

1-Butanethiol

MAK Value Documentation, supplement – Translation of the German version from 2019

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated the maximum concentration at the workplace (MAK value) of 1-butanethiol [109-79-5]. Available publications and unpublished study reports are described in detail. Additional data from a 90-day inhalation study in rats indicate that the critical effect is haematotoxicity. On the basis of the NOAEC of 9 ml/m³ and taking into account the increased respiratory volume at the workplace, the MAK value is increased to 1 ml/m³. Since a systemic effect is critical, Peak Limitation Category II with an excursion factor of 2 is assigned. The NOAEC for developmental toxicity in mice is 10 ml/m³ and the NOEC for rats is 152 ml/m³. After considering the increased respiratory volume at the workplace, the margin to the MAK value calculated based on the data from the rat is sufficiently large. In mice, the LOAEC for developmental toxicity is 68 ml/m³ and the NAEC is probably higher than 10 ml/m³, which results in a sufficient margin to the MAK value. Therefore, damage to the embryo or foetus is unlikely if the MAK value is not exceeded and 1-butanethiol remains classified in Pregnancy Risk Group C. According to skin absorption models, percutaneous absorption is expected to contribute significantly to systemic toxicity. Therefore, 1-butanethiol is designated with an “H”. 1-Butanethiol can cause sensitization of the skin in animals and is therefore designated with “Sh”.

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MAK value (2019)	1 ml/m³ ≅ 3.7 mg/m³
Peak limitation (2019)	Category II, excursion factor 2
Absorption through the skin (2018)	H
Sensitization (2018)	Sh
Carcinogenicity	–
Prenatal toxicity (2000)	Pregnancy Risk Group C
Germ cell mutagenicity	–
BAT value	–
CAS number	109-79-5
Molar mass	90.184 g/mol
Vapour pressure at 25 °C	60.7 hPa (NLM 2018)
log K _{OW}	2.28 (NLM 2018)
Solubility at 20 °C	597 mg/l water (NLM 2018)
1 ml/m³ (ppm) ≅ 3.742 mg/m³	1 mg/m³ ≅ 0.267 ml/m³ (ppm)

For 1-butanethiol, documentation from 2000 and a supplement on peak limitation from 2002 (Greim 2005, combined in one translation) are available.

In 2016, the Commission began using a revised approach for assessing substances with a MAK value based on systemic effects and derived from inhalation studies in animals or studies with volunteers at rest; this new approach takes into account that the respiratory volume at the workplace is higher than under experimental conditions. However, this does not apply to gases or vapour with a blood:air partition coefficient of < 5 (see List of MAK and BAT Values, Sections I b and I c). According to the formula of Buist et al. (2012), the blood:air partition coefficient of 1-butanethiol is 23.1. This supplement evaluates whether the MAK value and the Pregnancy Risk Group for 1-butanethiol need to be re-assessed as a result of the higher respiratory volume at the workplace.

For certain end points, also data for other thiols with a similar structure are included.

Mechanism of Action

As already described in the documentation of 2000 (Greim 2005), in the presence of suitable metal ions thiols can contribute to the formation of reactive oxygen species by autoxidation. The resulting disulfides can be reduced again to thiols. This redox cycling can lead to oxidative stress. Aliphatic thiols have a haemolytic effect, recognizable by the presence of Heinz bodies in the erythrocytes, which are formed by irreversibly denatured haemoglobin. As a result, the number of erythrocytes decreases as they lose their deformability and are destroyed in the reticulo-histiocytic system. Erythroclasia occurs mainly in the spleen, recognizable by enlargement and dark discoloration. A decrease in circulating erythrocytes stimulates compensatory erythropoiesis, but if too few new erythrocytes are formed this can lead to anaemia (Munday 1989).

Toxicokinetics and Metabolism

On the basis of toxicity studies in animals, absorption by the respiratory and gastrointestinal tract is to be assumed. However, quantitative data are not available (Greim 2005). There are also no quantitative studies available for dermal absorption. With mathematical models, a dermal flux of 0.27 mg/cm² and hour (Fiserova-Bergerova et al. 1990) or 0.01 mg/cm² and hour (Guy and Potts 1993; Wilschut et al. 1995) can be calculated. After the exposure of a skin area of 2000 cm² to a saturated aqueous solution for one hour, the total amount absorbed is thus between 20 mg and 540 mg.

