The MAK Collection for Occupational Health and Safety

Triethanolamine

MAK Value Documentation, addendum – Translation of the German version from 2010

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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 triethanolamine [102-71-6], considering all toxicological endpoints. Available publications and unpublished study reports are described in detail.

After single application, triethanolamine was not found to have any relevant irritation potential for the skin or mucous membranes. The systemic toxicity of triethanolamine via all routes of exposure is low. A 28-day inhalation study in rats with aerosol exposure revealed a LOAEC of 20 mg/m³ for inflammation of the larynx, the most sensitive toxicological end point. A benchmark calculation for focal laryngeal inflammation yielded a BMDL of 14.8 mg/m³ for male rats and 14.1 mg/m³ for female rats and the maximum concentration at the work place (MAK value) is set at 5 mg/m³ which also provides protection from systemic effects caused by triethanolamine.

Since the critical effect is local, Peak Limitation Category I is designated, with an excursion factor of 4 because the effects on the larynx were observed only after prolonged exposure to 20 mg/m³ and triethanolamine had, if at all, a very low acute irritative potency.

There are no conclusive studies on developmental toxicity available. Triethanolamine is therefore classified in Pregnancy Risk Group D.

Triethanolamine is not genotoxic in vitro or in vivo; there is no evidence of germ cell mutagenicity. Oral and dermal studies in rats and mice yielded no evidence of a carcinogenic potential.

Skin contact is not expected to contribute significantly to systemic toxicity.

The sensitizing potency of triethanolamine is only very slight. Triethanolamine has therefore not been designated with “Sh” or “Sa” (for substances which cause sensitization of the skin or airways).

Keywords

triethanolamine; 2,2′,2″-nitrilotriethanol; tris(2-hydroxyethyl)amine; trolamine; mechanism of action; toxicokinetics; metabolism; (sub)acute toxicity; (sub)chronic toxicity; irritation; allergenic effects; reproductive toxicity; fertility; developmental toxicity; genotoxicity; carcinogenicity; peak limitation; prenatal toxicity; germ cell mutagenicity; absorption through the skin; sensitization; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

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Triethanolamine

MAK value (2009)	**5 mg/m³ I (inhalable fraction)**
Peak limitation (2009)	**Category I, excursion factor 4**
Absorption through the skin	**–**
Sensitization (2006)	**–**
Carcinogenicity	**–**
Prenatal toxicity (2009)	**Pregnancy Risk Group D**
Germ cell mutagenicity	**–**
BAT value	**–**
Synonyms	2,2′,2″-nitrilotriethanol, tris(2-hydroxyethyl)amine, trolamine
Chemical name	2,2′,2″-nitrilotriethanol
CAS number	102-71-6
Structural formula	$N(CH2CH2OH)_3$
Molecular formula	$C6H15NO_3$
Molar mass	149.19 g/mol
Melting point	20.5 °C (SRC 2009)
Boiling point at 1013 hPa	335.4 °C (SRC 2009)
Vapour pressure at 25 °C	< 1.0 Pa (ECB 2000; IARC 2000; SRC 2009)
Density at 25 °C	1.12–1.13 g/cm³ (ECB 2000; IARC 2000)
log K_{OW}[1)]	–1.0 (calculated) (SRC 2009)
1 ml/m³ (ppm) ≙ 6.190 mg/m³	**1 mg/m³ ≙ 0.161 ml/m³ (ppm)**

A large number of reviews are available for the toxicological profile of triethanolamine: a report by the IARC (2000), a toxicological evaluation by BG-Chemie (1990), a BUA report (BUA 1995), a Cosmetic Ingredient Review (CIR 1983), a BIBRA Toxicity Profile (BIBRA 1990) and a detailed review of ethanolamines by

1) octanol/water partition coefficient

Knaak et al. (1997). Many earlier studies were described and evaluated in the ECB IUCLID dataset (ECB 2000). Therefore, only data relevant to the evaluation are described in detailed here; earlier studies are briefly mentioned for the sake of completeness.

Because of the very low vapour pressure, the theoretical concentration of an atmosphere saturated with triethanolamine vapour at 25 °C is only about 0.29 ml/m^3 (0.047 ppm).

1 Toxic Effects and Mode of Action

Local irritation of the laryngeal region of the upper respiratory tract was the most sensitive end point of toxicity. A 28-day inhalation study in Wistar rats revealed a dose-dependent increase in the incidence of focal, almost exclusively mild, laryngeal inflammation in rats at the low concentration of 20 mg/m^3 and above. Even after repeated dermal application, local irritation of the skin is the main effect in rats and mice. In long-term studies, triethanolamine induced chronic inflammation and acanthosis, erosion and ulcers at the application site after exposure to the low dose of 32 mg/kg body weight and day and above in rats and to 100 mg/kg body weight and day and above in mice. After single applications, triethanolamine was not found to have any relevant irritation potential for the skin or mucous membranes.

The systemic toxicity of triethanolamine was low after single and repeated doses via all routes. The systemic LOAEL (lowest observed adverse effect level) after long-term administration was 250 mg/kg body weight and day. After dermal application, reduced body weight gains and increased kidney weights were observed at this dose level and above.

The sensitizing potential of triethanolamine was only very slight (see documentation "Triethanolamine" 2007).

Screening studies and studies with repeated administration in rats and mice yielded no evidence of impaired fertility. There are no multi-generation studies or conclusive developmental toxicity studies available.

Triethanolamine did not reveal mutagenic or clastogenic effects in bacteria or mammalian cells in vitro or in the mouse micronucleus test in vivo.

Benign tumours or tumours that were not dose-dependent were sporadically observed in carcinogenicity studies with oral administration and dermal application. These studies yielded no evidence of a carcinogenic potential of triethanolamine in humans.

2 Mechanism of Action

There are far fewer studies of the mechanism of action of triethanolamine than for the structurally related diethanolamine (see supplement "Diethanolamine" 2007). Like diethanolamine, triethanolamine leads to a disturbance in choline homeo-

stasis and an imbalance in phospholipid metabolism, albeit to a lesser extent. An essential difference in the mechanism of action is that the structure of triethanolamine prevents its incorporation into cell membranes (Knaak et al. 1997), which could lead to toxic effects such as anaemia. Anaemia was not observed after doses of 500 to 1000 mg/kg body weight and day with the drinking water for 2 years (NTP 1987 a).

Effects on choline homeostasis

The potential of triethanolamine to induce choline deficiency in the liver was investigated in B6C3F1 mice and F344 rats. The acetone solvent, the maximum tolerated triethanolamine dose of 1000 mg/kg body weight and day or graded triethanolamine doses of 0, 10, 100 or 300 mg/kg body weight and day, dissolved in acetone, were applied to the skin of female mice on 5 days a week for 3 weeks. Triethanolamine doses of 0 or 250 mg/kg body weight and day were applied to female rats. Reduced levels of choline, phosphocholine and betaine, which is the oxidative metabolite of choline, were detected in mice, but not in rats. After the application of 1000 mg/kg body weight and day, betaine was reduced by about 26%, phosphocholine by about 35% and choline by about 13%. A subsequent in vitro study in the ovarian cells of Chinese hamsters revealed the uptake of [^{3}H]-choline into the cells to be inhibited in a dose-dependent manner after co-cultivation with triethanolamine (Stott et al. 2000).

Effects on phospholipid metabolism

An in vitro study showed that triethanolamine has an inhibitory effect on the incorporation of [^{32}P]-phosphate into phospholipids from human and rabbit tissues (IARC 2000).

Nitrosamine formation

In an in vitro study of the possible nitrosation of triethanolamine to *N*-nitrosodiethanolamine under various physiological conditions of the gastrointestinal tract, the incubation of triethanolamine in acid or the colon flora of mice merely led to slight nitrosation with the formation of a maximum of around 3% or 0.68% *N*-nitrosodiethanolamine. The research group could not demonstrate the formation of *N*-nitrosodiethanolamine in vivo in female B6C3F1 mice after either 7-day dermal application of 1000 mg/kg body weight and day or single bolus doses at this level and simultaneous treatment with sodium nitrite ($NaNO_2$) (Saghir et al. 2005). A possible carcinogenic effect of *N*-nitrosodiethanolamine formed by triethanolamine can therefore be ruled out.

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution and elimination

In vivo

Triethanolamine is rapidly absorbed via the oral route. In Wistar rats, about 63% of the dose was absorbed via the intestines within 1 hour (IARC 2000).

In C3H mice, the maximum level of [^{14}C]-triethanolamine in blood was determined 2 hours after the dermal application of 2000 mg/kg body weight, whereas the levels in the blood of F344 rats indicated that absorption via the skin after the dermal application of 1000 mg/kg body weight was somewhat delayed. Various experimental studies with [^{14}C]-triethanolamine doses of between 1000 and 2000 mg/kg body weight showed that dermal absorption in mice is more or less complete within 24 hours. A comparison 48 hours after application showed there to be no difference in the amount absorbed (about 90%) between C3H mice and F344 rats. After topical application of [^{14}C]-triethanolamine doses of 2000 mg/kg body weight, dissolved in acetone, to 2 cm^2 of the dorsal skin of mice, the level in blood was about 5 times higher than that after exposure to 1000 mg/kg body weight. When [^{14}C]-triethanolamine doses of 1000 mg/kg body weight, dissolved in acetone, were applied to about 2 cm^2 of the dorsal skin of mice, the level in blood at a similar time was about 1000 times higher than that after intravenous injection of 1 mg/kg body weight (Dow Chemical Company 1988; Stott et al. 2000).

