The MAK Collection for Occupational Health and Safety

Ethylamine

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

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Ethylamine / Ethanamine

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 ethylamine [75-04-7], considering all toxicological endpoints.
The critical effect is irritation of the nasal epithelium of rats with a NOAEC of 100 ml/m³ in a 24-week inhalation study. The maximum concentration at the workplace (MAK value) for ethylamine is derived by using additional data of the structurally related diethylamine. For diethylamine a MAK value of 2 ml/m³ was derived based on a two-year study in rats with a NOAEC of 16 ml/m³ for irritation of the nasal epithelium and a study in humans with a LOAEC of 10 ml/m³ for sensory irritation. As the inhalation toxicity of ethylamine is lower than that of diethylamine, the previous MAK value for ethylamine of 5 ml/m³ is retained. As the local effect is critical, ethylamine remains classified in Peak Limitation Category I. The excursion factor of 2 and the momentary value (concentration which must not be exceeded at any time) of 10 ml/m³ are retained.
There are no developmental toxicity studies and ethylamine remains assigned to Pregnancy Risk Group D. Ethylamine is not genotoxic in vitro, data on genotoxicity in vivo and carcinogenicity are lacking. There is, however, no corresponding structural alert. There are no data on sensitization. According to skin absorption models, percutaneous absorption does not contribute significantly to systemic toxicity.

Keywords

ethylamine; aminoethane; ethanamine; mechanism of action; toxicokinetics; metabolism; (sub) acute toxicity; (sub)chronic toxicity; irritation; genotoxicity; carcinogenicity; prenatal toxicity; germ cell mutagenicity; absorption through the skin; sensitization; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

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Ethylamine

[75-04-7]

Supplement 2019

MAK value (1996)	**5 ml/m³ (ppm) ≙ 9.4 mg/m³**
Peak limitation (2002)	**Category I, excursion factor 2**
Momentary value (2002)	**10 ml/m³ ≙ 19 mg/m³**
Absorption through the skin	**–**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (1994)	**Pregnancy Risk Group D**
Germ cell mutagenicity	**–**
BAT value	**–**
Synonyms	aminoethane
Chemical name (IUPAC name)	ethanamine
Molar mass	45.08 g/mol
Melting point	–81.2 °C (ECHA 2018)
Boiling point at 1013 hPa	16.6 °C (ECHA 2018)
Vapour pressure at 20 °C	990 hPa (ECHA 2018)
log K_{OW}[1)]	–0.27 (ECHA 2018)
Solubility	miscible with water (ECHA 2018)
pKa value	10.79 (ECHA 2018)
1 ml/m³ (ppm) ≙ 1.87 mg/m³	**1 mg/m³ ≙ 0.535 ml/m³ (ppm)**

Documentation for ethylamine was published in 1984 (documentation "Ethylamin" 1984, available in German only), followed by supplements in 1996 (supplement "Ethylamin" 1996, available in German only) and 2002 (supplement "Ethylamin" 2002, available in German only). Studies that are relevant to the evaluation have not been published since 2002. The MAK value of 5 ml/m³ for ethylamine was derived using

1) octanol/water partition coefficient

the data for diethylamine. This supplement was prepared because a re-evaluation of diethylamine resulted in the lowering of its MAK value to 2 ml/m³ (documentation "Diethylamine" 2016).

1 Toxic Effects and Mode of Action

Ethylamine is corrosive to the skin and eyes. In rabbits, oedemas of the cornea and nictitating membrane were observed at concentrations of 50 ml/m³ and above and histological changes were found in the lungs and heart after 6 weeks. Decreased body weights and severe irritation of the nasal epithelium were reported after subchronic exposure of rats to 500 ml/m³. Specific systemic effects were not observed. Ethylamine was not found to be genotoxic in in vitro studies.

2 Mechanism of Action

The irritant effects of the substance are caused by its alkalinity.

3 Toxicokinetics and Metabolism

A blood:air partition coefficient of 33.9 is calculated using the formula of Buist et al. (2012).

There are no data for the absorption of the substance through the skin. The data for acute toxicity cannot be used for the evaluation because of the damage that is incurred to the skin during the application of the corrosive substance.

According to ECHA (2018), a 70% aqueous ethylamine solution is corrosive to the skin. According to the Classification, Labelling and Packaging (CLP) regulation, irritation of the skin is to be assumed for these substances at concentrations of 1% and above. For a non-irritating solution of 0.5%, fluxes of 19.5, 3.1 and 10.2 μg/cm² and hour are calculated using the models of Fiserova-Bergerova et al. (1990), Guy and Potts (1993) and Wilschut et al. (1995), respectively. Assuming exposure of 2000 cm² of skin for 1 hour, the amounts absorbed correspond to 39, 6.2 and 20.4 mg, respectively.

