The MAK Collection for Occupational Health and Safety

Triethanolamine

MAK Value Documentation, addendum – Translation of the German version from 2018

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Triethanolamine / 2-[Bis(2-hydroxyethyl)amino]-ethanol

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 workplace (MAK value) of triethanolamine [102-71-6].
Critical effect is the inflammation of the larynx observed in a 28-day study in rats with a $BMDL_{05}$ of 14 mg/m³. An analysis of the studies with monoethanolamine, diethanolamine and 7 other studies with substances that cause inflammation of the larynx shows that the NOAEC in subchronic or chronic studies is lower than in subacute studies. Therefore, for a chronic exposure to triethanolamine at the workplace a decrease of the NOAEC cannot be excluded and the MAK value is lowered to 1 mg/m³ for the inhalable fraction.
Triethanolamine remains assigned to Peak Limitation Category I for locally acting substances. An excursion factor of 1 is set by analogy with the other ethanolamines.

Keywords

triethanolamine; 2-[Bis(2-hydroxyethyl)amino]ethanol; 2,2′,2″-nitrilotriethanol; tris(2-hydroxyethyl)amine; trolamine; (sub)acute toxicity; (sub)chronic toxicity; peak limitation; larynx inflammation; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

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Triethanolamine

[102-71-6]

Supplement 2018

MAK value (2017)	**1 mg/m³ I (inhalable fraction)**
Peak limitation (2017)	**Category I, excursion factor 1**
Absorption through the skin	**–**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (2015)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value	**–**

The sensitizing effect of triethanolamine was evaluated in 2007 (documentation "Triethanolamine" 2007); this evaluation was followed by a further documentation in 2010 (documentation "Triethanolamine" 2010) and a supplement in 2016 (supplement "Triethanolamine" 2016).

No new studies have since become available. The purpose of this supplement is to re-evaluate whether the findings obtained in the 28-day study critical for deriving the MAK value are dependent on exposure duration.

Animal Experiments and in vitro Studies

Subacute, subchronic and chronic toxicity

Inhalation

The 28-day inhalation study in rats with aerosol exposure revealed concentration-dependent increases in the incidences of laryngeal inflammation in rats at the low concentration of 20 mg/m³ up to and including 100 mg/m³; only grade 1 and grade 2 severities were recorded. A $BMDL_{05}$ of 14.8 mg/m³ was calculated. Grade 3 inflammation was observed at the high concentration of 400 mg/m³ in the 5-day range-finding study and at 500 mg/m³ in the 28-day study. However, most of the findings obtained at 500 mg/m³ in the 28-day study were of grade 2 severity (Table 1). In the 2016 supplement (supplement "Triethanolamine" 2016),

Table 1 Incidences and severity of laryngeal inflammation in Wistar rats in the 5-day and 28-day inhalation studies with triethanolamine (documentation "Triethanolamine" 2010)

Concentration (mg/m^3)	Incidences (%)				Study
	grade 1	grade 2	grade 3	grades 4 and 5	
0	0	0	0	0	5-day / 28-day
20	14	7	0	0	28-day
100	0	0	0	0	5-day
100	14	14	0	0	28-day
200	0	30	0	0	5-day
400	0	0	**70**	0	5-day
500	14	**36**	7	0	28-day

this was interpreted in such a way that the severity of the findings decreases after long-term exposure and an intensification of the effects over time thus does not have to be taken into account for the derivation of the MAK value. Therefore, only the extrapolation of data from animal studies to humans according to the method of Brüning et al. (2014) (1:3) was used and the previous MAK value of 5 mg/m^3 was confirmed.

However, as the NOAEC (no observed adverse effect concentration) of the 5-day study was 100 mg/m^3 and the $BMDL_{05}$ of 14.8 mg/m^3 that was established in the 28-day study is much lower, a decrease of the NOAEC over the course of the exposure period has been demonstrated. This may also apply for the extrapolation of the subacute $BMDL_{05}$ to long-term exposure.