A quantitative estimation of dermal absorption in rats and mice was derived from the following data. After a single application of undiluted [^{14}C]-triethanolamine to the skin of rats (1000 mg/kg body weight; 1.75 cm^2) or mice (2000 mg/kg body weight; 1.75 cm^2) for 48 hours, a higher rate of penetration was observed through the rat skin (2.4 mg/cm^2 and hour) than through mouse skin (0.4 mg/cm^2 and hour). According to the authors, this 6 times higher rate of penetration was the result of the 6 times higher dose per area in rats, rather than increased permeability, because the permeability constants (k_p) of rats ($k_p = 1.85 \times 10^{-2}$ cm and hour) and mice ($k_p = 1.8–2.0 \times 10^{-2}$ cm and hour) are very similar. In mice, the absorption rate was 0.8 mg/cm^2 and hour. The dermal absorption rates of about 30% aqueous (neutralized with HCl) or undiluted triethanolamine were similar in mice. This was evidence that triethanolamine increases its own penetration (Knaak et al. 1997). However, in rats, methodological problems arose (occlusion slipped out of position or dropped off in some cases resulting in a larger exposed area and possible oral uptake (Dow Chemical Company 1988)) which led to an increased uptake during the first 24 hours. Therefore, the data from rats are not reliable quantitatively, but a qualitative comparison shows absorption is poorer in rats than in mice within the first 24 hours.

In studies carried out under the National Toxicology Program, female F344 rats treated with doses of 68 mg/kg body weight (1 mg/cm^2) and 276 mg/kg body weight dermally absorbed only 20% and 30%, respectively, of the dose. In contrast, the amount dermally absorbed by female B6C3F1 mice treated with doses of 79 mg/kg

body weight (1 mg/cm^2) and 1120 mg/kg body weight (15 mg/cm^2) was 57% and 81%, respectively. Thus, mice absorbed 3 times more triethanolamine than rats. Possible species-specific factors, such as the thinner skin of mice, were assumed to be the reason for this difference (NTP 2004). The amounts eliminated with the urine and faeces after 24 hours show that mice absorb triethanolamine far more rapidly than rats at the same dose per skin area (1 mg/cm^2).

After the administration of a single oral dose of 350 mg per animal, male Wistar rats eliminated about 57% unchanged triethanolamine with the urine and about 23% with the faeces up to day 3. Likewise, after repeated doses, triethanolamine was eliminated mainly unchanged and 1.4% to 2.7% was eliminated as the glucuronide conjugate. The amount of unchanged triethanolamine eliminated remained constant throughout the 6-day observation period (IARC 2000).

In mice treated dermally with [^{14}C]-triethanolamine doses of 1000 mg/kg body weight, the substance was eliminated from the blood according to first order kinetics with a rapid and slow phase with half-lives of 1.9 and 31 hours, respectively. The clearance of radioactivity from the blood was about 955 ml/kg body weight and hour (Dow Chemical Company 1988; NTP 2004).

In mice, about 60% of a dermal dose of [^{14}C]-triethanolamine of 1000 mg/kg body weight was eliminated with the urine within 48 hours; faecal elimination was about 20%. Less than 10% remained on the skin around the application site. The tested rats eliminated 54% with the urine and 9% with the faeces (Dow Chemical Company 1988; Stott et al. 2000).

In vitro

In vitro diffusion cell studies investigated the penetration through human skin of 1% or 5% [^{14}C]-triethanolamine (about 0.5 µCi) in an oil-in-water emulsion (3 mg emulsion/cm^2). Persistence on the skin was 24 hours. At an initial pH of 8, about 1% of the test emulsion penetrated into the receptor fluid. Lowering the pH to 7 led to a reduction in absorption to 0.43% for the 1% triethanolamine emulsion and to 0.28% for the 5% triethanolamine emulsion. Irrespective of the pH, 80% to 90% of the triethanolamine was washed off the skin at the end of the study after 24 hours. The fractions remaining in the cornea and living skin (epidermis and dermis) were about the same and were 4.9% and 4.4% for the 1% triethanolamine emulsion and 2.4% and 3.1% for the 5% triethanolamine emulsion. As the fractions in the washing fluid or cornea were not bioavailable, the total dermal bioavailability (receptor fluid, epidermis and dermis) varied between 3.5% and 4.9% at a pH of 7 and was about 10% at a pH of 8. The amount absorbed increased only minimally when the collection time of the receptor fluid was extended to 72 hours. The steady state of penetration was reached after 12 hours (Kraeling and Bronaugh 2003).

3.2 Metabolism

Biodegradation of triethanolamine to monoethanolamine or diethanolamine or to any other metabolite has not been demonstrated in rodents, nor was the substance

found to be incorporated into other macromolecules. Likewise, there was no evidence of *N*-nitrosodiethanolamine forming under physiological conditions (IARC 2000).

In particular the possible metabolism of [^{14}C]-triethanolamine to monoethanolamine or diethanolamine was investigated in exposed mice after dermal application or intravenous injection. Mass spectroscopy did not reveal any of these potential metabolites. Instead, the fraction of unchanged triethanolamine in the urine was about 95% of the radioactivity. The total levels in tissue – the sum of the levels in the liver, kidneys, animal body and skin (without application site) – were between 3% and 8% (Dow Chemical Company 1988; IARC 2000; Knaak et al. 1997; Stott et al. 2000).

Slight conjugation with glucuronic acid was detected in rats (IARC 2000).

4 Effects in Humans

4.1 Single exposures

There are no data available.

4.2 Repeated exposure

Workers from the former Soviet Union who had been exposed to an aerosol spray from a coolant containing 1% triethanolamine and 0.3% sodium nitrite complained after 3 to 5 months of headaches. Most of the workers had high blood pressure. Changes in the organs, in the CNS or on the skin were not reported (BIBRA 1990). The study was inadequately documented; therefore, it has not been included in the evaluation.

4.3 Local effects on skin and mucous membranes

Triethanolamine was tested together with 3 other industrially used surfactants for its ability to stimulate the release of pro-inflammatory mediators in human skin. In a preliminary test, undiluted or 50% aqueous triethanolamine was applied occlusively to the forearms of 20 male subjects for 24 hours. The readings were carried out 15 minutes and 24 and 48 hours after removal of the patch. Triethanolamine was not found to cause irritation. Subsequently, amounts of 100 to 200 mg/cm^2 (765 µmol/cm^2) were applied occlusively to the forearms of 12 male subjects. After 24-hour application, suction blisters formed at the treated sites and the concentrations of eicosanoids, for example arachidonic acid and prostaglandins, and of interleukin-1α were investigated in the suction blister fluids. Unlike sodium lauryl sulfate, benzalkonium chloride and Tween 80, the other tested surfactants, triethanolamine did not lead to a response in the eicosanoid profile compared with the control values (Müller-Decker et al. 1998).

Immediately after the application of undiluted triethanolamine to the skin, 1 of 6 subjects reacted with a slight burning sensation and mild erythema. No persons reacted after 24-hour semi-occlusive application. Likewise, 24-hour occlusive application of technical-grade triethanolamine did not cause any reaction. Mild erythema was observed in 2 of the 5 persons when the test period was extended to 72 hours. However, 50% triethanolamine in olive oil or water did not produce irritation even in the two sensitive persons (ECB 2000).

A concentration of 50% triethanolamine in petrolatum did not cause irritation of the skin after a single 48-hour application (Meneghini et al. 1971).

After 3 days, daily application of a 5% triethanolamine solution in ethanol to the abraded skin of test persons caused mild irritation and a 10% solution caused marked irritation, whereas irritation of the intact skin was observed only after the application of undiluted triethanolamine (Frosch and Kligman 1976).

4.4 Allergenic effects

Sensitizing effects on the skin

One new study has become available since the sensitizing effects of the substance were evaluated in 2007.

Among metal workers with dermatitis on the hands (172 cases from 1996 to 2004), who were treated and observed for more than 6 weeks, only 4 reacted to triethanolamine (1996–2001; see also documentation "Triethanolamine" 2007). Follow-up studies of these 4 patients showed that possible or actual contamination with diethanolamine or monoethanolamine could be ruled out as the cause. As the 4 patients did not react to the triethanolamine from the IVDK base series that was tested simultaneously, and triethanolamine was no longer included in the IVDK test block "metal working fluids" as of 2001 and did not produce any reactions when tested separately, the authors concluded that the irritation was caused by the more potent alkanolamines monoethanolamine and diethanolamine tested in close proximity (Fartasch and Breuer 2007).

A recent publication summarizes all available studies on the sensitizing potential of alkanolamines, including triethanolamine. Only 0.4% of a total of 85 098 patients (IDVK) reacted in patch tests to 2.5% triethanolamine, but mild irritation was quite common. The authors concluded that the sensitizing potential of triethanolamine is only very slight (Lessmann et al. 2009).

Sensitizing effects on the airways

No new studies have become available since the sensitizing effects of the substance were evaluated in 2007.

4.5 Reproductive and developmental toxicity

There are no data available.

4.6 Genotoxicity

There are no data available.

4.7 Carcinogenicity

There are no data available.

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

Triethanolamine has very low acute toxicity, irrespective of the route of absorption.

5.1.1 Inhalation

An atmosphere saturated with triethanolamine vapour at 20 °C was not lethal for 12 exposed rats after 8-hour inhalation exposure (BASF AG 1966).

5.1.2 Oral administration

The LD_{50} values derived in a large number of studies were in the range between 4190 and 11 300 mg/kg body weight in rats (BASF AG 1966; BIBRA 1990; CIR 1983; Knaak et al. 1997; Union Carbide Corp 1984), between 5400 and 7800 mg/kg body weight in mice (BIBRA 1990; CIR 1983; Knaak et al. 1997), between 5160 and 5200 mg/kg body weight in rabbits (BIBRA 1990; Knaak et al. 1997; Sidorov et al. 1968) and between 5300 and 8000 mg/kg body weight in guinea pigs (BIBRA 1990; CIR 1983; Knaak et al. 1997). A study in rats reported lethal effects caused by the alkalinity in the gastrointestinal tract and another reported liver and kidney damage (BIBRA 1990); in another study, Sprague Dawley rats merely became apathetic; necropsy did not reveal any unusual findings (BASF AG 1966). Overall, the recorded symptoms were non-specific and do not suggest a particular hazard potential.

5.1.3 Dermal application

The LD_{50} values were higher than 17 000 mg/kg body weight in rats (Union Carbide Corp 1984) and higher than 20 000 mg/kg body weight in rabbits (Knaak et al. 1997; Union Carbide Corp 1984).

5.1.4 Intraperitoneal injection

A study in mice derived an LD_{50} value of 1500 mg/kg body weight after intraperitoneal injection. Convulsions were the only clinical observations (no other details; BASF AG 1966).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

Data from inhalation studies with triethanolamine are shown in detail in Table 1, the incidences and grading of laryngeal changes found in a 28-day inhalation study in rats are shown in Table 2.

