attributed to improper gavage administration and was not considered substance-related. Clinical signs in the test substance groups included immediate post-dose salivation, rales in the lungs, abnormal gait and stance, decreased activity and dyspnoea. The body weight gains in the high dose male animals were significantly reduced on day 28 and significantly increased during the recovery period on days 98 and 112. There was a statistically significant reduction in the body weights of the high dose male animals on day 28 of the study and from day 35 to day 84. The food intake of these animals was significantly reduced on day 7, from days 28 to 42 and from days 56 to 84. In the female animals of this dose group, body weight gains were significantly increased on day 14. The effects in the high dose group were regarded by the authors not to be substance-related. There were no substance-related effects on absolute organ weights. In male animals of the middle and high dose groups the phosphate level in blood was increased, in those of the high dose group also the chloride level, while the mean corpuscular volume (MCV) was decreased. Increased sodium levels were observed in the female animals of the high dose group. Ophthalmological and histopathological examinations did not reveal any substance-related findings (Texaco Inc 1989 b). Because of the statistically significant changes in clinico-chemical and haematological parameters in male and female animals of this dose group, the NOAEL is 3000 mg/kg body weight and day.

5.2.3 Dermal application

The dermal exposure of rabbits (number, sex, strain and mode of application not specified) to a 4-methyl-1,3-dioxolan-2-one dose of 1000 mg/kg body weight and day for 2 weeks did not result in pharmacotoxic or pathological effects (no other details; ECHA 2017).

5.2.4 Subcutaneous injection

Subcutaneous injections of 0%, 3.5%, 10.5% or 17.5% 4-methyl-1,3-dioxolan-2-one in physiological saline (application volume not specified) given daily to male Wistar rats (number not specified) for 1 month did not lead to any effects on food and water intake, body weights or body weight gains. Haematology, clinical chemistry, urinalysis, behavioural tests, organ weights and gross-pathological examination did not reveal any substance-related findings. Histopathological examination of the skin revealed hyperkeratosis in both high concentration groups and an increase in the number of basal cells at the treatment sites (ECHA 2017).

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

The irritating effects of 4-methyl-1,3-dioxolan-2-one on the skin were investigated in a study from 1985 carried out with 6 New Zealand White rabbits. An amount of 0.5 ml of the test substance was applied to the intact or abraded skin of the animals and occlusive exposure was carried out for 24 hours. After 24 and 72 hours, the skin was examined and evaluated according to the Draize scoring system. The Primary Dermal Irritation Index (PDII) was 0.2 after 24 and

72 hours. As a result, 4-methyl-1,3-dioxolan-2-one was assessed as minimally irritating. All effects were reversible after 72 hours (ECHA 2017). The individual irritation scores were not given.

In a study from 1960, 0.5 g of 4-methyl-1,3-dioxolan-2-one was applied occlusively for 20 hours to the intact or abraded skin of 4 Vienna White rabbits. Thereafter, the skin was washed. The skin findings were recorded after 1 minute, after 5 and 15 minutes, after 20 hours and for up to 8 days and evaluated using the Draize scoring system. The mean scores for erythema and oedema after 24 and 72 hours were 0, so the substance was regarded as not irritating (ECHA 2017).

In a study in 5 albino rabbits reported only in an abstract, 0.01 ml 4-methyl-1,3-dioxolan-2-one was found to be slightly irritating to the skin 24 hours after application (no information whether occlusive or non-occlusive exposure) (no other details; ECHA 2017).

In summary, 4-methyl-1,3-dioxolan-2-one is not or, at most, minimally irritating to the skin.

5.3.2 Eyes

In a study carried out according to OECD Test Guideline 405 from 2001, 0.1 ml 4-methyl-1,3-dioxolan-2-one (purity 100%) was applied to one eye of 3 New Zealand White rabbits, which were observed for 10 days. The corneal irritation scores were 0, 8.3 and 3.3 of a maximum of 80 after 1 hour, 1 day and 2 days, respectively. On the third day, the effects were completely reversible. For the iris, the irritation scores were 0 and 1.7 of a maximum of 10, respectively; on the second day, the findings were reversible. For the conjunctiva, the irritation scores were 13.3, 13.3, 10, 4.7, 3.3 and 1.0 of a maximum of 20 after 1 hour and 1, 2, 3, 4 and 7 days, respectively. The irritation was reversible within 10 days. Additional signs consisted of mucoid discharge, erythematous or thickened eyelids, haemorrhage of the nictitating membrane and dried secretion around the periorbital skin. The total irritation score on day 1 was 23.3 of a maximum of 110. Therefore, 4-methyl-1,3-dioxolan-2-one was regarded as moderately irritating (ECHA 2017).

