The MAK Collection for Occupational Health and Safety

Trimethylamine

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

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Trimethylamine / N,N-Dimethylmethanamine

MAK Value Documentation

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated the maximum concentration at the work place (MAK value) of trimethylamine [75-50-3] of 2 ml/m³, considering the endpoints local and systemic toxicity as well as developmental toxicity. Available publications are described in detail. Daily exposure of rats to trimethylamine for 14 days resulted in inflammation of the respiratory epithelium at 74 ml/m³, the lowest concentration tested. Since 2014, the Commission uses an empirical approach to set MAK values for substances with critical effects on the upper respiratory tract or the eyes. According to this approach, the MAK value would have to be lowered to 1 ml/m³. However, several data show, that the previous MAK value can be retained. Workers reported no irritation at 5 ml trimethylamine/m³. In addition cyclohexylamine and dimethylamine with a MAK value of 2 ml/m³ are used as a read-across due to similar alkalinity and RD50 values, and in a recent volunteer study a NOAEC of 2 ml cyclohexylamine/m³ is found. The MAK value will also protect from possible blue hazy vision which is caused by other tertiary amines since trimethylamine is assumed to be less effective than N,N-dimethylethylamine with a MAK value of 2 ml/m³. The assignment is to Peak Limitation Category I, because local effects are critical, and the excursion factor of 2 is confirmed. Developmental toxicity studies with trimethylamine show that damage to the embryo or foetus is unlikely if the MAK value is observed, and the assignment to Pregnancy Risk Group C is retained.

Keywords

trimethylamine; N,N-dimethylmethanamine; TMA; (sub)acute toxicity; (sub)chronic toxicity; irritation; developmental toxicity; peak limitation; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

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Trimethylamine

[75-50-3]

Supplement 2016

MAK value (2004)	**2 ml/m³ (ppm) ≙ 4.90 mg/m³**
Peak limitation (2004)	**Category I, excursion factor 2**
Absorption through the skin	**–**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (2006)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value	**–**
log K_{OW}[1)]	0.16 (US National Library for Medicine 2014) 0.245 (ECHA 2014)
Solubility	> 10 000 mg/l (ECHA 2014)
pKa value	9.78–9.8 (ECHA 2014)
1 ml/m³ (ppm) ≙ 2.452 mg/m³	**1 mg/m³ ≙ 0.408 ml/m³ (ppm)**

For the derivation of MAK values for substances with effects on the upper airways and eyes, since 2014 the Commission has been using a procedure based on physiological and empirical aspects (Brüning et al. 2014), in which also the criteria for categorization as a sensory irritant are described. The MAK value for trimethylamine from 2004 has been re-evaluated on the basis of this procedure.

There is documentation from 1983 available for trimethylamine (documentation "Trimethylamine" 1983) and supplements reviewing the MAK value and other classifications and designations (supplement "Trimethylamine" 2004) as well as the prenatal toxicity of the substance (supplement "Trimethylamine" 2007).

In 2004, the previous MAK value of 2 ml/m³ was derived for trimethylamine in analogy to other substances. To assess the irritative effects, the RD_{50} values of the methylamines and ethylamines in mice were compared. For the effect "blue veil vi-

1) octanol/water partition coefficient.

sion", which is to be expected after the exposure of workers to trimethylamine, but has not yet been demonstrated, the MAK values of the tertiary amines *N,N*-dimethylethylamine and triethylamine were taken into consideration.

For these two critical effects there are no new data available.

Effects in Humans

The exposure of workers to trimethylamine concentrations of 0.1 to 8 ml/m³ (8-hour mean value below 5 ml/m³), as measured by a manufacturer and by a consumer, had no toxic effects. This was shown by routine medical examinations. At concentrations of more than 20 ml/m³, trimethylamine is irritating to mucous membranes and the eyes. Even low concentrations are considered annoying due to the strong, unpleasant, fishy odour (documentation "Trimethylamine" 1983).

