The MAK Collection for Occupational Health and Safety

2-Aminoethanol

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

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2-Aminoethanol / monoethanolamine

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 2-aminoethanol [141-43-5], considering the endpoints respiratory tract irritation, developmental toxicity, and skin absorption. Available unpublished study reports are described in detail.

Critical effect of 2-aminoethanol is the local respiratory tract irritation. New 5-day and 28-day-guideline-studies with rats show time- and dose-dependent effects in larynx (squamous metaplasia, inflammation, necrosis), trachea (squamous metaplasia, inflammation), and lung (hyperplasia of mucous and goblet cells). The NOAEC is 10 mg/m^3 (3,95 ml/m^3). 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. Based on this approach, a concentration of 0.22 ml/m^3 for the work place air can be calculated from this study, resulting in a MAK value of 0.2 ml/m^3. Since the critical effect is irritation, Peak Limitation Category I is retained with an excursion factor of 1 as the substance is corrosive.

After scaling the oral NOAEL for developmental toxicity of 75, 225, and 500 mg/kg body weight and day for rabbits (dermal) and rats (dermal, oral), respectively, to an inhalation concentration at the work place, the differences to the MAK value, are considered sufficient, and damage to the embryo or foetus is unlikely when the MAK value is observed. Therefore, classification in Pregnancy Risk Group C is confirmed.

Absorption via skin does not contribute significantly to the systemic toxicity of 2-aminoethanol.

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Keywords

2-aminoethanol; ethanolamine; monoethanolamine; beta-aminoethyl alcohol; 2-hydroxyethylamine; toxicokinetics; metabolism; (sub)acute toxicity; (sub)chronic toxicity; irritation; peak limitation; prenatal toxicity; absorption through the skin; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

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2-Aminoethanol[1)]

[141-43-5]

Supplement 2016

MAK value (2015)	**0.2 ml/m³ (ppm) ≙ 0.51 mg/m³**
Peak limitation (2015)	**Category I, excursion factor 1**
Absorption through the skin	**–**
Sensitization (2001)	**Sh**
Carcinogenicity	**–**
Prenatal toxicity (1996)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value	**–**
1 ml/m³ (ppm) ≙ 2.53 mg/m³	**1 mg/m³ ≙ 0.395 ml/m³ (ppm)**

In 2014, the Commission started using a physiologically and empirically-based method for deriving MAK values for substances that have effects on the upper respiratory tract and eyes (Brüning et al. 2014; see Section I of the List of MAK and BAT Values); it also described criteria for classification as a sensory irritant. For this reason, the MAK value has been reviewed.

This is a supplement to the 1996 documentation (documentation "2-Aminoethanol" 1999) and the 2001 supplement (supplement "2-Aminoethanol" 2001, available in German only). Further studies have since become available with repeated inhalation exposure in rats.

Toxicokinetics and Metabolism

In an in vitro study, radioactively labelled 2-aminoethanol was applied undiluted or as a 22% aqueous solution to full-thickness skin from rats, mice, rabbits and humans. Amounts of 4 mg/cm² were applied to an area of skin of 1.77 cm². Radioactivity was determined in the receptor medium, wash solution and skin, as was the

1) The substance can simultaneously occur as a vapour and aerosol.