The data for the structurally analogous ethanolamines 2-aminoethanol (monoethanolamine) (supplement "2-Aminoethanol" 2016, available in German only) and diethanolamine (documentation "Diethanolamine" 2007) are used to determine the dependency on time of the NOAEC for laryngeal inflammation. For all three ethanolamines, inflammation in the laryngeal epithelium of rats is the critical effect for deriving a MAK value. The physico-chemical data and the results of the key toxicological studies with ethanolamines are summarized in Table 2. The studies were carried out in Wistar rats with head-only exposure on 5 days a week for 6 hours a day. The substances were always sprayed into the inhalation chambers. Therefore, the studies all used similar procedures and the results can easily be compared.

In the 5-day study, a NOAEC of 20 mg/m^3 was obtained for 2-aminoethanol (**monoethanolamine)** for the critical effect of laryngeal inflammation. However, as this is much lower than the LOAEC (lowest observed adverse effect concentration) of 200 mg/m^3, the NAEC (no adverse effect concentration) could also be higher. The derivation of the MAK value for monoethanolamine with the data obtained in the 5-day and 28-day studies revealed an intensification of the effects with increasing exposure time. Therefore, a MAK value of 0.2 ml/m^3 (0.51 mg/m^3) was established on the basis of the NOAEC of 10 mg/m^3 from the 28-day study. The method suggested by Brüning et al. (2014) was applied (extrapolation of the data from animal studies (1:3) and an assumed intensification of the effects after chronic exposure

based on a subacute study (1:6)) (supplement "2-Aminoethanol" 2016, available in German only). Monoethanolamine is a base that is corrosive to the skin. Local irritation of the respiratory tract is therefore plausible.

Diethanolamine was tested in rats in a 14-day study, but the larynx was not examined. In the 90-day study, the NOAEC for laryngeal inflammation was 3 mg/m^3 and the LOAEC was 8 mg/m^3. At 3 mg/m^3, slight focal squamous metaplasia was still observed at the base of the epiglottis. In 2006, the Commission considered these to be adverse effects, but according to recent findings, this severity grade is no longer regarded as adverse. In 2006, a MAK value of 1 mg/m^3 I was established on the basis of these data (documentation "Diethanolamine" 2007). The method suggested by Brüning et al. (2014) had not yet been published at this time. However, by applying this method, a MAK value of 0.5 mg/m^3 is obtained (extrapolation of the data from animal studies (1:3) and the assumed intensification of the effects after chronic exposure based on a subchronic study (1:2)). Diethanolamine is also a base, but is weaker than monoethanolamine. Accordingly, it is less irritating to the skin. As there is marked irritation of the eyes, irritation of the respiratory tract is plausible. Unlike monoethanolamine, diethanolamine is an aerosol at a concentration of 3 mg/m^3, whereas monoethanolamine exists almost exclusively as a vapour at 10 mg/m^3.

Triethanolamine is a weaker base than the other two ethanolamines and does not cause irritation of the skin or eyes. Therefore, irritation of the respiratory tract is not necessarily to be expected. Nevertheless, laryngeal inflammation was observed. In the 28-day study, the $BMDL_{05}$ for this end point was almost as high as the corresponding NOAEC of monoethanolamine. Triethanolamine is an aerosol at 0.03 mg/m^3 and above. Although triethanolamine is a weaker alkali, it could induce effects on the larynx because the local effects of the triethanolamine aerosol are stronger than those of the monoethanolamine vapour which is exhaled more easily off the epithelial cells than triethanolamine because of the much higher vapour pressure. The triethanolamine dose retained in the larynx may therefore be higher and counterbalance its weaker alkalinity.

A comparison of the data of the 5-day studies with those of the 28-day studies yields evidence of a decrease of the NOAEC with increasing exposure period for both monoethanolamine and triethanolamine.

In 4 of 7 NTP studies with F344 rats in which short-term and long-term exposures led to laryngeal inflammation, the NOAEC was lower in the long-term study than in the short-term study (Table 3). Both vapours and aerosols induced laryngeal inflammation. The NOAEC decreased with increasing exposure period after exposure to both vapours and aerosols.

Therefore, a decrease of the NOAEC for this end point after chronic exposure compared with that after subacute exposure cannot be excluded.