It is generally known that mercaptans are oxidized in the liver, whereby, among other substances, sulfides and sulfates are formed (Farr and Kirwin 1994; Greim 2005).

Animal Experiments and in vitro Studies

Acute toxicity

Inhalation

LC₅₀ values for 1-butanethiol after 4-hour inhalation exposure were reported to be 4020 and 6060 ml/m³ for the rat and 2500 ml/m³ for the mouse. They are thus in the same order of magnitude as those of ethanethiol at 4420 ml/m³ and 2770 ml/m³ for the rat and mouse, respectively. For 1-propanethiol, the values are slightly higher (rat: 7300 or > 8170 ml/m³, mouse: 4010 ml/m³). The 4-hour LC₅₀ values of 2-methyl-2-propanethiol are much higher (rat: 22 220 or 26 643 ml/m³; mouse: 16 500 ml/m³). Lacrimation, hunched posture, tremor, staggering gait, muscular weakness, cyanosis and sedation, and also mucous membrane irritation (rubbing of eyes and nose, eye closure, watering of the eyes, corneal opacity) and retraction of the head were observed (OECD 2010).

Oral administration

The oral LD₅₀ of 1-butanethiol is 1500 mg/kg body weight for the rat and is thus similar to the values for 1-propanethiol of 1790 and 1848 mg/kg body weight. The value for ethanethiol is lower (682 mg/kg body weight), that for 2-methyl-2-propanethiol higher (4756 mg/kg body weight). Ruffled fur, lacrimation, staggering, bloody stains around the nose and sedation were observed in the animals (OECD 2010).

Dermal application

The dermal LD₅₀ value for 1-butanethiol is greater than 2000 mg/kg body weight, as is that for ethanethiol, 1-propanethiol and 2-methyl-2-propanethiol. For 1-butanethiol and ethanethiol these values were obtained in the rat, while for 1-propanethiol and 2-methyl-2-propanethiol studies were carried out in the rabbit. Apart from skin reactions, no effects were observed (OECD 2010).

Subacute, subchronic and chronic toxicity

Inhalation

Since the documentation of 2000 (Greim 2005), no new studies with 1-butanethiol have been conducted. However, the results of histopathological follow-up studies (Phillips Chemical Company 1983, 1984) of the 90-day inhalation study (Phillips Chemical Company 1982) have been evaluated, which were not available in 2000. The studies of repeated inhalation exposure of rats to 1-butanethiol are shown in Table 1.

Tab. 1 Toxicity studies after repeated inhalation exposure to 1-butanethiol

Species, strain, number per group	Exposure	Findings	References
rat, Sprague Dawley, 10 ♂, 10 ♀	14 days, 0, 204, 1114, 1900 ml/m ³ , 6 hours/day, 7 days/week, dose-finding, (histopathological examination only of the kidneys, only at 1900 ml/m ³)	≥ 204 ml/m³ : relative kidney weights ↑; ♂: relative weights of lungs and trachea ↑ ≥ 1114 ml/m³ : body weight development ↓; ♀: relative weights of spleen, lungs, trachea and heart ↑, dark-coloured kidneys; 1/20 died 1900 ml/m³ : clinical signs (tremor, respiratory distress, lacrimation), mortality (20/20 dead or moribund), pulmonary congestion, renal tubular degeneration	Phillips Petroleum Company 1981
rat, Sprague Dawley, 15 ♂, 15 ♀	90 days, 0, 9, 70, 150 ml/m ³ , 6 hours/day, 5 days/week, (histopathological examination only at 0, 150 ml/m ³ ; follow-up examination of kidneys and lungs: 9 and 70 ml/m ³ , lungs: additional repeated examination 0, 150 ml/m ³)	9 ml/m³ : NOAEC for systemic effects 70 ml/m³ : follow-up examination: evidence of Sendai virus due to chronic multifocal interstitial pneumonia (perivascular and peribronchiolar distribution with focal interstitial infiltration with lymphocytes, plasma cells and macrophages – no macrophages in pulmonary regions without this damage); ♂: absolute weights of trachea and lungs ↑ NOAEC for local effects ≥ 70 ml/m³ : ♂: relative weights of trachea and lungs ↑; ♀: erythrocytes ↓ (week 12), haemoglobin ↓ 150 ml/m³ : alveolar macrophages ↑ (11/15 ♂, 12/15 ♀; follow-up examination), “interstitial pulmonary fibrosis”, diagnosed in follow-up examination as an artifact of tissue processing; ♂: inflammation in nasal turbinates (2/15); ♀: neutrophils ↑ (week 12), lymphocytes ↓ (week 12), erythrocytes ↓ (week 6)	Phillips Chemical Company 1982, 1983, 1984