Using the Henry's constant (H_{pc}) of 0.0000123 atm × m³/mol (SRC 2018), it was calculated that a concentration of 0.0183 g/l would result in an aqueous film on the surface of the skin after exposure to gaseous ethylamine at the level of the MAK value. Applying the three models above, a maximum amount of 10 mg ethylamine would be absorbed through the skin after 8-hour whole-body exposure (18 000 cm²) at this concentration level.

4 Effects in Humans

A communication published in 1949 reported that ethylamine induced blue haze vision in exposed workers (documentation "Ethylamin" 1984, available in German

only). There are no other studies of this end point. There are no findings of sensitizing effects induced by ethylamine.

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

The RD_{50} of ethylamine was 151 ml/m³ in mice (supplement "Ethylamin" 1996, available in German only).

The 4-hour LC_{50} was 6830 ml/m³ in male and female rats (ECHA 2018).

5.1.2 Oral administration

The oral LD_{50} was 400 mg/kg body weight in rats (documentation "Ethylamin" 1984, available in German only).

5.1.3 Dermal application

The dermal LD_{50} was 265 mg/kg body weight in rabbits (documentation "Ethylamin" 1984, available in German only). Damage to the skin probably led to increased absorption of the substance.

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

In rabbits (strain not specified), oedema of the cornea and nictitating membrane were observed after exposure to ethylamine, diethylamine or triethylamine concentrations of 50 ml/m³ and above and histological changes were reported in the lungs and heart after 6 weeks. The severity of the effects induced in the lungs and in the eyes by ethylamine, diethylamine and triethylamine was similar. However, the noses of the animals were not examined (Brieger and Hodes 1951; documentation "Ethylamin" 1984, available in German only; supplement "Ethylamin" 1996, available in German only).

After 10-day exposure of F344 rats to an ethylamine concentration of 1000 ml/m³, moderate necrotising inflammatory effects were observed in the nasal epithelium; these were slight at a concentration of 250 ml/m³. After similar exposure to a **diethylamine** concentration of 500 ml/m³, moderate to severe inflammatory effects were reported; these effects were moderate after exposure to a **triethylamine** concentration of 1000 ml/m³ (NIOSH 1984; supplement "Ethylamin" 1996, available in German only). The conclusion drawn from this comparison is that the local effects induced by ethylamine are weaker than those induced by diethylamine. Triethylamine was also less potent than diethylamine.

In a 24-week inhalation study, male and female F344 rats were exposed to ethylamine concentrations of 0, 10, 100 or 500 ml/m³ for 6 hours a day, on 5 days a week. Reduced body weights and severe irritation of the nasal epithelium were observed at a concentration of 500 ml/m³, but not at 100 ml/m³. This concentration was also the NOAEC (no observed adverse effect concentration) for systemic effects (NIOSH 1984; supplement "Ethylamin" 1996, available in German only).

A NOAEC of 247 ml/m³ was determined after 28-week exposure of F344 rats to **triethylamine** concentrations of 25 or 247 ml/m³ for 6 hours a day, on 5 days a week (Lynch et al. 1990). By contrast, marked irritation of the nasal epithelium was observed after 24-week exposure of F344 rats to a **diethylamine** concentration of 250 ml/m³ for 6 hours a day, on 5 days a week. The animals exposed to a **diethylamine** concentration of 25 ml/m³ were not examined (Lynch et al. 1986). The studies confirmed that diethylamine causes more severe irritation than triethylamine. The NOAEC for nasal damage was 16 ml/m³ after exposure of F344 rats to **diethylamine** for 6 hours a day, on 5 days a week, for 3 months (NTP 2011).

It can be concluded from the overall data that of the three amines, diethylamine causes the most severe nasal irritation. The comparison with triethylamine is carried out only with regard to irritation, as the actual critical effect of triethylamine which determines the MAK value is impaired vision caused by corneal swelling. There is no evidence that this effect is also induced by ethylamine.

5.2.2 Oral administration

There are no data available.

5.2.3 Dermal application

There are no data available.

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

Aqueous ethylamine was corrosive to the skin of rabbits (supplement "Ethylamin" 1996, available in German only).

5.3.2 Eyes

Aqueous ethylamine was corrosive to the eyes of rabbits (supplement "Ethylamin" 1996, available in German only).

5.4 Allergenic effects

There are no data available.

5.5 Reproductive and developmental toxicity

There are no data available.

5.6 Genotoxicity

5.6.1 In vitro

Ethylamine was not mutagenic in Escherichia coli and Salmonella typhimurium (documentation "Ethylamin" 1984, available in German only).

In the Salmonella mutagenicity test with preincubation, ethylamine was not mutagenic in the strains TA98, TA100, TA1535 and TA1537 at concentrations up to 10 mg/plate both with and without the addition of metabolic activation (ECHA 2018).

Ethylamine slightly increased the frequency of sister chromatid exchange in V79 cells (supplement "Ethylamin" 1996, available in German only).

5.6.2 In vivo

There are no data available.

5.7 Carcinogenicity

There are no data available.

6 Manifesto (MAK value, classification)

The critical effect is nasal irritation in rats.