Rats

In a range-finding study, groups of 5 male and 5 female Wistar rats were exposed to triethanolamine concentrations of 0, 100, 200 or 400 mg/m^3 with a mass median aerodynamic particle diameter of 1.0 µm for 6 hours a day, for 5 days. The animals were exposed nose-only to an aerosol. There was no evidence of substance-induced changes in clinical, clinico-chemical or haematological parameters except for a reddish discharge without blood that was observed in some animals of the high concentration group. No animals died, and the organ weights and body weight gains were not affected. Inflammatory oedema was found in the larynx of the exposed animals at 200 mg/m^3 and above. The incidences were 0/5, 0/5, 1/5 and 3/5 in the males and 0/5, 0/5, 2/5 and 4/5 in the females at 0, 100, 200 and 400 mg/m^3, respectively. The severity of the inflammatory oedema was given a score of 2 (of a maximum of 5) after exposure to 200 mg/m^3 and a score of 3 at 400 mg/m^3 (BG Chemie 1991, 1993; Gamer et al. 2008).

In the subsequent study, which was carried out according to OECD Test Guideline 412 taking into account potential neurotoxicity (functional observation battery), groups of 10 male and 10 female Wistar rats were exposed nose-only to triethanolamine aerosol concentrations of 0, 20, 100 or 500 mg/m^3 for 28 days (20 exposures) for 6 hours a day. The mass median aerodynamic particle diameter was between 0.6 and 1.0 µm. Lethal effects, signs of systemic toxicity or evidence of a neurotoxic potential were not observed. There were no clinical findings other than mild irritation of the upper respiratory tract in the form of reddish crusts around the nose, which became manifest at the high concentration in the second

Table 1 Effects of triethanolamine after repeated inhalation

Species, strain, number per group	Exposure	Findings	References
rat, Wistar, 5 ♂/5 ♀	**5 days**, 0, 100, 200, 400 mg/m³ 6 hours/day aerosol / nose-only	**100 mg/m³**: ♂/♀: NOAEC local irritation of the upper respiratory tract **200 mg/m³ and above**: ♂/♀: laryngeal oedema, grade 2 of a maximum of 5 (♂: 1/5; ♀: 2/5) **400 mg/m³**: ♂/♀: NOAEC systemic toxicity; laryngeal oedema, grade 3 of a maximum of 5 (♂: 3/5; ♀: 4/5); reddish discharge without blood	BG Chemie 1991, 1993; Gamer et al. 2008
rat, F344, 5 ♂/5 ♀	**16 days**, 0, 125, 250, 500, 1000, 2000 mg/m³ 6 hours/day, 5 days/week, 12 exposures aerosol / whole-body	**125 mg/m³and above**: ♂/♀: mild inflammation of the laryngeal mucosa in individual animals (not dose-dependent; see text), accompanied by lymphocyte, plasma cell and neutrophil infiltration **500 mg/m³ and above**: ♂: relative kidney weights ↑, ♀: absolute kidney weights ↑ **1000 mg/m³ and above**: ♂/♀: NOAEC systemic toxicity **2000 mg/m³**: ♂/♀: body weight gains ↓ ♂: relative liver weights ↑, absolute kidney weights ↑, ♀: relative kidney weights↑	Union Carbide Corp 1985 a
rat, Wistar, 10 ♂/10 ♀	**28 days**, 0, 20, 100, 500 mg/m³ 6 hours/day, 5 days/week, 20 exposures aerosol / nose-only OECD Test Guideline 412	**20 mg/m³ and above**: ♂/♀: minimal to slight focal laryngeal inflammation (see Table 2) **500 mg/m³**: ♂/♀: NOAEC systemic toxicity; reddish crusts around the nose in the second half of the study, minimal to moderate focal laryngeal inflammation (see Table 2)	BG Chemie 1993, Gamer et al. 2008
mouse, B6C3F1, 5 ♂/5 ♀	**16 days**, 0, 125, 250, 500, 1000, 2000 mg/m³ 6 hours/day, 5 days/week, 12 exposures aerosol / whole-body	**125 mg/m³ and above**: ♂/♀: erythrocytes ↑, haemoglobin ↑, haematocrit ↑, ♀: body weight gains ↓ **250 mg/m³ and above**: ♂/♀: mild inflammation of the laryngeal mucosa (lymphocyte, plasma cell and neutrophil infiltration) in individual animals **1000 mg/m³**: ♀: absolute and relative thymus weights, absolute heart weights ↓ **2000 mg/m³**: ♀: body weights ↓, relative kidney weights ↑, leukopenia with relative neutrophilia	Union Carbide Corp 1985 b

NOAEC: no observed adverse effect concentration

Table 2 Inflammatory changes in the rat larynx after exposure to triethanolamine aerosol for 28 days (BG Chemie 1993; Gamer et al. 2008)

		triethanolamine concentration (mg/m³)			
		0	20	100	500
focal laryngeal inflammation					
grade 1	♂	0/ 7	2/ 7	1/ 7	0/ 7
	♀	0/ 7	0/ 7	1/ 7	2/ 7
	♂/♀	**0/14**	**2/14**	**2/14**	**2/14**
grade 2	♂	0/ 7	1/ 7	1/ 7	3/ 7
	♀	0/ 7	0/ 7	1/ 7	2/ 7
	♂/♀	**0/14**	**1/14**	**2/14**	**5/14**
grade 3	♂	0/ 7	0/ 7	0/ 7	1/ 7
	♀	0/ 7	0/ 7	0/ 7	0/ 7
	♂/♀	**0/14**	**0/14**	**0/14**	**1/14**
grades 4 and 5	♂	0/ 7	0/ 7	0/ 7	0/ 7
	♀	0/ 7	0/ 7	0/ 7	0/ 7
	♂/♀	**0/14**	**0/14**	**0/14**	**0/14**

half of the study. The histopathological examination revealed minimal to slight focal inflammatory changes (grade 1 and 2 of a maximum of 5) in the submucosa of the larynx (see Table 2) of a few animals at the two low concentrations of 20 and 100 mg/m³ with a flat concentration–effects relationship. About twice as many animals were affected at the concentration of 500 mg/m³ with an increase in the effect size. There were no laryngeal findings in the control animals (BG Chemie 1993; Gamer et al. 2008).

In earlier 16-day range-finding inhalation studies, F344 rats were exposed to triethanolamine under the US National Toxicology Program. Dermal exposure resulting from whole-body exposure has to be taken into account here (the report described damp fur following aerosol exposure). Groups of 5 male and 5 female animals were exposed to aerosol concentrations of 0, 125, 250, 500, 1000 or 2000 mg/m³ (mass median aerodynamic particle diameter: 2.0–2.7 µm) in a whole-animal exposure chamber for 6 hours per day. No rats died and no clinical symptoms were observed. The relative kidney weights of the males were increased at 500 mg/m³ and above. Body weight gains were reduced in the animals of the group exposed to 2000 mg/m³. At necropsy, the relative liver weights were increased in the males of this group and the relative kidney weights were increased in the females. Mild inflammation (grading was not reported) of the laryngeal submucosa was accompanied by the infiltration of lymphocytes, plasma cells and neutrophils. The incidences were 0/5, 1/5, 0/5, 0/5, 1/5 and 3/5 in the males

and 0/5, 2/5, 0/5, 0/5, 1/5 and 2/5 in the females at 0, 125, 250, 500, 1000 and 2000 mg/m³, respectively (Union Carbide Corp 1985 a). It must be borne in mind that the animals were exposed in whole-animal chambers and that the incidences were minimal apart from at the high concentration and did not reveal any dose–response relationship. The results are consistent with those obtained in recent studies by BG Chemie (1991, 1993).

Mice

In earlier 16-day range-finding inhalation studies, triethanolamine was investigated in B6C3F1 mice under the US National Toxicology Program. Dermal exposure resulting from whole-body exposure has to be taken into account here (the report described damp fur following aerosol exposure). Groups of 5 male and 5 female animals were exposed to aerosol concentrations of 0, 125, 250, 500, 1000 or 2000 mg/m³ (mass median aerodynamic particle diameter: 2.0–2.7 µm) in a whole-animal exposure chamber for 6 hours per day. Body weight gains were reduced in all exposed females, erythrocyte counts, haemoglobin concentrations and haematocrit values were increased in animals of both sexes, and leukopenia was observed in the males. In female mice, the absolute and relative thymus weights and the absolute heart weights were increased at 1000 mg/m³ and above. At 2000 mg/m³ and above, the relative kidney weights were increased, the body weights were reduced and likewise leukopenia with relative neutrophilia was observed. The histopathological examination revealed mild inflammation of the laryngeal mucosa (grading was not reported) in the animals exposed to 250, 500, 1000 or 2000 mg/m³. The incidences were 0/4, 0/1, 1/5, 1/4, 1/4 and 3/5 in the males and 0/5, 0/4, 1/5, 1/5, 1/4 and 0/4 in the females after exposure to 0, 125, 250, 500, 1000 and 2000 mg/m³, respectively (Union Carbide Corp 1985 a). Thus, the laryngeal findings were minimal also in B6C3F1 mice and revealed a flat dose–response relationship over a wide exposure range. As in the 28-day inhalation study in rats, the male animals seemed to be more sensitive also in mice.

Summary and evaluation

The systemic toxicity of triethanolamine was found to be only very slight in 3 inhalation studies in rats and an inhalation study in mice. In all studies, effects on the larynx were the most important. The longest inhalation study in rats, which was carried out for 28 days according to OECD Test Guideline 412, revealed focal laryngeal inflammation at the low concentration of 20 mg/m³ and above; the severity up to and including concentrations of 100 mg/m³ was given scores of 1 and 2 of a maximum of 5. Grade 3 inflammation was observed at 500 mg/m³ and above in this study and at 400 mg/m³ and above in the 5-day range-finding study. This indicates that the effects on the larynx are not time-dependent to any great extent.