In the 13-week inhalation study already described in detail in the documentation of 2000 (Greim 2005), in which 15 Sprague Dawley rats per sex and group were exposed to 1-butanethiol concentrations of 0, 9, 70 or 150 ml/m³ for 6 hours daily, on 5 days per week, the NOAEC (no observed adverse effect level) for systemic effects was 9 ml/m³. At the two higher concentrations, a slight but statistically significant decrease in the number of erythrocytes was observed in the female animals in the sixth (150 ml/m³) and twelfth week (at 70 ml/m³ and above) which correlated with a slight decrease in haemoglobin. At 150 ml/m³, the number of neutrophils increased and that of lymphocytes decreased. The changes were within the range of the historical control data of the laboratory and were therefore assessed by the authors as not related to the treatment. However, since these effects, in particular the decrease in the erythrocyte count, are characteristic of thiols (see Section “Mechanism of Action”), they are considered by the Commission to be treatment-related. At the concentrations 70 ml/m³ and 150 ml/m³, there was a statistically significant increase in the relative lung weights in the male animals (absolute weights only in the middle group), and slight to moderate fibrosis of the lungs was reported in rats of both sexes at 150 ml/m³. Histopathological examination was initially performed only in the controls and the high concentration group (see Greim 2005; Phillips Chemical Company 1982). In a follow-up examination, histological sections of the kidneys and lungs were evaluated for the two remaining groups. For the lungs, the controls and high concentration group were also re-evaluated. In the middle concentration group, evidence of a Sendai virus infection was obtained, as chronic multifocal interstitial pneumonia was observed in the affected animals. The affected areas were characterized by perivascular and peribronchiolar distribution with focal interstitial infiltration of lymphocytes, plasma cells and macrophages. Macrophages were detected only in the affected lung areas. The animals of the other treatment groups were not affected. Substance-related lung effects were observed in the animals of the 150 ml/m³ group which showed an increase in alveolar macrophages. The “interstitial lung fibrosis” diagnosed in the original evaluation was interpreted as an artifact of tissue processing (Phillips Chemical Company 1983, 1984). Since in the high concentration group 2 of 15 animals displayed inflammation in the nasal turbinates and considerably more animals exhibited lung effects (male animals: 11/15, female animals: 12/15), it can be assumed that the lungs are more sensitive than the upper respiratory tract. For this reason, 70 ml/m³ is regarded as the NOAEC for local effects in the lungs and the nose.

The analogue **2-methyl-2-propanethiol** was tested at the same time under the same conditions. The concentrations used were 0, 9, 97 and 196 ml/m³. Changes in haematological parameters likewise occurred, but were interpreted by the authors of the study as not biologically relevant. The number of erythrocytes in the female animals decreased at 97 ml/m³ and above. The absolute and relative kidney weights of the male animals were increased; this was probably the result of chronic nephrosis (see below) (Phillips Chemical Company 1982). Here, too, a follow-up examination with the evaluation of histological sections of the kidneys and lungs was performed for all groups. In the kidneys of the male animals, chronic nephrosis was observed in all groups exposed to 2-methyl-2-propanethiol (9, 97, 196 ml/m³: 3/15, 13/14, 14/15) (Phillips Chemical Company 1983, 1984); this was attributed to α 2u-globulin nephropathy. As this is species-specific, it is not relevant for humans. In the study itself, there was no immunohistochemical evidence of α 2u-globulin, but evidence was found in the screening study described in the Section “Oral administration”.

The NOAEC for systemic effects in both studies, based on haematological changes typical of thiols, such as a decrease in the erythrocyte count, was 9 ml/m³. The females were found to be more sensitive than the males. For 1-butanethiol the NOAEC for local effects was 70 ml/m³; at 150 ml/m³ there was a significant increase in alveolar macrophages in the lungs.