Table 2 Physico-chemical data, EU classification of irritation (ECHA 2017 a, b, c) and summary of the results of the relevant studies of 2-aminoethanol, diethanolamine and triethanolamine in rats

	2-Aminoethanol	Diethanolamine	Triethanolamine
CAS No.	[141-43-5]	[111-42-2]	[102-71-6]
vapour pressure	0.5 hPa	0.00037 hPa at 25 °C (NLM 2017 b)	4.8×10^{-6} hPa at 25 °C (NLM 2017 c)
boiling point	167 °C	270 °C	about 320 °C
pka	9.5	9	7.86
pH of 0.1 N solution	12 (NLM 2017 a)	11 (NLM 2017 b)	10.5 (NLM 2017 b)
solubility in water	miscible	miscible	miscible
vapour saturation concentration calculated from vapour pressure	1250 mg/m³	1.6 mg/m³	0.03 mg/m³
EU classification irritation skin/eyes	H314: causes severe skin burns and eye damage	H315: causes skin irritation H318: causes serious eye damage	not irritating
5 days			
NOAEC	20 mg/m³ (v)		100 mg/m³ (a)
LOAEC	200 mg/m³ (a/v): **laryngeal inflammation and lesions in the nasal epithelium**		200 mg/m³ (a) **laryngeal oedema/inflammation** MMAD 1 µm
28 days			
NOAEC	**10 mg/m³** (5% a)	14-day study: larynx not examined	$BMDL_{05}$: **14 mg/m³**
LOAEC	50 mg/m³ (50% a) **laryngeal inflammation (5/10 animals)**		20 mg/m³ (a) **laryngeal inflammation (3/14 animals)** MMAD 0.6–1 µm

Table 2 (continued)

	2-Aminoethanol	Diethanolamine	Triethanolamine
90 days			
NOAEC	–	**3 mg/m³** (a)	–
LOAEC	–	8 mg/m³ (a) **laryngeal inflammation (6/20 animals)** MMAD 0.6–0.7 µm	–
MAK value	0.2 ml/m³ ≙ 0.51 mg/m³ (according to Brüning et al. 2014)	1 mg/m³ ≙ 0.23 ml/m³	5 mg/m³ ≙ 0.8 ml/m³ (no time extrapolation)
Peak Limitation Category, excursion factor	I, 1	I, 1	I, 2

a = aerosol, v = vapour, MMAD = mass median aerodynamic diameter

Table 3 Time-dependency of the NOAEC for laryngeal inflammation in NTP studies in rats and mice

Substance and conclusion	Exposure		
	subacute for 2 weeks	subchronic for 13 weeks	chronic for 2 years
o-chlorobenzalmalononitrile (NTP 1990) aerosol rat: no time-dependent decrease of NOAEC mouse: no laryngeal inflammation		0.4, 0.75, 1.5, 3, 6 mg/m³ rat: LOAEC: 1.5 mg/m³ NOAEC: 0.75 mg/m³	0.075, 0.25, 0.75 mg/m³ rat: LOAEC: – NOAEC: 0.75 mg/m³
cobalt sulfate (NTP 1991) liquid aerosol rat: time-dependent decrease of NOAEC mouse: no time-dependent decrease of NOAEC	0.1, 0.5, 5, 50, 200 mg/m³ rat: LOAEC infl./necrosis: 50 mg/m³ NOAEC: 5 mg/m³	0.3, 1, 3, 10, 30 mg/m³ rat: LOAEC: 1 mg/m³ NOAEC: 0.3 mg/m³	
	mouse: LOAEC infl./necrosis: 5 mg/m³ NOAEC: 0.5 mg/m³	mouse: LOAEC: 10 mg/m³ NOAEC: 3 mg/m³	
1,6-hexanediamine dihydrochloride (NTP 1993 a) aerosol rat: no time-dependent decrease of NOAEC mouse: time-dependent decrease of NOAEC	10, 30, 89, 267, 800 mg/m³ rat ♂: LOAEC infl./necrosis: 10 mg/m³ NOAEC: – ♀: LOAEC infl./necrosis: 89 mg/m³ NOAEC: 30 mg/m³	1.6, 5, 16, 50, 160 mg/m³ rat ♂: LOAEC: 50 mg/m³ NOAEC: 16 mg/m³ ♀: LOAEC: 160 mg/m³ NOAEC: 50 mg/m³	
	mouse: LOAEC infl./necrosis: 267 mg/m³ NOAEC: 89 mg/m³	mouse ♂: LOAEC: – NOAEC: 160 mg/m³ ♀: LOAEC: 5 mg/m³ NOAEC: 1.6 mg/m³	

Table 3 (continued)