In a second study from 2001 carried out according to OECD Test Guideline 405, 0.1 ml 4-methyl-1,3-dioxolan-2-one (purity 99.9%) was applied to one eye of 3 New Zealand White rabbits. The observation period was 7 days. Initially, a severe pain reaction was observed. The corneal irritation scores were 13.3, 16.7, 20, 20 and 20 of a maximum of 80 after 1 hour, 1, 2, 3 and 4 days, respectively. For the iris, the irritation scores were 0 of a maximum of 10 after 1 hour and 3.3 on days 1 to 4. For the conjunctiva, the irritation scores were 13.3, 14, 9.3, 6 and 5.3 of a maximum of 20 after 1 hour and 1, 2, 3 and 4 days, respectively. In addition, mucoid discharge, thickened, erythematous or convoluted eyelids, haemorrhage of the nictitating membrane and dried secretion around the periorbital skin and an irregular corneal surface were observed. All findings were reversible within 7 days. The total irritation score on day 1 was 34 of a maximum of 110. Therefore, 4-methyl-1,3-dioxolan-2-one was regarded as moderately irritating (ECHA 2017).

The irritating effects of 4-methyl-1,3-dioxolan-2-one on the eyes were investigated in a study from 1985 with 6 New Zealand White rabbits. An amount of 0.1 ml of the test substance was applied to one eye of each animal. The animals were observed for 7 days and evaluated according to the Draize scoring system. After 1 hour and 24, 48 and 72 hours, the irritation scores were 12.5, 9.8, 5.1 and 4.8 of a maximum of 110, respectively, which was evaluated as minimally irritating. After 7 days all effects were reversible (ECHA 2017).

In a study from 1972, 0.1 to 0.2 ml aqueous dilutions (10.5% or 17.5%) or undiluted 4-methyl-1,3-dioxolan-2-one were instilled into one eye of 3 rabbits per group. The procedure was repeated daily for 2 weeks. After 7 days, lacrimation was observed (no data at which concentration). The eyes became red and exhibited signs of inflammation (no other details; ECHA 2017).

In a study from 1960, one drop of 4-methyl-1,3-dioxolan-2-one (50 mm^3) was instilled into one eye of 3 Vienna White rabbits, and the animals were observed for 8 days. After 1 hour slight oedema and cloudiness appeared, after 24 hours slight cloudiness, which was not reversible after 8 days (no other details; ECHA 2017).

In another study available only in the form of an abstract, after the instillation of 0.5 ml 4-methyl-1,3-dioxolan-2-one into the conjunctival sac of rabbits, marked erythema of the conjunctiva, vascularization of the sclera and oedema

of the eyelids and nictitating membrane within 24 hours were reported. After 7 days, all effects were reversible (no other details; ECHA 2017).

In summary, 4-methyl-1,3-dioxolan-2-one is moderately irritating to the eyes.

5.4 Allergenic effects

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

In a range-finding study from 1990, 6 Sprague Dawley rats per group were given gavage doses of 4-methyl-1,3-dioxolan-2-one of 0, 3000, 4000 or 5000 mg/kg body weight and day from days 6 to 15 of gestation and the pups were delivered by caesarean section on day 20 of gestation. At 3000 mg/kg body weight and above, severe maternal toxicity occurred. The clinical signs observed were dyspnoea, abnormal gait and stance, post-dose salivation, decreased activity, ptosis, piloerection and prostration. Embryotoxic or teratogenic effects (malformations not further specified) were observed in 29 foetuses. The findings were not further characterized. Two of 68 foetuses in 1 of 5 litters were affected at 3000 mg/kg body weight, 18 of 89 foetuses in 2 of 6 litters at 4000 mg/kg body weight, and 9 of 50 foetuses in 3 of 4 litters at 5000 mg/kg body weight. Based on these results, dose levels of 0, 750, 1500 and 3000 mg/kg body weight and day were selected for the main study (ECHA 2017).