radioactivity adhering to the apparatus. Only 60% of the undiluted 2-aminoethanol was recovered, while 70% to 90% of the diluted 2-aminoethanol was recovered. The remainder presumably evaporated. In the receptor medium 6%, 17%, 8.7% and 0.6% was found after 6 hours for rats, mice, rabbits and humans; the respective values for the diluted substance were 1%, 25%, 2% and 1%. The fluxes were 42.5, 123.1, 73.8 and 7.9 µg/cm^2 and hour for rats, mice, rabbits and humans; fluxes of 11.7, 169.4, 25.3 and 9.7 µg/cm^2 and hour were calculated for the diluted substance (ECHA 2015). If the amount found in the skin is included, the flux for diluted 2-aminoethanol is 50 µg/cm^2 and hour for human skin. An absorbed amount of 100 mg is calculated from the flux of the diluted solution for humans after the exposure of a 2000 cm^2 skin surface area for 1 hour. This concentration presumably causes irritation. Taking a concentration that no longer causes irritation (see below) of 5% as a basis, after linear extrapolation the amount expected to be absorbed is 22.7 mg. From the ratios of the amounts absorbed determined in vitro in mice, rats and rabbits together with the amount dermally absorbed of about 50% determined in hairless mice in vivo, the dermal absorption in vivo of 17% of the substance is estimated for rats (50% × 6% / 17%) and of 25% for rabbits (50% × 8.7% / 17%) (documentation "2-Aminoethanol" 1999).

For comparison: Assuming the exposure of a surface area of 2000 cm^2 of skin for 1 hour (log K_{OW}[2)] –2.3), fluxes of 49, 0.9 and 4.5 µg/cm^2 and hour, which would correspond to absorbed amounts of 98, 1.8 and 9 mg, respectively, are calculated with the models of Fiserova-Bergerova et al. (1990), Guy and Potts (1993) and Wilschut et al. (1995) for a 5% 2-aminoethanol solution that is not irritating in humans (see Section "Effects in Humans"). The mean of the 3 calculated values agrees well with the amount of 22.7 mg estimated for human skin above; therefore, this level is used for the evaluation of dermal absorption. The 2001 supplement (supplement "2-Aminoethanol" 2001, available in German only) assumed a 0.5% solution to be the concentration that no longer causes irritation because irritative effects were still reported in animal studies with 1.5% solutions. Therefore, systemic absorption calculated on the basis of a 5% solution (see Section "Effects in Humans") represents the worst case.

Effects in Humans

In asthma patients, the inhalation of aerosols generated from up to 10% solutions did not cause irritation, but an odour nuisance. The actual concentrations in the air were not reported (see documentation "2-Aminoethanol" 1999). The irritation threshold for human skin is unclear. In some cases, irritation was still observed with a 0.5% solution while in maximization tests with test persons, concentrations of 5.9% were not irritating (documentation "2-Aminoethanol" 1999).

2) Octanol/water partition coefficient.

Animal Experiments and in vitro Studies

Subacute, subchronic and chronic toxicity

Inhalation

After repeated exposure to vapour for a period of up to 3 months, systemic effects were reported in rats, guinea pigs and dogs at concentrations of up to 5 ml/m³ (12 mg/m³) in the air, but there were no local effects of irritation. Medium-term exposure caused dermal necrosis at the higher concentrations of 29 mg/m³ (rats) and 37 mg/m³ (dogs), but effects on the respiratory tract were not reported. However, signs of severe systemic toxicity were observed at these concentrations (Weeks et al. 1960).

In a 5-day inhalation study carried out according to OECD Test Guideline 412, groups of 5 male Wistar rats were exposed nose-only to 2-aminoethanol concentrations of 0, 20, 200 or 500 mg/m³ for 6 hours per day. The animals were exposed to vapour or aerosol depending on the concentration. The vapour fraction was 100% at 20 mg/m³ and 11.2% at 500 mg/m³. Under the study conditions, the vapour saturation conditions were 50 to 60 mg/m³. The MMAD (mass median aerodynamic diameter) was 1.7 to 1.8 µm. Body weight gains were significantly reduced in the animals of the high concentration group. In the middle and high exposure groups, adverse morphological changes were observed with increasing incidence and severity in the epithelia of the larynx, trachea and lungs. The findings were most pronounced in planes of section I and II of the larynx. The NOAEC (no observed adverse effect concentration) in this study was 20 mg/m³ (BASF SE 2011).