In a 90-day inhalation study carried out according to OECD Test Guideline 413, 10 Sprague Dawley rats per sex and group were exposed whole-body to **2-butanethiol** concentrations of 0, 25, 99 or 400 ml/m³ for 6 hours daily, on 5 days per week. After exposure to 99 ml/m³, haemosiderin accumulation in the spleen and eosinophilic inclusions in the nasal turbinates were observed in the male animals; this reached statistical significance only at the high concentration. Another target organ is the kidney, in which hyaline droplets in the tubules, granular inclusions, pyelonephritis and tubular degeneration or regeneration were observed in the male animals of the 400 ml/m³ group; pyelonephritis was found also in the female animals. Immuno-histochemical staining of α 2u-globulin was not performed (Kim et al. 2009). Effects were thus initially observed at 99 ml/m³, so that, contrary to the authors’ statement, the NOAEC in this study was 25 ml/m³. The changes in the animals’ noses are regarded as a consequence of the irritant effect of 2-butanethiol.

Oral administration

No studies with 1-butanethiol are available.

In a screening study according to OECD Test Guideline 422, 12 male and 17 female Sprague Dawley rats per group were given gavage doses of **2-methyl-2-propanethiol** of 0, 10, 50 or 200 mg/kg body weight and day on 7 days a week (5 of the female animals were used to investigate developmental toxicity). Treatment began 14 days before mating and lasted for a total of 6 weeks in the males and 7 weeks in the females (until the 4th day after birth). Satellite groups of 5 animals for the control group and the 200 mg/kg body weight group, consisting of 5 female animals which were not pregnant and 5 male animals, were examined 12 days after the end of the treatment. Effects on the kidneys were observed in the male animals of all treatment groups. These effects were due to immunohistochemically proven α 2u-globulin nephropathy and are therefore not relevant for humans. At 50 mg/kg body weight and day and above, hepatocellular centrilobular hypertrophy and periportal fatty degeneration of the liver as well as increased absolute and relative liver weights were observed in the male animals (50, 200 mg/kg body weight: +29%, +41% compared with the control values (absolute), +35%, +64% compared with the control values (relative)). In the high dose group, changes in haematological and clinico-chemical parameters were observed in both sexes in addition to delayed body weight gains and reduced feed intake (see Table 2). Haemosiderin deposits were observed in the spleen. Hepatocellular, centrilobular hypertrophy was observed in the liver of the female animals. The α 2u-globulin nephropathy observed in male rats at and above 10 mg/kg body weight and day is not considered relevant for humans. Therefore, the NOAEL (no observed adverse effect level) of this study is 10 mg/kg body weight and day for the male animals and 50 mg 2-methyl-2-propanethiol/kg body weight and day for the female animals (MHLW 2006).

Tab. 2 Results of a study according to OECD Test Guideline 422 after oral administration of 2-methyl-2-propanethiol

Species, strain, number per group	Exposure	Findings	References
rat, Sprague Dawley, 12 ♂, 12 ♀	6–7 weeks, 0, 10, 50, 200 mg/kg body weight and day in corn oil, 7 days/week, gavage, OECD Test Guideline 422	<p>10 mg/kg body weight: ♂: swollen and pale kidneys (1/12), NOAEL</p> <p>≥ 10 mg/kg body weight: ♂: absolute and relative kidney weights ↑, hyaline droplets in the proximal tubular epithelium (dose-dependent increase in severity), basophilic renal tubules ↑ (demonstrated α2u-globulin nephropathy)</p> <p>50 mg/kg body weight: ♀: NOAEL</p> <p>≥ 50 mg/kg body weight: cholesterol ↑, absolute and relative liver weights ↑ (by 29% and 35%, respectively, compared with values for controls); ♂: hepatocellular, centrilobular hypertrophy, periportal fatty degeneration of hepatocytes, swollen and pale kidneys (3/12), MCHC ↓, phospholipids ↑</p> <p>200 mg/kg body weight: body weight development ↓, food uptake ↓, erythrocytes ↓, glucose ↓, α1-globulin ↓, albumin ↑, phospholipids ↑, haemosiderin deposits in spleen; ♂: Hb ↓, haematocrit ↓, thrombocytes ↓, α2u-globulin ↑, γ-GTP ↑, swollen liver (2/12), swollen and pale kidneys (4/12), absolute thymus weights ↓; ♀: reticulocytes ↑, total protein content ↑, A/G ratio ↑, hepatocellular, centrilobular hypertrophy, absolute and relative liver weights ↑</p> <p>no effects in FOB examination</p>	MHLW 2006