The inflammation observed may be a precursor of metaplasia or may develop into chronic inflammation. An overall evaluation of all animals affected by laryngeal

inflammation revealed a concentration–effects relationship, which was manifest in the form of both a slight increase in the incidence of animals affected and a slight increase in the severity (Table 2). Therefore, the effects at 20 mg/m^3 and above are considered to be adverse. The males seemed to be more sensitive and have a steeper concentration–effect relationship, but in view of the small number of animals tested it is not clear whether the sex-specific sensitivity has been over-interpreted.

A benchmark calculation published for focal laryngeal inflammation in the 28-day inhalation study yielded a BMDL (benchmark dose lower confidence limit) of 14.8 mg/m^3 for male rats and 14.1 g/m^3 for female rats. Furthermore, the authors added a factor of 3 for the extrapolation to medium-term exposure; this resulted in a calculated no effect concentration of 4.7 mg/m^3 (Gamer et al. 2008).

5.2.2 Oral administration

Rats

Triethanolamine was investigated in F344 rats in oral range-finding studies under the US National Toxicology Program. Groups of 5 male and 5 female rats were given triethanolamine concentrations of 0%, 0.5%, 1%, 2%, 4% or 8% with the drinking water for 14 days. This corresponds to a normal uptake of about 500, 1000, 2000, 4000 or 8000 mg/kg body weight and day; however, water consumption (no other details) was reduced at 4% and above; palatability was assumed to be the reason for this. The females had increased kidney weights at 2% triethanolamine in the drinking water and above (no other details). At 4% and above, body weight gains were reduced, and there was a significant decrease in liver, thymus, heart and lung weights. In the last 4 days of the study, 8 animals of the high concentration group died or had to be sacrificed in a moribund state. Moreover, the animals of this concentration group began to lose weight and had brown, smeared noses; dehydration resulted in increased erythrocyte counts, haemoglobin concentrations and haematocrit values. There were no unusual gross-pathological or histopathological findings (NTP 1987 a).

Triethanolamine was given to groups of 50 male and 50 female F344 rats in concentrations of 0%, 1% or 2% with the drinking water (corresponding to doses of about 1000 or 2000 mg/kg body weight and day). Because of severe nephrotoxicity, the concentrations in the females were reduced by half as from week 69 of the study (0.5% and 1% corresponding to doses of about 500 and 1000 mg/kg body weight and day). A dose-dependent decrease in body weight gains was observed in all exposed animals. The mortality of the females was increased in a dose-dependent manner (16%, 32% and 42% in the controls, low dose and high dose groups) and was presumably the result of the kidney damage observed. At the low dose and above, increased absolute and relative kidney weights and mineralization of the renal papilla were observed in the males and females. Pyelonephritis, hydronephritis and chronic nephropathy were found in the females at the low dose and above and in the males only at the high dose. In the high dose group, animals of both sexes were found to have nodular hyperplasia of the pelvic mucosa (Maekawa et al. 1986).

Because of the effects on the kidneys, the LOAEL was about 1000/500 mg/kg body weight and day and the NOAEL (no observed adverse effect level) was lower than 500 mg/kg body weight and day.

Mice

An oral range-finding study was also carried out in B6C3F1 mice under the US National Toxicology Program. Groups of 5 male and 5 female rats were given triethanolamine concentrations of 0%, 0.5%, 1%, 2%, 4% or 8% with the drinking water for 14 days. This corresponds to a normal uptake of about 1000, 2000, 4000, 8000 or 16 000 mg/kg body weight and day; however, water consumption (no other details) was reduced at 4% and above; palatability was assumed to be the reason for this. There was a statistically significant decrease in thymus weights in the 4% group (no other details). At a drinking water concentration of 8% and above, body weight gains were reduced, and dehydration and histopathological changes in the liver were found. There were no unusual gross-pathological or histopathological findings (NTP 1987 b).

The chronic toxicity potential of triethanolamine was investigated in groups of 50 male and 50 female B6C3F1 mice given triethanolamine concentrations of 0%, 1% or 2% (corresponding to doses of about 0, 1600 and 3200 mg/kg body weight and day) ad libitum in the drinking water for 82 weeks. There was no substance-induced increase in mortality. In the high dose group, the body weight gains were slightly reduced in the males during the first 3 to 4 months and in both sexes as from week 60 of the study (Konishi et al. 1992). Non-neoplastic findings in the organs were not reported.

A number of studies are mentioned below for the sake of completeness, even though they are only available as brief or secondary information, they were published some while ago or do not comply with current testing and evaluation requirements.

When Sherman rats were given triethanolamine doses of 6 to 2610 mg/kg body weight and day with the diet for 90 days, lethal effects and liver and kidney changes were observed at 730 mg/kg body weight and day and above, and body weight gains were reduced at 1270 mg/kg body weight and day and above. The highest tested dose without effects was 80 mg/kg body weight and day (Smyth et al. 1951).

A study from the 1970 s in which triethanolamine doses of 250 to 1000 mg/kg body weight and day were given to groups of 20 male and 20 female CoxCD rats with the diet for 91 days did not yield any adverse findings in the clinical, haematological, gross-pathological or histopathological examinations (Confidential 1989).

In another study from the 1970 s, triethanolamine concentrations of 1.4 mg/l were given to rats with the drinking water for 6 months (this corresponds to doses of 140 mg/kg body weight and day for a drinking water consumption of 100 ml/kg body weight and day). Changes in liver, kidney and CNS functions (no other details) and an increase in neutrophils and lymphocytes in the blood were reported (CIR 1983).

A study from the 1940 s described slight changes in the liver, kidneys and optic nerves in rats given triethanolamine doses of 200 to 1800 mg/kg body weight and day with the diet for 60 or 120 days; the changes were not specified in detail (BIBRA 1990; CIR 1983; Knaak et al. 1997).

This research group also published similar findings in guinea pigs given gavage doses of triethanolamine of 200 to 1600 mg/kg body weight and day throughout the same test period (BIBRA 1990; CIR 1983; Knaak et al. 1997).

5.2.3 Dermal application

Rats

Dermal application studies with triethanolamine are shown in Table 3.

Triethanolamine was investigated for toxicity after dermal application in range-finding studies under the US National Toxicology Program. Doses of 0, 141, 281, 563, 1125 or 2250 mg/kg were applied undiluted to the shaved dorsal skin of the interscapular region (about 6 cm^2) in groups of 5 male and 5 female F344 rats on 5 days a week, for 16 days (12 applications altogether). The control group remained untreated. None of the doses was lethal. The application sites were brownish in colour and all animals of the 3 high dose groups developed inflammation in the region of the application site; some animals of the groups treated with 141 and 281 mg/kg were also affected. This local inflammation was observed somewhat later in female rats. Feed consumption was reduced only slightly by a maximum of 4% in all exposed animals. In the high dose group, body weight gains were reduced by 23.1% in the males and by 9.1% in the females. The relative liver and kidney weights were increased in the females of this dose group. In male rats, the relative kidney weights were increased in the two high dose groups, and the relative heart weights were increased and the absolute thymus and lung weights were reduced in the high dose group. Further changes in the organ weights of the high dose group were related to the reduced body weights (NTP 1985 a, 1987 a).

In the subsequent medium-term study, triethanolamine doses of 0, 125, 250, 500 or 1000 mg/kg body weight and day dissolved in acetone or undiluted triethanolamine doses of 2000 mg/kg body weight and day were applied topically to the shaved dorsal skin of groups of 10 male and 10 female F344 rats on 5 days a week, for 90 days. No animals died. At the end of the study, the body weights were significantly reduced in both sexes of the group treated with 2000 mg/kg and in the females of the group treated with 1000 mg/kg. Local inflammation at the application site was the only clinical observation in the three high dose groups. In the high dose group, leukocyte counts were increased in the males, and the MCV and haematocrit were reduced in both sexes. Further changes in the blood count resulted from the inflammation on the skin. The serum aspartate aminotransferase and alanine aminotransferase levels were increased in the males and females of the high dose group, and the females also had increased albumin and urea levels. In the high dose group, the relative thymus weights and the specific gravity of the urine

were increased in the males and the glucose level was increased in the females. At 1000 mg/kg body weight and day and above, the specific gravity of the urine and the relative kidney weights were increased in the females, and the males had increased relative spleen weights. The protein concentrations in the urine of the males were increased at 500 mg/kg body weight and day and above, and the relative kidney weights were increased at 250 mg/kg body weight and day and above. Further changes in organ weights were related to the reduced body weights. The histopathological examination revealed a dose-dependent increase in the incidence of nephropathy in the females and hypertrophy of the pituitary gland in both sexes at the low dose and above. Chronic inflammation including acanthosis was observed on the skin at the application site in the males at 250 mg/kg body weight and day and above and in the females at 500 mg/kg body weight and day and above. Because of the effects on the kidneys and pituitary gland, the LOAEL for systemic toxicity was 125 mg/kg body weight and day. The NOAEL for local irritation was 125 mg/kg body weight and day for male rats and 250 mg/kg body weight and day for female rats (NTP 1987 a).

A 6-month study reported functional changes in the liver and CNS in rats after dermal treatment with a 13% triethanolamine solution for 1 hour a day, on 5 days a week (no other details; BIBRA 1990).

In a dermal NTP carcinogenicity study, triethanolamine doses dissolved in acetone were topically applied to the shaved dorsal skin of groups of 60 male and 60 female F344 rats on 5 days a week, for 103 weeks (see also Section 5.7.2). The doses were 0, 32, 63 or 125 mg/kg body weight and day for males and 0, 63, 125 or 250 mg/kg body weight and day for females. Mortality was slightly increased compared with in the control animals only in the females of the high dose group. At the end of the study, the body weights of the females of the high dose group were significantly reduced by 9% to 12%. Local changes at the application site in the form of chronic inflammation and acanthosis were the clinical observations recorded in the females of all dose groups. There was also an increased incidence of erosion and ulcers at the middle dose of 125 mg/kg body weight and day and above. Similar findings and incidences were observed in the males of the high dose group of 125 mg/kg body weight and day. Haematology and clinical pathology did not reveal any substance-induced findings. At the interim sacrifice after 15 months, only the females of the high dose group of 250 mg/kg body weight and day were found to have increased absolute and relative kidney weights. The incidence of renal hyperplasia was similar in all dose groups (9/50, 8/50, 7/49 and 6/50 at 0, 32, 63 and 125 mg/kg body weight and day), but the severity increased in the two high dose groups (NTP 1999). In this long-term study, the systemic NOAEL was 125 mg/kg body weight and day. The LOAEL, at which reduced body weight gains and increased kidney weights were observed in female rats, was 250 mg/kg body weight and day.