In a study carried out according to OECD Test Guideline 412, groups of 5 male and 5 female Wistar rats were exposed nose-only to 2-aminoethanol aerosol (with a vapour fraction; purity of the test substance: 99.93%) for 28 days, for 6 hours a day, on 5 days a week. The test concentrations were 0, 10, 50 or 150 mg/m³ (analysed concentrations: 10.2, 49.1 and 155.9 mg/m³; MMAD = 1.1 to 1.2 µm, with about 70% of the particles below 3 µm; the aerosol fraction was 0.5, 26.4 and 134.5 and the vapour fraction was 9.8, 22.7 and 21.4 mg/m³).

Effects on the larynx, trachea and lungs were found at 150 mg/m³ and above. There were no adverse systemic effects. The MCHC (mean corpuscular haemoglobin concentration) was increased in male rats at 50 mg/m³ and above. As this increase was not accompanied by any other changes in red blood cell parameters, the effect was regarded as substance-related, but not as adverse. In addition, at 150 mg/m³, the triglyceride values of the males were reduced. This effect was not regarded as adverse because no concomitant findings were observed. The relative liver weights of all treated males were significantly decreased, but the decrease was not concentration-dependent. This finding was not regarded as substance-related because there was no concentration–effect relationship or histopathological correlate.

Minimal or slight focal or multifocal hyperplasia of mucous cells was found in the bronchi of the lungs of all male rats and of 2 female rats of the group exposed to 150 mg/m³. The number of goblet cells was minimally or slightly increased in the affected bronchi.

Minimal to slight inflammation of the trachea was observed in 1 male after exposure to 10 mg/m³ as well as in 4 males after exposure to 150 mg/m³. In addition, at

the high concentration, minimal or slight focal squamous metaplasia was observed in the area of the carina in males. There were no treatment-related findings in the trachea of the females. However, 1 female control animal was found to have minimal focal inflammation of the trachea. The inflammation of the trachea observed in 1 male exposed to 10 mg/m³ was not concentration-dependent; therefore, it was not induced by the substance.

At the entrance to the ventral pouch of the larynx (plane of section III), minimal (grade 1) focal squamous metaplasia was observed in 1 female at 50 mg/m³ as well as in 1 male and 2 females at 150 mg/m³. Minimal hyperplasia occurred in all males and in 4 females (concentration not specified). Minimal inflammation was found in 2 males and 3 females at 50 mg/m³ as well as in all males and 4 females at 150 mg/m³.

At the base of the epiglottis in the larynx (plane of section I), submucosal inflammation characterized by infiltrates of granulocytes and lymphoid cells occurred in all males and females at 50 mg/m³ and above. At 150 mg/m³, the inflammation was accompanied by degeneration of the submucosal glands. In addition, focal epithelial necrosis was observed at the base of the epiglottis in 4 males and 3 females of the high concentration group. In the same region, focal squamous cell metaplasia was observed in 3 male and 2 female rats at 50 mg/m³, and all animals were affected at 150 mg/m³. Minimal inflammation at the base of the epiglottis was detected in 1 female exposed to 10 mg/m³ (REACH Ethanolamines Consortium SE 2010).

This finding is not regarded as adverse because it occurs also as an incidental finding (Kaufmann et al. 2009).

To summarize, the two inhalation studies in rats carried out according to OECD Test Guideline 412 revealed adverse morphological changes to the epithelium in the larynx (metaplasia of the squamous epithelium, inflammation and necrosis at the base of the epiglottis), trachea (inflammation and squamous metaplasia) and lungs (hyperplasia of the mucous cells in the bronchi and an increased number of goblet cells) with an increasing incidence and severity. The effects were markedly increased between days 5 and 28. The resulting local NOAEC for rats after 28-day exposure was 10 mg/m³, and the systemic NOAEC was 150 mg/m³.

Local effects on skin and mucous membranes

Local application of 2-aminoethanol to the skin and eyes of rabbits induced severe irritation and corrosion (see documentation "2-Aminoethanol" 1999).