Animal Experiments

Subacute, subchronic and chronic toxicity

In an inhalation study (which can be evaluated only with difficulty due to inadequate information regarding the method and experimental data), groups of 12 rats were exposed to trimethylamine concentrations of 0, 25 or 75 mg/m³ (0, 10 or 31 ml/m³) for 5 hours a day, for 7 months. From the 4th month onwards, decreased lymphocyte counts and neutrophilia were found in the animals of the high exposure group. After the end of the study, bronchopneumonia with haemorrhage in the lung tissue was observed in the animals of this exposure group. In the low exposure group, similar but less pronounced changes were reported (no other details) (Rotenberg and Mashbits 1967; documentation "Trimethylamine" 1983; supplement "Trimethylamine" 2004). No information is given as to whether the animals were found to have a lung infection.

In another inhalation study, groups of 10 male Sprague Dawley rats were exposed nose-only to trimethylamine concentrations of 0, 74, 240 or 760 ml/m³ (purity 99.76%) for 6 hours a day, on 5 days per week for 2 weeks. Five animals per group were examined after the end of the exposure, the other five animals two weeks later. Even at the low concentration of 74 ml/m³, irritation was observed in the nose in the region of the respiratory epithelium, with findings of hyperaemia and oedema (4/5), slight epithelial degeneration (5/5) and squamous metaplasia (1/5). The changes were not reversible; the animals of the recovery group still exhibited these effects. In addition, reversible, slight inflammation or necrosis of the trachea was found in one animal at 74 ml/m³. In the middle and high concentration groups the erythrocyte count was increased. In animals exposed to 760 ml/m³, signs of dehydration, body weight stagnation, emphysematous alveoli, and inflammation or necrosis of the trachea were seen. In addition, increased relative heart and lung weights, reduced relative spleen and thymus weights and changed blood parameters were found; only the increase in the lung weights compared with those in the controls was statistically significant. No clinical signs of irritation were found

(Kinney et al. 1984, 1990; supplement "Trimethylamine" 2004). The lowest tested concentration of 74 ml/m^3 is the LOAEC (lowest observed adverse effect concentration); no NOAEC (no observed adverse effect concentration) was obtained.

Local effects on skin and mucous membranes

The corrosive effects of trimethylamine on the skin and eyes of rabbits already described in the documentation from 1983 (documentation "Trimethylamine" 1983) and in the supplement from 2004 (supplement "Trimethylamine" 2004) have been confirmed by further studies.

Skin

In a study of acute skin irritation, 4 and 2 rabbits were treated occlusively with a 45% trimethylamine solution in water over periods of 3 minutes and 4 hours, respectively. After the end of exposure the treated skin area was washed with a 50% poloxamer solution. The readings were carried out 24 hours, 48 hours and 8 days after the end of treatment, but not after 72 hours. After 4-hour exposure the readings after 24 and 48 hours yielded an average score of 4 for erythema formation and of 2 for oedema formation (on a scale with a maximum of 4 in each case). The effects were not reversible by the end of the 8-day observation period; necrosis occurred at the site of application. The 45% trimethylamine solution was classified as corrosive or highly irritating to the skin (ECB 2000; ECHA 2014).

Eyes

In a study of acute eye irritation, 0.1 ml of a 45% trimethylamine solution in water was instilled into one eye of three rabbits. The average score after 24, 48 and 72 hours was 2.5 for the cornea (maximum score: 4), 1.0 for the iris (maximum score: 2), 2.0 for the conjunctiva (maximum score: 3) and 2.4 for chemosis (maximum score: 4). Reddish-brown discoloration of the mucous and nictitating membranes was observed. After 24 hours, ciliary injections in the conjunctiva were seen in all three animals. After 8 days one animal was found to have severe corneal opacity; the eyes of the two other animals could not be evaluated due to purulent secretion. None of these changes was reversible within 14 days. The substance therefore causes serious eye damage (ECHA 2014).

Manifesto (MAK value/classification)

The critical effects of trimethylamine are local irritation of the respiratory epithelium of the nose and the blue veil vision observed after exposure to tertiary amines.

MAK value. The blue veil vision observed after the exposure of workers to the tertiary amines *N*,*N*-dimethylethylamine and triethylamine cannot be excluded for trimethylamine because of its structural similarity with these substances; therefore,

both the irritative effects and blue veil vision must to be taken into account for the MAK value of trimethylamine.