Table 3 Effects of triethanolamine after repeated dermal application

Species, strain, number per group	Exposure	Findings	References
rat, F344, 5 ♂/5 ♀	**16 days**, 0, 141, 281, 563, 1125, 2250 mg/kg body weight and day 5 days/week, 12 applications in acetone	**141 mg/kg body weight**: ♂/♀: feed consumption ↓(by a maximum 4%), shift in the differential blood count (from lymphocytes to neutrophils), ♂: local irritation at the application site (erythema, inflammation), leukocyte count ↓, ♀: NOAEL local irritation, leukocyte count ↑ **281 mg/kg body weight and above**: ♀: local irritation at the application site (erythema, inflammation) **563 mg/kg body weight**: ♂: NOAEL systemic toxicity **1125 mg/kg body weight and above**: ♂: relative kidney weights ↑, ♀: NOAEL systemic toxicity **2250 mg/kg body weight**: ♂: absolute thymus and lung weights ↓, ♀: relative liver and kidney weights↑	NTP 1985 a, 1987 a
rat, F344, 10 ♂/10 ♀	**90 days**, 0, 125, 250, 500, 1000, 2000 mg/kg body weight and day 5 days/week, applications in acetone	**125 mg/kg body weight**: ♂/♀: LOAEL systemic toxicity; nephropathy, pituitary hypertrophy, ♂: NOAEL local irritation **250 mg/kg body weight and above**: ♂: relative kidney weights ↑, local irritation at the application site (erythema, inflammation), ♀: NOAEL local irritation **500 mg/kg body weight and above**: ♂: protein in the urine ↑, ♀: local irritation at the application site (erythema, inflammation), relative kidney weights ↑ **1000 mg/kg body weight**: ♂: relative spleen weights ↑, ♀: body weight gains ↓, relative kidney weights ↑, specific gravity of urine ↑ **2000 mg/kg body weight**: ♂/♀: MCV ↓haematocrit ↓, serum aspartate transferase and alanine aminotransferase ↑, ♂: body weight gains ↓, relative thymus weights ↑, leukocytes ↑, specific gravity of urine ↑, ♀: serum albumin and urea levels ↑, glucose in the urine↑	NTP 1987 a, 1999

Table 3 (continued)

Species, strain, number per group	Exposure	Findings	References
rat, F344, 60 ♂/60 ♀	**103 weeks**, ♂: 0, 32, 63, 125 mg/kg body weight and day; ♀: 0, 63, 125 and 250 mg/kg body weight and day 5 days/week, applications in acetone	**63 mg/kg body weight**: ♀: local irritation at the application site (acanthosis) **125 mg/kg body weight and above**: ♂/♀: NOAEL systemic toxicity; local irritation at the application site (acanthosis, erosions, ulcers) **250 mg/kg body weight**: ♀: mortality slightly increased, body weight gains ↓, absolute and relative kidney weights↑	NTP 1999
mouse, B6C3F1, 5 ♂/5 ♀	**16 days**, 0, 214, 427, 843, 1686, 3370 mg/kg body weight and day 5 days/week, 12 applications in acetone	**214 mg/kg body weight and above**: ♂: local irritation at the application site (erythema, inflammation), ♀: fibrosis at the application site **3370 mg/kg body weight:** ♂/♀: NOAEL and systemic toxicity	NTP 1985 b, 1987 b
mouse, B6C3F1, 10 ♂/10 ♀	**90 days**, 0, 250, 500, 1000, 2000, 4000 mg/kg body weight and day 5 days/week, applications in acetone	**250 mg/kg body weight**: ♂/♀: local irritation at the application site (acanthosis) **1000 mg/kg body weight**: ♂/♀: NOAEL: systemic toxicity **2000 mg/kg body weight and above**: ♂/♀: relative kidney weights ↑, ♂: relative liver weights ↑, ♀: haematocrit ↓, local irritation in the form of chronic inflammation **4000 mg/kg body weight and above**: ♂: local irritation in the form of chronic inflammation, ♀: relative liver weights ↑, leukocytes ↑, haemoglobin↑	NTP 1987 b
mouse, CH3/heJ, 15 ♂/15 ♀	**95 days**, 0%, 10%, 33% or 100% triethanolamine in acetone, (♂: about 140, 460, 2000 mg/kg body weight and day; ♀: about 160, 540 and 2300 mg/kg body weight and day) 3 days/week, 37 applications in acetone	**140/160 mg/kg body weight**: ♂/♀: NOAEL systemic toxicity; LOAEL local irritation; slight epidermal hyperplasia at the application site **2000 mg/kg body weight**: ♂: lymphocytes ↓, alkaline phosphatase↓	De Pass et al. 1995

Table 3 (continued)

Species, strain, number per group	Exposure	Findings	References
mouse, B6C3F1, 60 ♂/60 ♀	**104–105 days**, ♂: 0, 200, 630, 2000 mg/kg body weight and day; ♀: 0, 100, 300, 1000 mg/kg body weight and day 5 days/week, applications in acetone	**100/200 mg/kg body weight**: ♂/♀: LOAEL systemic toxicity and local irritation; chronic inflammation, ulceration at the application site, eosinophilic liver foci ↑ **2000 mg/kg body weight**: ♂: body weight gains ↓	NTP 2004

Mice

In range-finding studies for toxicity after dermal application under the US National Toxicology Program, triethanolamine doses of 0, 214, 427, 843, 1686 or 3370 mg/kg body weight and day were applied to the shaved interscapular region (about 2 cm^2) of groups of 5 male and 5 female B6C3F1 mice on 5 days a week, for 16 days (12 applications altogether). No animals died. Inflammation and necrosis or fibrosis were sporadically observed around the application site in the males at 214 mg/kg body weight and day and above, whereas the females had no inflammatory skin reactions; only fibrosis was observed at 214 mg/kg body weight and day and above. There were no substance-induced findings for feed consumption, body weight gains, organ weights or haematological parameters (NTP 1985 b, 1987 b).

In the medium-term study carried out over 90 days, groups of 10 male and 10 female B6C3F1 mice were treated with 0, 250, 500, 1000, 2000 or 4000 mg/kg body weight and day according to the same pattern of treatment as in the 16-day range-finding study. There were no treatment-related deaths, and the body weight gains corresponded to those of the control animals at the end of the study. Local, inflammatory findings such as irritation, scaling and discoloration at the application site were observed in both sexes in the high dose group and were the only clinical symptoms. In female mice, there was a statistically significant decrease in the haematocrit value at 2000 mg/kg body weight and day and above, and the leukocyte count and MCHC (mean corpuscular haemoglobin concentration) were significantly increased in the high dose group. A few changes in clinico-chemical parameters were observed in isolated groups, but they were not dose-dependent and were thus not regarded as the result of treatment. At necropsy, the relative liver weights were significantly increased in male mice of the groups treated with 250 mg/kg and 2000 mg/kg and in both sexes of the group treated with 4000 mg/kg. The relative kidney weights were increased in the females of the group treated with 250 mg/kg and in both sexes at 2000 mg/kg body weight and day and above. The relative spleen

weights of the females were significantly increased at 4000 mg/kg body weight and day. The histopathological examination revealed chronic inflammation and acanthosis of the skin in the females at 2000 mg/kg body weight and day and above and in the males of the group treated with 4000 mg/kg. There were no treatment-related changes to the internal organs. With regard to local irritation, a NOAEL of 1000 mg/kg body weight was established for the occurrence of skin inflammation, whereas minimal acanthosis was caused even by the low dose of 250 mg/kg body weight and day (NTP 1987 b).

In another medium-term study, groups of 15 male and 15 female C3H/HeJ mice were exposed to 0%, 10%, 33% or 100% triethanolamine solutions in acetone on 3 days a week, for 95 days (37 applications). The daily doses corresponded to about 140, 460 or 2000 mg/kg body weight and day for the males and 160, 540 or 2300 mg/kg body weight and day for the females. All exposed animals were found to have slight epidermal hyperplasia at the application site. Moreover, the lymphocyte count in the males of the high dose group was significantly reduced and the alkaline phosphatase activity in the serum was reduced. There were no other systemic effects (De Pass et al. 1995).

In the NTP carcinogenicity study with B6C3F1 mice (see Section 5.7.2), triethanolamine in acetone was applied topically to the shaved dorsal skin of groups of 60 males and 60 females on 5 days a week for 104 to 105 weeks. The doses were 0, 200, 630 or 2000 mg/kg body weight and day for the males and 0, 100, 300 or 1000 mg/kg body weight and day for the females. Survival was not adversely affected by the test substance in any dose group. In the high dose group, the body weight gains of the males were significantly reduced. Changes at the application site were observed in all exposed animals; the histopathological examination revealed epidermal ulceration and an increased incidence of chronic inflammation in the area of the epidermis and dermis. Increased incidences of eosinophilic liver foci in the animals of both sexes were the only non-neoplastic changes: ♂: 9/50, 20/50, 31/50, 30/50 at 0, 200, 630, 2000 mg/kg body weight and day; ♀: 16/50, 22/50, 28/50, 32/50 at 0, 100, 300, 1000 mg/kg body weight and day (NTP 2004). The LOAEL in this long-term study in mice was 200 mg/kg body weight and day.

Continuous dermal exposure of guinea pigs to 100% triethanolamine in doses of 8000 mg/kg body weight and day was lethal for the animals after 2 to 17 applications. Damage to the kidneys, adrenal glands, liver and lungs was observed (no other details; BIBRA 1990).