In a range-finding study from 1988, conducted under GLP conditions, groups of 6 Sprague Dawley rats were given gavage doses of 4-methyl-1,3-dioxolan-2-one of 0, 500, 1000, 2000, 3000 or 5000 mg/kg body weight and day from days 6 to 15 of gestation. Caesarean section and examination of the foetuses was carried out on day 20 of gestation. One animal in the 2000 mg/kg group exhibited post-dose salivation, ptosis, piloerection, decreased activity, dyspnoea, cyanosis and rales from gestation days 9 to 13. No other clinical signs were observed. One animal of the 2000 mg/kg group died on day 10 of gestation. Necropsy did not reveal any unusual findings. There were no significant differences in the number of implantation sites, corpora lutea, viable foetuses, early or late resorptions, or the number of pre and post-implantation losses in all treated animals. No gross structural malformations were found (ECHA 2017).

In the subsequent study carried out in 1988 according to OECD Test Guideline 414, 27 Sprague Dawley rats per dose group were given gavage doses of 0, 1000, 3000 or 5000 mg/kg body weight and day from gestation days 6 to 15. Caesarean section and examination of the foetuses were performed on day 20 of gestation. Maternal toxicity occurred in the form of mortality in the middle and high dose groups; the substance was lethal to 2 and 5 animals, respectively. In addition, food intake was reduced at 3000 mg/kg body weight and day, and body weight gains were reduced at 5000 mg/kg body weight and day. Salivation immediately after administration of the substance was observed in the majority of the animals in the middle and high dose groups. Further clinical signs in these animals included decreased activity, rales, abnormal gait and stance, dyspnoea, piloerection, flaccid body tone, poor grooming, nasal discharge, cyanosis and red discoloration around the mouth. No embryotoxic or teratogenic effects were observed up to 5000 mg/kg body weight and day. The NOAEL for maternal toxicity was 1000 mg/kg body weight and day (ECHA 2017). The NOAEL for developmental toxicity was 5000 mg/kg body weight and day, the highest dose tested.

5.6 Genotoxicity

5.6.1 In vitro

A valid mutagenicity test from 1985 carried out in the Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 with and without the addition of a metabolic activation system and 48-hour pre-incubation yielded negative results at concentrations of 50, 167, 500, 1667 or 5000 µg/plate. A range-finding study did not indicate cytotoxicity. The positive control substance showed that the test system was sensitive (ECHA 2017).

In an insufficiently described mutagenicity test in Salmonella typhimurium (data for cytotoxicity, and negative and positive controls are not given) with pre-incubation (duration not specified) from the 1980s, the Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 were incubated against 4-methyl-1,3-dioxolan-2-one at concentrations of 10 to 1000 µg/plate. The test result was negative with and without the addition of a metabolic activation system (no other details; ECHA 2017).

In a valid UDS test from 1985, 4-methyl-1,3-dioxolan-2-one concentrations of 0, 40, 133, 400, 1333 or 4000 µg/plate did not induce increased DNA repair in primary hepatocytes of male F344 rats. The hepatocytes were exposed to the test substance for 18 to 20 hours. A total of 60 cells per concentration were evaluated; cytotoxicity did not occur. The result with the positive control 2-acetylaminofluorene demonstrated that the test system was sensitive (ECHA 2017).

5.6.2 In vivo

A valid micronucleus test from 1986 was performed in 5 male and 5 female CD-1 mice with intraperitoneal administration of 4-methyl-1,3-dioxolan-2-one. The bone marrow of the femur was examined and samples were taken 30, 48 and 72 hours after treatment. A total of 1000 polychromatic erythrocytes (PCE) per animal were counted. The single dose of 1666 mg/kg body weight resulted in a statistically significant increase in micronuclei in the first test after 72 hours, which could not be confirmed in a second test using 10 male and 10 female CD-1 mice. The ratio between PCE and normochromatic erythrocytes was not affected. In the range-finding study with 500, 1000, 1666, 3000 and 5000 mg/kg body weight the two high doses were lethal, so that 1666 mg/kg body weight was chosen as the maximum tolerated dose. In the first test, 1666 mg/kg body weight resulted in abnormal gait and decreased body tone. In the second test, writhing immediately after dosing and decreased body tone were observed. The positive control, 0.5 mg triethylene melamine/kg body weight administered intraperitoneally, was functional. Due to the second negative result with a higher number of animals, the test was evaluated as negative (ECHA 2017).

5.7 Carcinogenicity

In a carcinogenicity study from 1990, carried out according to GLP, 50 µl 4-methyl-1,3-dioxolan-2-one was applied dermally to the skin of 50 male C3H/HeJ mice twice a week for 104 weeks. No mortality occurred. The body weights were reduced compared with those of the control animals. Histopathological examination of the skin did not reveal any substance-related findings. No skin tumours were observed at the treatment site (ECHA 2017).