MAK value. There are no data available in humans that can be used to derive a limit value. Specifically, unlike for triethylamine (supplement "Triethylamine" 1999) and *N*,*N*-dimethylethylamine (supplement "*N*,*N*-Dimethylethylamine" 2018), there

Table 1 NOAEC and LOAEC for nasal effects in F344 rats

Substance	Exposure period	NOAEC	LOAEC	References
ethylamine	24 weeks	100	500	NIOSH 1984
diethylamine	24 weeks	–	250	Lynch et al. 1986
	13 weeks	16	32	NTP 2011
	2 years	–	32	NTP 2011
triethylamine	28 weeks	247	–	Lynch et al. 1990

are no reliable data available for impaired vision. For this reason, the MAK value has been derived on the basis of the data for inhalation exposure of rats (Table 1).

On the basis of the NOAEC of 100 ml/m³ determined in the 24-week study in rats and using the preferred value approach, a MAK value of about 10 ml/m³ would be derived for the systemic effects induced by ethylamine (extrapolation to chronic exposure (1:2), extrapolation of data from animal studies to humans (1:2), increased respiratory volume (1:2) = 13 ml/m³). The MAK value based on irritation would likewise be about 10 ml/m³ (extrapolation to chronic exposure (1:2), extrapolation of data for local effects from animal studies to humans (1:3) = 17 ml/m³). The data from this study were not used to derive the MAK value in the supplement from 1996 (supplement "Ethylamin" 1996, available in German only). Compared with the NOAEC of 16 ml/m³ for the structurally similar diethylamine in a 3-month study, the NOAEC of 100 ml/m³ determined for ethylamine is very high (NTP 2011). Such a large difference in irritant potency in the respiratory tract would not be expected on the basis of the RD_{50} values of the two substances (ethylamine: 151 ml/m³; diethylamine 202 ml/m³). However, the concentration–effect relationship of ethylamine is steeper than that of diethylamine (Gagnaire et al. 1989), which means that the no-effect concentration (RD_0) of ethylamine is higher than that of diethylamine. Ethylamine causes weaker local effects in rats than diethylamine, but effects of similar severity to those induced by triethylamine (NIOSH 1984; Lynch et al. 1986, 1990). On the other hand, significant differences were not found in the lungs and eyes of rabbits after exposure to the three amines (Brieger and Hodes 1951). However, the noses of the animals were not examined.

The derivation of a MAK value for ethylamine is based on the similarity of the RD_{50} values for ethylamine and diethylamine (supplement "Ethylamin" 1996, available in German only). At the time, a MAK value of 5 ml/m³ was derived for diethylamine on the basis of a volunteer study with a LOAEC of 10 ml/m³. A MAK value of 5 ml/m³ was thus established also for ethylamine. The MAK value for diethylamine has in the meantime been lowered to 2 ml/m³ on the basis of data from a new 2-year study in mice and rats. A comparison of the studies with repeated inhalation exposure (Table 1), however, shows that diethylamine causes more severe local effects than ethylamine, so that the MAK value of 5 ml/m³ for ethylamine has been retained.

Peak limitation. As irritation is the critical effect of ethylamine, the substance remains classified in Peak Limitation Category I. The excursion factor of 2 and the momentary value of 10 ml/m³ have been retained (supplement "Ethylamin" 2002, available in German only).

Prenatal toxicity. There are no data available. The substance remains classified in Pregnancy Risk Group D.

Carcinogenicity. There are no studies of carcinogenic effects. However, taking the structure into consideration, these are not to be expected. A chronic study in rats and mice with diethylamine did not yield evidence of a substance-induced increase in tumour incidence; by analogy, ethylamine is not expected to cause carcinogenic effects. For this reason, the substance is not classified in one of the categories for carcinogens.

Germ cell mutagenicity. Ethylamine is not genotoxic in vitro. No in vivo tests are available. However, taking the structure into consideration, these kinds of effects are not to be expected. Therefore, the substance is not classified in one of the categories for germ cell mutagens.

Absorption through the skin. Using model calculations (Section 3), a maximum dermal absorption of 39 mg is estimated for humans after exposure to a non-irritating 0.5% solution under standard conditions (2000 cm^2 of skin, one-hour exposure). After 8-hour whole-body exposure (18 000 cm^2) to gaseous ethylamine at the level of the MAK value, a maximum of 10 mg is absorbed through the skin.

The systemically tolerable concentration of 13 ml/m^3 (24 mg/m^3) estimated above is equivalent to an absorbed amount of 240 mg assuming 100% absorption by inhalation and a respiratory volume of 10 m^3.

Therefore, even in the case of simultaneous exposure to aqueous and gaseous ethylamine, the amount absorbed through the skin would be less than 25% of the systemically tolerable amount and the substance is not designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. There are no data available for the sensitizing effects of ethylamine. Therefore, ethylamine is not designated with "Sh" or "Sa" (for substances which cause sensitization of the skin or airways).

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