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

In vitro

The mode of action of cutting oils and their individual components (including triethanolamine) was investigated in a screening study using isolated perfused porcine skin flaps (IPPSFs) or human epidermal keratinocytes (HEKs). The exposure of

all treatment groups in the IPPSF model resulted in a time-dependent increase in the interleukin-8 (IL-8) biomarker for inflammation/skin irritation within 8 hours only if mineral oil was used as the solvent. The use of polyethylene glycol as the solvent did not lead to any increase in this system. However, this approach in the IPPSF model does not allow conclusions to be drawn about the individual components. In the HEK model, incubation with 0.3% to 6.0% triethanolamine for 24 hours induced a concentration-dependent decrease in cell vitality while concentrations of up to a maximum of 0.15% had no cytotoxic effects (Monteiro-Riviere et al. 2006).

In vivo

A patch test with undiluted triethanolamine (purity: 98%) did not produce irritation in 2 rabbits after short-term exposure for 1 minute, 5 minutes or 15 minutes (BASF AG 1971). These findings were more or less the same as those obtained in earlier studies with (technical-grade) triethanolamine (BASF AG 1956, 1967).

In a study based on OECD Test Guideline 404 with 4-hour occlusive application of a mixture of 85% triethanolamine and 15% diethanolamine to the intact skin of 3 rabbits, neither erythema nor oedema was recorded throughout the observation period (4, 24, 48 and 72 hours after application) (BASF AG 1983 a).

The exposure of 2 rabbits to undiluted triethanolamine (purity: 98%) for 20 hours in a patch test induced slight erythema on the dorsal skin and skin of the ears, which subsided within 8 days. In addition, isolated yellow "dots" were observed on the dorsal skin; they were also reversible within 8 days (BASF AG 1971).

This corresponded to the results obtained in an earlier study with technical-grade triethanolamine that used the same pattern of treatment and led to erythema and scab formation on the dorsal skin and erythema on the ear (BASF AG 1967).

An earlier study with technical-grade triethanolamine led to severe erythema and slight necrosis after application for 20 hours to the dorsal skin of rabbits (no other details). Slight erythema and severe scaling were still observed 8 days after treatment. No signs of irritation on the ear were recorded (BASF AG 1966).

Further studies showed no, or at most, mild irritation in rabbits after a single treatment of the intact skin with triethanolamine (Dutertre-Catella et al. 1982; ECB 2000; Weil 1973) or after 7 applications of triethanolamine (CTFA 1959).

Moderate erythema, oedema and necrosis were observed after 3 semi-occlusive applications, each lasting 24 hours, to the abraded skin of rabbits (CTFA 1959).

The 28-day dermal application of a 2.5% aqueous triethanolamine solution (2 ml/kg body weight and day) induced mild dermatitis in rabbits (NTP 2004). In guinea pigs, the repeated occlusive application of undiluted triethanolamine doses of 8 g/kg body weight and day on 5 days per week led to the death of the animals after 2 to 17 applications. Inflammation of the skin was observed at the application site (no other details; Montelius 2003; NTP 2004).

The range-finding studies and carcinogenicity studies in rats and mice described in Sections 5.2.3 and 5.7.2 showed that prolonged dermal application of high concentrations of triethanolamine in acetone induced chronic inflammation and acanthosis, erosion and ulcers at the application site (NTP 2004).

In a screening study of the mode of action of cutting oils and their individual components, up to 8-hour occlusive dermal exposure of female pigs to 200 µl of a 5% triethanolamine solution did not yield any macroscopic (according to the Draize scale) or microscopic evidence of skin irritation irrespective of the solvent used (mineral oil or polyethylene glycol) (Monteiro-Riviere et al. 2006).

Summary

Triethanolamine induced no or slight irritation of the intact skin of rabbits after single applications lasting for up to 20 hours. Prolonged application of high triethanolamine concentrations (dissolved in acetone), however, induced chronic inflammation and acanthosis, erosion and ulcers at the application site in rats and mice.

5.3.2 Eyes

In vitro

A study which investigated 114 chemicals in total also examined the cytotoxicity of triethanolamine in cultivated Hep G2 cells. According to the authors, this study can be used as a further in vitro alternative for testing eye irritation. A 50% reduction in the cellular protein content was used as a measure of cytotoxicity. A PI_{50} of 15 mM and thus low cellular cytotoxicity was determined for triethanolamine (Dierickx 1989).

In vivo

In an eye irritation study carried out in conformity with OECD Test Guideline 405, the instillation of 0.1 ml undiluted triethanolamine (purity: 99%) into the conjunctival sac of one rabbit eye caused mild conjunctival redness in only 1 of 3 rabbits after 1 hour. No abnormalities were detected in the cornea, iris or mucous membrane after 24, 48 and 72 hours (Koch et al. 1985).

This agrees with the results obtained in an eye irritation study carried out according to French test guidelines. In this study, no changes were found in the cornea or mucous membranes of 3 New Zealand White rabbits after instillation of 0.1 ml undiluted triethanolamine (purity: 98%) into the conjunctival sac of one eye. Two different technical-grade products caused minimal to mild eye irritation. The observation periods were 24, 48, 72 and 96 hours and 7 days (Dutertre-Catella et al. 1982).

A comparative study of the effect of applying different volumes of undiluted triethanolamine (purity: 98%) only revealed a very low eye irritation potential. After the instillation of 0.01 ml into the conjunctival sac of one rabbit eye, no irritative effects were observed in 6 animals throughout the observation period of 21 days. The findings obtained with 0.03 ml on day 1 after treatment yielded an irritation index of 1

on a scale of up to 110. Irritation indices of 4, 2 and 2 were obtained after instillation of 0.1 ml on days 1, 3 and 7, respectively (Griffith et al. 1980).

The instillation of 0.1 ml undiluted triethanolamine into the conjunctival sac induced moderate pain (no other details) and swelling in rabbits (number not specified). Mild conjunctival redness subsided within 48 hours. When the eyes were washed immediately after instillation, no signs of irritation were observed (CTFA 1959).

In an earlier range-finding study with 2 rabbits, the instillation into the conjunctival sac of 0.05 ml of the pure, undiluted product (98%) induced only mild findings. In both animals, slight redness and swelling were observed after 1 hour and slight redness was recorded after 24 hours, which was reversible after 8 days (BASF AG 1971). Therefore, the irritative effects on the mucous membranes caused by the pure product were less pronounced than those induced by the technical-grade product in earlier studies. The findings included inflammatory redness and swelling, which subsided within 8 days, corneal clouding and sporadic haemorrhages in the nictitating membrane that persisted for more than 1 week (BASF AG 1966, 1967).

Another study showed that a 20% aqueous triethanolamine solution did not cause irritation of the rabbit eye in either its non-neutralized form (pH: > 10) or in its neutralized form (pH: about 8), but the eyes were rinsed with water immediately after instillation of the test substance (BASF AG 1956).

In an earlier study carried out in 5 rabbits with a method that is not reproducible and thus of limited validity, grade 5 damage to the cornea on a scale from 0 to 10 was observed after the instillation of 0.02 ml into the eyes (Carpenter and Smyth 1946).

Summary

Pure triethanolamine caused no or only slight, reversible irritation of the rabbit eye.

5.4 Allergenic effects

No new data have become available since the sensitizing effects of the substance were evaluated in the documentation "Triethanolamine" 2007).

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

In a study by the US NIH (National Institute of Health) from 1988, male and female F344 rats were treated dermally with triethanolamine doses of 500 mg/kg body weight dissolved in acetone 10 weeks before mating and during mating, gestation and lactation. No effects were observed on fertility, the mating success, or the growth or viability of the offspring. A similar study, in which doses of 2000 mg/kg body weight and day were applied to the skin of male and female CD-1 mice, like-

wise did not provide evidence of toxic effects of triethanolamine on reproduction or development (no other details; NTP 1999).

Dermal doses of 0, 500, 1000 or 2000 mg/kg applied to groups of 10 male and 10 female F344 rats and 0, 1000, 2000 or 4000 mg/kg body weight and day applied to groups of 10 male and 10 female B6C3F1 mice did not affect the length of the oestrus cycle, the oestrus phases or the organ weights of the epididymis, caudae epididymidis or testes, nor were effects on the motility, morphology or concentration of epididymis sperm observed (see also Section 5.2.3; NTP 1999).

Likewise, short-term, medium-term and long-term studies (see Section 5.2) did not reveal effects on the reproductive organs after all routes of exposure.

5.5.2 Developmental toxicity

No studies of developmental toxicity carried out in conformity with test guidelines are available after inhalation, oral or dermal exposure; there is only a 3-phase Chernoff-Kavlock screening assay for possible toxic effects on reproduction or development in mice. In phase I, groups of 3 female, non-pregnant CD-1 mice were given gavage doses of triethanolamine of 10, 100 or 1000 mg/kg body weight and day on 5 consecutive days. No animals died and no clinical signs of toxicity were observed. In phase II, daily treatment with gavage doses between 600 and 9600 mg/kg body weight from days 6 to 15 of gestation produced signs of systemic toxicity in 4 pregnant mice and mortality. The calculated combined mortality from phases I and II yielded an LD_{10} value of 1125 mg/kg body weight and day, which was used as the dose for phase III. Here, 50 CD-1 mice were given daily gavage doses of 1125 mg/kg body weight as an aqueous solution (1125 mg triethanolamine in 10 ml) from days 6 to 15 of gestation. After birth, the dams and pups were observed for 3 days. In this study, triethanolamine did not affect maternal toxicity or the number of live foetuses, the litter size, the birth weights of the foetuses, the percentage of surviving foetuses or their body weight gains (NIOSH 1987; Union Carbide Corp 1990). The study is only of limited validity because of inadequate test parameters.

In a range-finding study for an oral teratogenicity study, groups of 10 Sprague Dawley rats were given aqueous triethanolamine solutions in doses of 0, 100, 500, 1000, 2500 or 5000 mg/kg body weight and day by gavage from days 6 to 15 of gestation. The foetuses were delivered by caesarean section on day 20 of gestation. The number of implantations, resorptions, live and dead foetuses and the uterus weights were investigated. In the group treated with 2500 and 5000 mg/kg, 1 of 8 and 3 of 9 pregnant animals died prematurely. It seems questionable whether this was an effect of the substance alone because there was also evidence of an injury to the oesophagus. As from day 8 of gestation, the body weight gains of the dams were slightly reduced in the two high dose groups, but the decrease was statistically significant only in the high dose group. One dam of this group resorbed all foetuses. Except for a slight decrease in the mean foetal weights in the high dose group, which was not statistically significant, there were no other signs of developmental toxicity (NIEHS 1990). Inadequate test parameters also limit the validity of this study with regard to the developmental toxicity of triethanolamine.