6 Manifesto (MAK value/classification)

The critical effect is the eye irritation caused by 4-methyl-1,3-dioxolan-2-one.

MAK value. 4-Methyl-1,3-dioxolan-2-one is moderately irritating to the eyes of rabbits. The systemic toxicity after inhalation, oral or dermal exposure is low. In a 13-week whole-body inhalation study with 4-methyl-1,3-dioxolan-2-one aerosol in male and female F344 rats, no systemic effects occurred up to the highest concentration tested of 1000 mg/m^3. At concentrations of 100 mg/m^3 and above the periocular tissue of the male animals was swollen. This effect occurred also in the eye irritation studies, so that it is to be regarded as substance-related. Due to the weak dose–response

relationship in the male animals, the LOAEC of 100 mg/m³ (24 ml/m³) was extrapolated to a NAEC (no adverse effect concentration) of 50 mg/m³ (12 ml/m³).

The vapour saturation concentration is 167 mg/m³, which is why the MAK value is given in ml/m³. Assuming a NAEC of 12 ml/m³ (LOAEC of 24 ml/m³ / 2) and after extrapolating the data for an eye irritant from an animal experiment to humans (1:3) according to Brüning et al. (2014) and taking into account a possible increase in the effects over time (1:2), the MAK value is 2 ml/m³ (8.5 mg/m³).

Peak limitation. Due to its irritant effect, the substance is assigned to Peak Limitation Category I with an excursion factor of 1, since the LOAEC for eye irritation was used to obtain the NAEC via extrapolation with a factor of 2. With an excursion factor of 2 the concentration could again be within the range of the local effect.

Prenatal toxicity. Studies of prenatal developmental toxicity in rats with gavage administration did not reveal any substance-related embryotoxic or teratogenic effects at maternally toxic dose levels of up to 5000 mg/kg body weight and day. The NOAEL for developmental toxicity is 5000 mg/kg body weight and day, which is the highest dose tested. The following toxicokinetic data are taken into consideration for the extrapolation of the NOAEL of 5000 mg/kg body weight and day to a concentration in workplace air: the corresponding species-specific correction value (1:4) for the rat, the assumed oral absorption (100%), the body weight (70 kg) and respiratory volume (10 m³) of the person, and the assumed 100% absorption by inhalation. The concentration calculated from this is 8750 mg/m³, which corresponds to 2065 ml/m³. Since no developmental toxicity occurred and the margin to the MAK value of 2 ml/m³ is more than 1000-fold, 4-methyl-1,3-dioxolan-2-one has been assigned to Pregnancy Risk Group C.

Carcinogenicity. After dermal application of 50 µl 4-methyl-1,3-dioxolan-2-one twice a week for 2 years, no skin tumours were induced in male C3H/HeJ mice. Since 4-methyl-1,3-dioxolan-2-one is not genotoxic and, due to its structure, a carcinogenic potential is not to be expected, there is no reason to classify the substance in one of the categories for carcinogens.

Germ cell mutagenicity. 4-Methyl-1,3-dioxolan-2-one is not genotoxic. There is no reason to classify it in one of the categories for germ cell mutagens.

Absorption through the skin. In humans, dermal absorption of a maximum amount of 140 mg can be estimated from an in vitro study with human skin (Section 3) exposed to undiluted 4-methyl-1,3-dioxolan-2-one under standard conditions (2000 cm² skin surface, 1-hour exposure). The NOAEC for systemic effects in a subchronic inhalation study in rats was 1000 mg/m³. The following toxicokinetic data are taken into consideration for the extrapolation of this concentration (as the NOAEL for systemic effects) to humans: the respiratory volume over 8 hours (10 m³), the assumed 100% absorption by inhalation, the possible increase in effects over time (1:2), the extrapolation of data from animal experiments to humans (1:2) and the increased respiratory volume at the workplace (1:2). This results in a systemically tolerable amount of 1250 mg. This means that absorption through the skin is less than 25% of the systemically tolerable amount. The substance has therefore not been designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. There are no positive findings of sensitizing effects on the skin and airways. 4-Methyl-1,3-dioxolan-2-one has therefore not been designated with "Sh" or "Sa" (for substances which cause sensitization of the skin or airways).

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