Manifesto (MAK value/classification)

The critical effects are the local effects on the lungs, larynx and trachea that were observed in 5-day and 28-day inhalation studies in rats as well as the severe irritation and corrosion to the skin and eyes of rabbits.

MAK value. The data available for the effects in humans are not suitable for the derivation of a MAK value for 2-aminoethanol. Two studies are available in Wistar rats, a 5-day inhalation study and a 28-day inhalation study carried out according to OECD Test Guideline 412. Both inhalation studies revealed adverse morphological

changes to the epithelium of the larynx (squamous metaplasia, inflammation and necrosis at the base of the epiglottis), trachea (inflammation and squamous metaplasia) and lungs (hyperplasia of the mucous cells in the bronchi and an increased number of goblet cells) with increasing incidence and severity in accordance with the increase in the concentration. The effects were markedly increased between days 5 and 28. The NOAEC was 10 mg/m³ after 28 days of exposure. Assuming exposure to 10 mg/m³ and taking into consideration the expected increase in the effects after long-term exposure, a concentration of 1.67 mg/m³ and thus a NOAEC of about 0.56 mg/m³ (0.22 ml/m³) is obtained for humans according to the method described in Brüning et al. (2014) for local irritation. As the substance was exclusively present as a vapour at 10 mg/m³, the MAK value is given in ml/m³ and has been established at 0.2 ml/m³ in line with the preferred value approach.

Peak limitation. 2-Aminoethanol is classified in Peak Limitation Category I because of local irritation. As there are no data available for humans, but the substance is corrosive, a default excursion factor of 1 has been established.

Prenatal toxicity. There are no new studies available for developmental toxicity. In studies of the toxic potential of 2-aminoethanol on reproduction, maternal toxicity was observed at the highest tested doses of 75 (rabbit, dermal), 225 (rat, dermal) and 500 (rat, oral) mg/kg body weight, but there were no toxic effects on reproduction (documentation "2-Aminoethanol" 1999). The following toxicokinetic data are used to extrapolate this NOAEL to a concentration in workplace air: the corresponding species-specific correction values for the rat and rabbit determined on the basis of the toxicokinetic data (1:4; 1:2.4), the assumed oral (100%) or estimated dermal absorption (17% for the rat and 25% for the rabbit), the body weight (70 kg) and the respiratory volume (10 m³) of the person, and the assumed 100% absorption by inhalation. This results in the respective concentrations of 875 mg/m³ (350 ml/m³; rat, oral), 67 mg/m³ (27 ml/m³; rat, dermal) and 55 mg/m³ (22 ml/m³; rabbit, dermal) in the air. As these NOAELs (no observed adverse effect levels) are 1750 times,134 times and 110 times higher than the MAK value of 0.2 ml/m³ (0.5 mg/m³) and thus far above this value, 2-aminoethanol remains in Pregnancy Risk Group C.

Absorption through the skin. In an in vitro study, dermal absorption from a 5% solution was estimated to be 22.7 mg for humans under standard conditions (assuming the exposure of a surface area of skin of 2000 cm² for one hour). As the systemic subacute NOAEC was 150 mg/m³ after inhalation in rats (highest tested concentration; REACH Ethanolamines Consortium SE 2010), a systemically tolerable amount of 125 mg is obtained for humans if this NOAEC is extrapolated to long-term exposure in humans (150 mg/m³ × 10 m³ / 6 / 2). However, because higher concentrations were not tested, the actual systemically tolerable amount might be even higher. The documentation from 1996 (documentation "2-Aminoethanol" 1999) reported an oral NOAEL of 320 mg/kg body weight from an earlier 90-day study in rats, which corresponds to 1400 mg after corresponding extrapolation to humans. The amount absorbed through the skin is thus less than 25% of the systemically tolerable amount, which means that the substance is not designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

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