Table 4 Genotoxicity of triethanolamine in vitro

End point	Test system	Concentration	Effective concentration	Cytotoxicity	Result		Remarks	References
					−m. a.	+m. a.		
bacteria								
gene mutation	Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	0, 4, 20, 100, 500 or 2500 µg/plate	–	not specified	not examined	–		BASF AG 1981
gene mutation	Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	0, 125, 250, 500, 1000, 2000 or 4000 µg/plate	–	not specified	–	–		Dean et al. 1985
gene mutation	Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	1, 10, 100, 1000, 2000, 4000, 8000, 10 000 or 100 000 µg/plate	–	> 100 000 µg/plate	–	–		Dow Chemical Company 1980
gene mutation	Salmonella typhimurium TA98, TA100, TA1535, TA1537	0, 33, 100, 333, 1000 or 3333 µg/plate	–	≥ 3333 µg/plate	–	–		Mortelmans et al. 1986
gene mutation	Salmonella typhimurium TA98, TA100	0, 1, 5, 10, 50, 100, 500, 1000, 5000, 10 000 or 20 000 µg/plate	–	> 20 000 µg/plate	–	–		Inoue et al. 1982
gene mutation	Escherichia coli WP2 and WP2uvrA	0, 125, 250, 500, 1000, 2000 or 4000 µg/plate	–	not specified	–	–		Dean et al. 1985
gene mutation	Escherichia coli WP2	0, 10, 50, 100, 500, 1000, 5000 or 10 000 µg/plate	–	> 10 000 µg/plate	–	–		Inoue et al. 1982
gene mutation	Bacillus subtilis TKJ5211	0, 6.75, 13.5, 20.3 or 27 mg/plate	–	not specified	–	–		Hoshino and Tanooka 1978

Table 4 (continued)

End point	Test system	Concentration	Effective concentration	Cytotoxicity	Result		Remarks	References
					–m. a.	+m. a.		
gene mutation	Bacillus subtilis H17, M45	0, 40, 200, 800, 2000 or 4000 µg/plate	–	> 4000 µg/plate	–	not examined		Inoue et al. 1982
yeasts								
mitotic recombination	Saccharomyces cerevisiae JD1	not specified	–	not specified	–	–		Dean et al. 1985
mammalian cells								
SCE	CHO cells	–m. a.: 0, 100, 330, 630, 1010, 1260 or 2520 µg/ml/plate +m. a.: 0, 330, 1010 or 10 100 µg/ml	–m. a.: 2520 µg/ml	–m. a.: 2520 µg/ml	–	–	–m. a.: delay in cell cycle; no other details	Galloway et al. 1987
UDS	primary rat hepatocytes	0, 0.005, 0.010, 0.025, 0.050, 0.100, 0.250, 0.500 or 1000 µl/ml	–	0.5 µl/ml and above	–	not examined		BASF AG 1982 a, b
UDS	primary rat hepatocytes	0, 10-8–10-1 M (0, 0.002, 0.015, 0.149, 1.49, 14.9, 149, 1491 or 14 919 µg/ml)	–	10-1 M (14 919 µg/ml)	–	not examined		Dow Chemical Company 1979
CA	RL1 and RL4 (rat liver cell line)	1/8, 1/4 or 1/2 of the concentration that causes 50% growth inhibition	–	not specified	–	not examined		Dean et al. 1985

Table 4 (continued)

End point	Test system	Concentration	Effective concentration	Cytotoxicity	Result		Remarks	References
					–m. a.	+m. a.		
CA	CHL cells	0, 5, 10, 25, 50 or 100 µg/ml, 24 or 48 hours	–	100 ug/ml, 48 hours	–	not examined		Inoue et al. 1982
CA	CHO cells	–m. a.: 0, 1510, 2010 or 4030 µg/ml +m. a.: 0, 6040, 8060 or 10 070 µg/ml; 10.5 hours	–	–m. a.: 4030 µg/ml	–	–		Galloway et al. 1987
CA	human lymphocytes	0, 10–5–10–2 M, 72 hours, no other details	not specified	not specified	(+)	not examined		Arutiunian et al. 1987

–: negative; (+): weakly positive; m. a.: metabolic activation;
CA: chromosomal aberration test; CHL: Chinese hamster lung cells; SCE: sister chromatid exchange; UDS: test for unscheduled DNA synthesis

Table 5 Genotoxicity of triethanolamine in vivo

End point/ test system	Species, number per group	Exposure	Result	References
Drosophila				
SLRL	Drosophila melanogaster	0, 0.1, 0.2 or 0.3 µl, injection, once	–	Yoon et al. 1985
SLRL	Drosophila melanogaster	0, 20 000 or 30 000 ppm, diet, 3 days	–	Yoon et al. 1985
mammals				
MN, peripheral blood, erythrocytes	mouse, B6C3F1, 10 ♂/10 ♀	0, 1000, 2000 or 4000 mg/kg body weight and day, dermal, 5 days/week, 13 weeks	–	NTP 1999; Witt et al. 2000

MN: micronucleus; SLRL: test for sex-linked, recessive lethal mutations

5.6 Genotoxicity

5.6.1 In vitro

The results of the in vitro studies of genotoxicity are shown in Table 4.

Triethanolamine was not mutagenic in several bacterial mutagenicity tests carried out in different laboratories with and without the addition of a metabolic activation system. The investigations were carried out using the strains Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537 and TA 1538. An Ames test with Escherichia coli WP2 and WP2uvrA and a test for mitotic recombination in wSaccharomyces cerevisiae JD 1 likewise yielded negative results (BASF AG 1981; Dean et al. 1985; Dow Chemical Company 1980; Inoue et al. 1982; Hoshino and Tanooka 1978; Mortelmans et al. 1986).

Studies in primary rat hepatocytes provided no evidence of possible DNA damage (UDS) caused by triethanolamine (BASF AG 1982 a, b; Dow Chemical Company 1979).

Triethanolamine did not increase the incidence of sister chromatid exchange in CHO cells and did not induce chromosomal aberrations in CHO, CHL, RL1 or RL4 cells (Dean et al. 1985; Galloway et al. 1987; Inoue et al. 1982). A study that was published in Russian and is available only as a brief translation reported that triethanolamine led to an increase in sister chromatid exchange and chromosomal aberrations in human lymphocytes (Arutiunian et al. 1987). As these conclusions cannot be reproduced and there is no further information, for example about the use of a metabolic activation system, this study has not been included in the evaluation.

5.6.2 In vivo

The results of the in vivo studies of genotoxicity are shown in Table 5.

When triethanolamine was given to 24-hour-old male Drosophila melanogaster either as single injections of 0.2 or 0.3 µl or with the diet in concentrations of 20 000 or 30 000 ppm, sex-linked recessive lethal mutations were not found (Yoon et al. 1985).

In a micronucleus test in the peripheral erythrocytes of B6C3F1 mice dermally exposed to triethanolamine doses of 0, 1000, 2000 or 4000 mg/kg body weight and day, the incidence of micronuclei was not increased and there was no change in the percentage of polychromatic erythrocytes. Triethanolamine therefore had no genotoxic effects (NTP 1999).

Summary

After taking into consideration all the available in vitro studies, triethanolamine is not assumed to have a genotoxic potential in vitro. The data obtained in bacteria and mammalian cells do not provide any clear evidence of gene mutations or a chromosome-damaging effect. Furthermore, triethanolamine did not induce recessive lethal mutations in Drosophila in vivo or micronuclei in the peripheral erythrocytes of mice. Further in vivo studies are not available. Overall, triethanolamine was not genotoxic in vitro or in vivo.

5.7 Carcinogenicity

5.7.1 Short-term studies

Female, homozygous Tg.AC mice were treated with triethanolamine in a transgenic tumour model used to investigate the induction of epidermal papillomas. Triethanolamine was dissolved in acetone and applied to the shaved dorsal skin (about 5 to 7 cm^2) in doses of 120, 400 or 1200 mg/kg body weight and day (0, 3, 10 or 30 mg/animal) on 5 days a week, for 20 weeks. A control group was treated with acetone alone. The animals were given 1.25 µg 12-0-tetradecanoylphorbol-13-acetate (TPA) dissolved in acetone as a positive control twice a week, for 20 weeks. Treatment with triethanolamine did not result in substance-induced

Table 6 Cell transformation tests with triethanolamine in vitro

Test system	Concentration	Result	Remarks	References
Balb/3T3 cells	0, 3.33, 6.67, 10, 15 or 18.75 µl/ml	negative	+ S9 mix	BASF AG 1982 c, 1983 b
Balb/3T3 cells	0, 0.25, 1, 2, 2.5 or 3.125 µl/ml	negative	– S9 mix	BASF AG 1982 c, 1983 b
hamster embryo cells	0, 25, 50, 100, 200 or 500 µg/ml	negative	– S9 mix	Inoue et al. 1982

skin tumours and had no effect on survival or body weight gains (Spalding et al. 1999, 2000).

Cell transformation

In a cell transformation test with cultivated Balb/3T3 cells with and without the addition of a metabolic activation system (S9 mix from Aroclor 1254-induced rat liver), triethanolamine did not cause morphological cell transformations in the concentration range between 3.33 to 18.75 µl/ml (see Table 6). In this concentration range, solubility was guaranteed and cytotoxicity did not occur. Likewise, in the test without a metabolic activation system, an increased incidence of transformed colonies was not observed in the concentration range between 0.25 and 3.125 µl/ml. This range corresponded to the 10% to 90% survival found in a preceding cytotoxicity test (BASF AG 1982 c, 1983 b).

In a cell transformation assay with cultivated embryonic hamster cells, triethanolamine did not induce cell transformations in the concentration range between 25 and 500 µg/ml (see Table 6; Inoue et al. 1982).