A/G: albumin/globulin ratio; FOB: functional observational battery; GTP: γ-glutamyl transpeptidase; Hb: haemoglobin; MCHC: mean cellular haemoglobin concentration

Summary

Target organs of the tested thiols are the haematopoietic system, the liver and in male rats the kidneys. However, the effects on the kidneys are species and sex-specific and therefore not relevant for humans. The systemic NOAEC is 9 ml/m³ for 1-butanethiol and 2-methyl-2-propanethiol and 25 ml/m³ for 2-butanethiol. In two simultaneously performed inhalation studies in rats with 1-butanethiol and 2-methyl-2-propanethiol and subsequent histopathology of the lungs of all animals, the local NOAEC for 1-butanethiol was 70 ml/m³, that for 2-methyl-2-propanethiol 9 ml/m³, due to a significant increase in alveolar macrophages at 150 ml 1-butanethiol/m³ and at 97 ml 2-methyl-2-propanethiol/m³ and above. In a 90-day inhalation study, eosinophilic inclusions in the olfactory epithelium occurred at 99 ml 2-butanethiol/m³, the NOAEC was 25 ml/m³.

Local effects on skin and mucous membranes

The occlusive application of 0.5 ml 1-butanethiol to the intact shaved skin of 6 rabbits for 4 hours did not lead to any skin reactions (OECD 2010).

The instillation of 0.1 ml 1-butanethiol into the eye of a rabbit led to slight irritant effects (no other details; Fairchild and Stokinger 1958). However, damage to the iris within the first 14 hours and slight to moderate conjunctival irritation for up to 72 hours after application have also been reported (no other details; Farr and Kirwin 1994).

Allergenic effects

In a local lymph node assay (LLNA) according to OECD Test Guideline 429, **1-butanethiol** (purity 99.2%) yielded positive results. Groups of 4 female CBA/J mice were treated with 5%, 10%, 25% and 50% test substance preparations in acetone:olive oil (4:1) and with the undiluted substance. The corresponding stimulation indices were 0.67, 0.43, 2.45, 5.38 and 14.4; thus, a tripling of the stimulation index, compared with the value for the controls, was exceeded

with the 50% and 100% solution. The EC3 value (concentration required to triple lymphocyte proliferation) is 30%. The undiluted solution resulted in dry skin and a slight increase in ear thickness in all 4 animals (15.15% increase in ear thickness between day 1 and day 6) and an erythematous reaction in 1 animal. In preliminary experiments with the undiluted substance no irritant effects were observed in 2 animals (Arkema France & Chevron Phillips Chemical Company LP 2011 a).

In an LLNA performed in the same way with **2-methyl-2-propanethiol** (purity 98.71%), stimulation indices of 1.73, 1.77, 3.62, 4.26 and 30.43 were determined without any increase in ear thickness. From this, an EC3 value of 20% was calculated (Arkema France & Chevron Phillips Chemical Company LP 2011 b).

In a Buehler test with **2-methyl-2-propanethiol** in 10 female and 10 male Hartley guinea pigs, the undiluted substance was used for induction treatment. The challenge treatment was carried out with a 75% preparation of the test substance in mineral oil. After both 24 and 48 hours, weak to marked reactions (grades 1 to 3) were observed in all 20 animals. In the 10 control animals, weak reactions were observed in 10 and 9 of the animals after 24 and 48 hours, respectively (Elf Atochem 1995).

There is also an incompletely documented test with 10 guinea pigs available; an erythematous reaction was reported in 1 of the 10 animals only 24 hours, but not 48 and 72 hours after challenge with 25% **1-butanethiol** in acetone. Induction treatment was performed with a 50% preparation of the test substance in the same vehicle (Phillips Petroleum Company 1982). As the substance was not characterized in detail, the frequency of the induction treatment is not apparent and it is not possible to determine whether induction treatment was open or occlusive, this result cannot be used for the evaluation.