Substance and conclusion	Exposure		
	subacute for 2 weeks	subchronic for 13 weeks	chronic for 2 years
glutaraldehyde (NTP 1993 b) vapour rat: no time-dependent decrease of NOAEC mouse: no time-dependent decrease of NOAEC	0.16, 0.5, 1.6, 5, 16 ml/m³ rat ♂: LOAEC infl./necrosis: 1.6 ml/m³ NOAEC: 0.5 ml/m³ ♀: LOAEC infl./necrosis: 0.5 ml/m³ NOAEC: 0.16 ml/m³ mouse ♂: LOAEC infl./necrosis: 5 ml/m³ NOAEC: 1.6 ml/m³ ♀: LOAEC infl./necrosis: 1.6 ml/m³ NOAEC: 0.5 ml/m³	0.063, 0.125, 0.25, 0.5, 1 ml/m³ rat: LOAEC: – NOAEC: 1 ml/m³ mouse: LOAEC: – NOAEC: 1 ml/m³	
gallium arsenide (NTP 2000) aerosol rat: time-dependent decrease of NOAEC mouse: no time-dependent decrease of NOAEC, but difficult to interpret because LOAEC not determined in the 2-year study	1, 10, 37, 75, 150 mg/m³ rat: LOAEC: – NOAEC: 150 mg/m³ mouse: LOAEC: 75 mg/m³ NOAEC: 37 mg/m³	0.1, 1, 10, 37, 75 mg/m³ rat: LOAEC: – NOAEC: 75 mg/m³ mouse: LOAEC: – NOAEC: 150 mg/m³	0.01, 0.1, 1 mg/m³ rat: LOAEC: 1 mg/m³ NOAEC: 0.1 mg/m³ mouse: LOAEC: – NOAEC: 1 mg/m³

Table 3 (continued)

Substance and conclusion	Exposure		
	subacute for 2 weeks	subchronic for 13 weeks	chronic for 2 years
vanadium pentoxide (NTP 2002) aerosol rat: time-dependent decrease of NOAEC mouse: no laryngeal inflammation, only laryngeal metaplasia		0, 1, 2, 4, 8, 16 mg/m³ rat: LOAEC: – NOAEC: 16 mg/m³	0.5, 1, 2 mg/m³ rat: LOAEC: 0.5 mg/m³ NOAEC: –
1-bromopropane (NTP 2011) vapour rat: time-dependent decrease of NOAEC mouse: unclear because LOAEC not determined		62.5, 125, 250, 500 ml/m³ rat: LOAEC: – NOAEC: 500 ml/m³	125, 250, 500 ml/m³ rat: LOAEC: 250 ml/m³ NOAEC: 125 ml/m³
		mouse: LOAEC: – NOAEC: 500 ml/m³	62.5, 125, 250 ml/m³ mouse: LOAEC: – NOAEC: 250 ml/m³

infl.: inflammation

Manifesto (MAK value/classification)

The critical effect is inflammation in the laryngeal epithelium of rats after 28-day inhalation exposure.

MAK value. By extrapolating the data from animal studies to humans (1:3) and assuming an intensification of the effects found in a subacute study over time (1:6), a concentration of 0.8 mg/m³ is obtained from the $BMDL_{05}$ of 14.8 mg/m³ according to the method described by Brüning et al. (2014). As in the case of substances that have effects on the nose or eyes and for which there are human data for sensory irritation, it is assumed that not only adverse effects on the larynx are avoided in humans at this concentration, but also sensory irritation. This concentration would mathematically correspond to 0.13 ml/m³ and would thus be lower than the MAK value of 0.2 ml/m³ for monoethanolamine in relation to the molar mass. As the corrosive monoethanolamine is a considerably stronger base and triethanolamine did not cause irritation of the skin or eyes in the Draize test, a MAK value of 1 mg/m³ I (mathematically corresponds to 0.16 ml/m³) has been justified instead of the 0.5 mg/m³ that would have resulted with the preferred value approach. The fact that the severity of the laryngeal inflammation caused by triethanolamine did not increase in the 28-day study supports this value.

Peak limitation. As local irritation is the critical effect, triethanolamine remains in Peak Limitation Category I. As no human data are available for the sensory irritation of triethanolamine, an excursion factor of 1 has been established in line with that for the other ethanolamines.

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