The size of the alkyl groups of the amine seems to play a role in the occurrence of blue veil vision since triethylamine has a stronger effect than *N,N*-dimethylethylamine with regard to this end point. Trimethylamine has no ethyl groups, but instead three methyl groups at the nitrogen atom; it can therefore be assumed that its effect is weaker than that of *N,N*-dimethylethylamine, which has a MAK value of 2 ml/m³. A MAK value of 2 ml/m³ for trimethylamine would therefore provide protection also against blue veil vision.

With regard to the irritative effects of trimethylamine, the 14-day inhalation study and analogy to other alkylamines can be used for the derivation of the MAK value. In the 14-day inhalation study, a LOAEC of 74 ml/m³ was obtained with irritation in the nose in the region of the respiratory epithelium. Following the procedure described by Brüning et al. (2014), a NAEC (no adverse effect concentration) of about 25 ml/m³ can be calculated from the LOAEC of 74 ml/m³. There are no studies available with longer-term exposure. Taking into consideration a possible increase in the effects after long-term exposure, a concentration of 4.2 ml/m³ is obtained and thus for humans a concentration of 1.4 ml/m³, which, using the preferred value approach, would result in a MAK value of 1 ml/m³. According to a citation from the documentation of 1983 (documentation "Trimethylamine" 1983), irritation of the eyes and mucous membranes occurred in exposed workers at concentrations of 20 ml/m³ and above. In general, the concentration of 5 ml/m³ had no effects, except for odour nuisance. Although this information was insufficiently documented, the reported concentration range in which effects occurred is nevertheless above the previous MAK value by one order of magnitude, so that this value is supported also by these reported workplace experiences. It therefore does not appear necessary to lower the MAK value to 1 ml/m³, as calculated on the basis of data from animal studies according to the procedure of Brüning et al. (2014). As in the supplement from 2004 (supplement "Trimethylamine" 2004), additionally the irritative effects of various amines in mice are compared using the RD_{50} values: The RD_{50} for cyclohexylamine is 50 ml/m³, that for dimethylamine 70 ml/m³; the MAK values are 2 ml/m³ in each case. The RD_{50} for trimethylamine is 61 ml/m³. For cyclohexylamine a more recent volunteer study is available in which a NOAEC of on average 2 ml/m³ with concentration peaks of 4 ml/m³ was obtained (Juran et al. 2012). This study confirms the MAK value of 2 ml/m³. The MAK value for dimethylamine was derived on the basis of a 2-year study with a LOAEC of 10 ml/m³; at this concentration minimal effects on the nasal epithelium of mice and rats occurred. Taking into account the results from the volunteer study with cyclohexylamine and the similar RD_{50} values for trimethylamine, cyclohexylamine and dimethylamine, the MAK value for trimethylamine of 2 ml/m³ has been retained.

Peak limitation. The critical effect is local irritation. Trimethylamine therefore remains in Peak Limitation Category I. For cyclohexylamine, dimethylamine and *N,N*-dimethylethylamine an excursion factor of 2 has been set to limit exposure peaks. In analogy to these substances the excursion factor of 2 for trimethylamine has been retained.

Prenatal toxicity. There are no new data available for the developmental toxicity of the substance. In 2006, the prenatal toxicity was re-evaluated and the substance classified in Pregnancy Risk Group C (see supplement "Trimethylamine" 2007). This was based on a screening study according to OECD Test Guideline 422 in rats with a NOAEL (no observed adverse effect level) for fertility and developmental toxicity of 200 mg/kg body weight and day, and the results of a developmental toxicity study with intraperitoneal administration in mice which shows that although trimethylamine is embryotoxic at high doses, it does not lead to skeletal or visceral abnormalities.

The following toxicokinetic data are taken into consideration for the extrapolation of this NOAEL to a concentration in workplace air: the corresponding species-specific correction values for the rat (1:4), the assumed oral absorption (100%), the body weight (70 kg) and respiratory volume (10 m^3) of the person, and the assumed 100% absorption by inhalation. The concentration calculated from this is 350 mg trimethylamine/m^3 (142.8 ml/m^3). The 71-fold difference between this concentration and the MAK value is sufficiently large to retain the classification of trimethylamine in Pregnancy Risk Group C.

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