This applies also to the results of an open patch test in 5 female and 5 male guinea pigs with application of a 20% **1-butanethiol** preparation in acetone, already cited in the documentation of 2000 (Greim 2005). The test preparation (0.2 ml) was applied to one flank of each of the animals for up to 10 consecutive days or until signs of contact dermatitis appeared. One month later, challenge treatment with the same test preparation was performed on the other flank. While single applications of dodecanethiol and octanethiol already led to signs of sensitization in about half of the animals, the result with 1-butanethiol was negative even after 10 days (Cirstea 1972).

Reproductive and developmental toxicity

Fertility

In the screening study according to OECD Test Guideline 422 described in detail in the section “Subacute, subchronic and chronic toxicity” and Table 2, in which Sprague Dawley rats were treated with **2-methyl-2-propanethiol** doses of 0, 10, 50 or 200 mg/kg body weight and day, no effects on the reproduction parameters mating index (high dose group 11/12), duration of mating, duration of pregnancy, implantation index, number of pups, number of live pups, 4-day survival index and sex ratio were found. The histopathological examination of the reproductive organs did not reveal any unusual, substance-related findings. The NOAEL for fertility in this study was 200 mg/kg body weight and day, which was the highest dose tested (MHLW 2006).

Developmental toxicity

Developmental toxicity studies after inhalation exposure of rats and mice are available, which are described in detail in the documentation of 2000 (Greim 2005). In the CD-1 mouse, inhalation of 68 ml 1-butanethiol/m³ caused lethality and an increased incidence of malformations (especially cleft palates) with simultaneous maternal toxicity in the form of delayed body weight gains and mortality. The NOAEC for developmental toxicity is 10 ml/m³ for the mouse and the NOAEC for the rat is 152 ml/m³, which was the highest concentration tested (Greim 2005).

The screening study with **2-methyl-2-propanethiol** according to OECD Test Guideline 422 described in the sections “Subacute, subchronic and chronic toxicity” and “Fertility” is not used for the evaluation of the developmental toxicity, as studies with 1-butanethiol itself are available.

Manifesto (MAK value/classification)

Critical are the effects on the erythrocytes, the lungs and the liver, possibly also irritation of the mucous membranes and the odour.

MAK value. The previously valid, provisional MAK value of 0.5 ml/m³ was derived in analogy to that for methyl mercaptan (methanethiol). In the meantime, the MAK value of methyl mercaptan has been re-evaluated and confirmed (see Hartwig and MAK Commission 2020).

As with all thiols, 1-butanethiol is a substance with a strong, unpleasant odour. Due to the low perception threshold of between 0.0001 and 0.01 ml 1-butanethiol/m³ (Greim 2005), the odour effect is probably the most important factor, but it is unclear at which concentration the unpleasant odour of 1-butanethiol represents an intolerable nuisance for humans.

In the 90-day inhalation study with 1-butanethiol in Sprague Dawley rats, the most sensitive end point is a decrease in the erythrocyte count, correlated with a slight decrease in the haemoglobin content, with a LOAEL (lowest observed adverse effect level) of 70 ml/m³ and a NOAEC of 9 ml/m³. Since this NOAEC is derived from animal experiments (1 : 2), and taking into account the increased respiratory volume at the workplace (1 : 2) and a possible increase in the effect with increasing exposure duration (1 : 2), a MAK value of 1 ml/m³ is obtained for 1-butanethiol after application of the preferred value approach.

Similar systemic effects were observed in several studies with inhalation exposure of rats to 1-butanethiol and other butanethiols. The NOAECs obtained in these studies are of the same order of magnitude (Table 3). The MAK value of 1 ml 1-butanethiol/m³ also avoids local effects, as can be seen from the data with 1-butanethiol and from the comparison with the data of 2-methyl-2-propanethiol and 2-butanethiol (Table 3).

Tab. 3 Summary of results from available studies with 1-butanethiol, 2-methyl-2-propanethiol and 2-butanethiol in rats and the MAK values calculated from them

	Exposure	NOAEC/NOAEL [ml/m ³]	LOAEC/LOAEL [ml/m ³]	End points	calculated MAK value ^{a), b)}
1-butanethiol	inhalation 90 days histopathology of kidneys and lungs of all groups during follow-up examinations	systemic: 9 local: 70	systemic: 70 local: 150	systemic: haematologi- cal effects local: increase in alveolar macrophages	<u>systemic</u> : 1 ml/m ³ <u>local</u> : 10 ml/m ³
2-methyl-2- propanethiol	inhalation 90 days see 1-butanethiol	systemic and local (lungs): 9	97	systemic: haematologi- cal effects local: increase in alveolar macrophages	<u>systemic</u> : 1 ml/m ³ <u>local</u> : 2 ml/m ³
	gavage 6–7 weeks	systemic: 10 mg/kg body weight	50 mg/kg body weight	hepatocellular hypertro- phy	0.5 ml/m ³
2-butanethiol	inhalation 90 days	systemic and local: 25	99	systemic: haemosidero- sis local: olfactory epithe- lium (eosinophilic inclu- sions)	<u>systemic</u> : 2 ml/m ³ <u>local</u> : 5 ml/m ³

^{a)} Calculation for inhalation: NOAEC / 2 (extrapolation from animal studies to humans) / 2 (increased respiratory volume of humans at the workplace in the case of systemic effects) / 2 (extrapolation to chronic exposure), subsequent application of the preferred value approach

^{b)} Calculation for oral administration: NOAEL / 4 (kinetics) / 4 (extrapolation to chronic exposure) / 2 (extrapolation from animal studies to humans) × 70 kg body weight / 10 m³ (respiratory volume per working day) × 7/5 (for daily exposure compared with 5 days/working week), subsequent application of the preferred value approach

Peak limitation. Since the MAK value for 1-butanethiol was derived from systemic effects, the substance is assigned to Peak Limitation Category II. No information on the half-life is available. Therefore, the default excursion factor of 2 for substances with systemic effects has been set. This means that the permissible short-term peak concentration is also below the calculated limit value for the local effect (Table 3).

Prenatal toxicity. For the evaluation of developmental toxicity, only studies with 1-butanethiol are used.

Developmental toxicity studies in rats and mice are available, which were already described in detail in the documentation of 2000 (Greim 2005). In the CD-1 mouse, inhalation of 68 ml/m³ led to lethality and an increased incidence of malformations (cleft palates) with simultaneous maternal toxicity in the form of delayed body weight gains and mortality. The NOAEC for developmental toxicity is 10 ml/m³ for the mouse and the NOAEC for the rat is 152 ml/m³, the highest concentration tested. This led to the assignment of 1-butanethiol to Pregnancy Risk Group C in 2000. Taking into account the increased respiratory volume (1 : 2), the NOAECs for developmental toxicity in rats and mice are, respectively, 76 and 5 times as high as the MAK value of 1 ml/m³. The LOAEC (lowest observed adverse effect concentration) for developmental toxicity in mice is 34 times the MAK value. Thus, the NOAEC could also be higher. In view of this, together with the sufficiently large margin of the NOAEC obtained from the developmental toxicity study in rats to the MAK value of 1 ml/m³, the assignment of 1-butanethiol to Pregnancy Risk Group C has been retained.

Absorption through the skin. Calculations based on physicochemical data and mathematical models yield values for dermal absorption of between 20 mg and 540 mg 1-butanethiol under standard conditions. From the systemic NOAEC of 1.1 ml/m³ (4.2 mg/m³) derived for the workplace (Table 3, before application of the preferred value approach), a tolerable amount of about 42 mg is calculated for that absorbed by inhalation assuming complete pulmonary absorption and a respiratory volume of 10 m³. Dermal absorption can therefore account for more than

25% of the systemically tolerable amount, so that 1-butanethiol has been designated with an “H” (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. There are no findings of skin sensitization caused by 1-butanethiol in humans. A positive result in a valid local lymph node assay (LLNA) indicated that 1-butanethiol has a low sensitization potential. The structurally very similar **2-methyl-2-propanethiol** yielded a similar result in the LLNA. Data for respiratory sensitization are not available. 1-Butanethiol is therefore designated with “Sh” (for substances which cause sensitization of the skin) but not with “Sa” (for substances which cause sensitization of the airways).

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