5.7.2 Long-term studies

Oral administration

Groups of 50 male and 50 female F344 rats were given triethanolamine ad libitum in the drinking water for 2 years in concentrations of 0%, 1% or 2% (corresponding to doses of about 1000 or 2000 mg/kg body weight and day). Because of severe nephrotoxicity, the concentrations in the females were reduced by half as from week 69 of the study (0.5% and 1% corresponding to doses of about 500 and 1000 mg/kg body weight and day). All animals were exposed up to the end of week 104 and were given pure drinking water up to the end of week 113, at which time they were sacrificed for examination. The survival of the male rats was not affected. In the female animals there was a dose-dependent increase in cumulative mortality: 16% in the controls, 32% at the low dose (500/1000 mg/kg body weight and day) and 42% at the high dose (1000/2000 mg/kg body weight and day). This was probably caused by the kidney damage manifest as an increased incidence of animals with chronic nephropathy. A large number of tumours spontaneously developed in all animals treated with triethanolamine, but the statistical significance of their incidence did not differ from that of the respective control group. The result of a targeted Peto analysis revealed a positive trend for liver tumours (neoplastic nodules and hepatocellular carcinomas) in the males and for uterine endometrial sarcomas and renal cell adenomas in the females. In addition, mineralization of the renal papilla, nodular hyperplasia of the pelvic mucosa and pyelonephritis with or without papillary necrosis were especially prevalent in the females. Thus, triethanolamine was concluded to be not carcinogenic but nephrotoxic (IARC 2000; Maekawa et al. 1986).

Groups of 50 male and 50 female B6C3F1 mice were given triethanolamine ad libitum in the drinking water for 82 weeks in concentrations of 0%, 1% or 2% (corresponding to doses of about 1600 or 3200 mg/kg body weight and day). There was no substance-induced increase in mortality, and survival was 43/50 (86%), 46/50 (92%) and 48/50 (98%) in the males of the control, low and high concentration groups and 50/50 (100%) in each case in the females. In the high concentration group, body weight gains were slightly reduced in the males during the first 3 to 4 months and in both sexes as from week 60 of the study. There were no substance-induced deviations in water consumption or organ weights. A large number of spontaneous tumours developed in all groups, but their incidence and severity did not differ from that in the control group (Konishi et al. 1992).

In another study, groups of 40 male and 40 female ICR-JCL mice were given triethanolamine with the diet throughout their life span (up to 123 weeks) in concentrations of 0%, 0.03% and 0.3% (corresponding to doses of about 45 and 450 mg/kg body weight and day). Triethanolamine was added to the powdered diet and this mixture was heated at 100 °C for 40 minutes. The survival of 50% of the animals was attained in the males after about 65 weeks and in the females after about 85 weeks; this corresponded to the survival in the control group. The incidence of malignant tumours was increased in the female mice of the two dose groups compared with that in the control group; these were mainly tumours of the lymphatic tissue, such as lymphomas, lymphoblastomas, reticular cell tumours and plasmacytomas of the thymus. These types of tumours were not found in the male mice. Malignant tumours were also found in other organs in both sexes, for example lung adenomas, renal cell carcinomas, stomach carcinomas and mammary adenocarcinomas; they were, however, not related to the dose or test substance. Liver tumours were not reported (Hoshino and Tanooka 1978). This study does not allow conclusions to be drawn about the carcinogenicity of triethanolamine because the heating of triethanolamine in the feed at a high temperature for a long period has been shown to lead to the formation of nitrosamines (nitrosodiethanolamine) and according to the authors possibly also other genotoxic components.

Dermal application

The dermal carcinogenicity studies are shown in Table 7.

Triethanolamine dissolved in acetone was applied topically to the shaved dorsal skin of groups of 60 male and 60 female F344 rats on 5 days a week, for 103 weeks. The doses were 0, 32, 63 and 125 mg/kg body weight and day for the males and 0, 63, 125 and 250 mg/kg body weight and day for the females. Groups of 10 male and 10 female satellite animals were sacrificed for an interim examination after 15 months to determine organ weights and to examine the organs histopathologically. Mortality was slightly increased compared with that in the control animals only in the females of the high dose group. At the end of the study, the body weights of the females were significantly reduced in the high dose group. Local changes were observed at the application site in the form of chronic inflammation of the skin and acanthosis in the females of all dose groups, and the incidence of erosion and ulcers

was increased at the middle dose of 125 mg/kg body weight and day and above. Similar findings and incidences were recorded in the males of the high dose group of 125 mg/kg body weight and day. The histopathological examination revealed an increase in the incidence of renal adenomas only in the males of the 2 high dose groups, but it was not statistically significant and not clearly dose-dependent (1/50, 2/50, 6/49 and 4/50 at 0, 32, 63 and 125 mg/kg body weight and day). Although chronic irritation was observed, the incidence of skin tumours was not increased (NTP 1999).

The study in B6C3F1 mice carried out at the same time as the dermal NTP carcinogenicity study in F344 rats had to be repeated because there was histochemical evidence of a virus infection with Helicobacter hepaticus, which led to virus-induced hepatitis in the male animals; the effects of this on liver tumorigenesis could not be assessed with any accuracy at the time. In the males, the incidences of hepatocellular adenomas or carcinomas were 27/50, 27/50, 29/50

Table 7 Dermal carcinogenicity studies with triethanolamine in rats and mice

Author:	NTP 1999				
Substance:	triethanolamine (purity: ≥ 98%)				
Species:	F344 rats (main group: 50 ♂, 50 ♀; satellite group: 10 ♂, 10 ♀)				
Exposure:	dermal, dissolved in acetone, 1× per day, 5 days/week				
Concentration:	♂: 0, 32, 63, or 125 mg/kg body weight and day ♀: 0, 63, 125, or 250 mg/kg body weight and day				
Duration:	main group: 103 weeks satellite group: 15 months				
Toxicity:	survival ♀: slightly reduced at 250 mg/kg body weight and day body weights ♀: 9% to 12% reduction in treatment weeks 73 to 93 at 250 mg/kg body weight and day skin irritation around the application site in all dose groups				
		dose (mg/kg body weight and day)			
		♂: 0 ♀: 0	♂: 32 ♀: 63	♂: 63 ♀: 125	♂: 125 ♀: 250
surviving animals:	♂	22/50	13/50	18/49	19/50
	♀	26/50	30/50	27/50	18/50
tumours:					
kidneys					
tubular cell adenomas (standardized number of sections)	♂	0/50*	1/50	4/49	2/50
	♀	1/50	1/50	0/50	0/50
tubular cell adenomas (standardized and increased number of sections)	♂	1/50	2/50	6/49	4/50

*$p \leq 0.05$; **$p \leq 0.01$ (NTP 1999)

Table 7 (continued)

Author:	NTP 2004				
Substance:	triethanolamine (purity: > 99%)				
Species:	B6C3F1 mice (50 ♂, 50 ♀)				
Exposure:	dermal, dissolved in acetone, 1× per day, 5 days/week				
Concentration:	♂: 0, 200, 630 or 2000 mg/kg body weight and day ♀: 0, 100, 300 or 1000 mg/kg body weight and day				
Duration:	♂: 104 weeks ♀: 104 to 105 weeks				
Toxicity:	body weights ♂: 9% to 12% reduction in treatment weeks 17 to 93 at 2000 mg/kg body weight and day skin irritation around the application site in all dose groups				
		dose (mg/kg body weight and day)			
		♂: 0 ♀: 0	♂: 200 ♀: 100	♂: 630 ♀: 300	♂: 2000 ♀: 1000
surviving animals:	♂	41/50	44/50	36/50	40/50
	♀	37/50	35/50	41/50	37/50
non-neoplastic findings:					
liver					
eosinophilic hepatocellular foci	♂	9/50	20/50*	31/50**	30/50**
	♀	16/50	22/50	28/50*	32/50**
tumours:					
liver					
hepatocellular adenomas (including multiple)/poly-3 test	♂	19/50	18/50	23/50	20/50
	♀	9/50	18/50*	20/50**	33/50**
hepatocellular carcinomas	♂	17/50	14/50	14/50	11/50
	♀	6/50	8/50	4/50	5/50
haemangiosarcomas	♂	1/50	0/50	6/50*	1/50
all organs					
haemangiosarcomas	♂	3/50	2/50	9/50*	2/50

*$p \leq 0.05$; **$p \leq 0.01$

and 37/50 (adenomas/number of animals) and 15/50, 20/50, 15/50 and 14/50 (carcinomas/number of animals) at 0, 200, 630 and 2000 mg/kg body weight and day. In the females, the incidences were 22/50, 22/50, 24/50 and 40/50 (adenomas) and 1/50, 4/50, 7/50 and 5/50 (carcinomas) at 0, 100, 300 and 1000 mg/kg body weight and day, respectively (NTP 1999). When the results of the repeated study were available, a differentiated, retrospective data analysis showed that this infection

influenced the induction of liver tumours in the male mice, but not in the female mice (Stout et al. 2008).

In the repeated study, which only differed from the preceding one in that the animals were obtained from a different, controlled source and the animal feed used was different, triethanolamine dissolved in acetone was applied topically to the shaved dorsal skin of groups of 60 male and 60 female B6C3F1 mice on 5 days a week, for 104 to 105 weeks. The doses were 0, 200, 630 and 2000 mg/kg body weight and day for the males and 0, 100, 300 and 1000 mg/kg body weight and day for the females. The survival of the animals was not adversely affected by the substance in any dose group. At the end of the study, the body weights of the males were significantly reduced in the high dose group (2000 mg/kg body weight and day). Local changes at the application site were observed in the animals of all dose groups treated with triethanolamine; the histopathological examination revealed epidermal ulceration and an increased incidence of chronic inflammation in the region of the epidermis and dermis. An increased incidence of liver adenomas was established by histopathology in all female animals, whereas the incidence of liver carcinomas was not increased. Increased incidences of eosinophilic liver foci in the animals of both sexes were the only non-neoplastic changes; they were regarded as precursors of adenomas. Although there was chronic irritation, the incidence of skin tumours was not increased (NTP 2004).

Summary

In valid oral carcinogenicity studies, triethanolamine did not induce increased tumour incidences in either rats (Maekawa et al. 1986) or mice (Konishi et al. 1992).

In dermal carcinogenicity studies, benign kidney tumours were observed in male F344 rats; their incidence was not significantly increased or dose-dependent (NTP 1999). Significantly increased liver adenomas, but no liver carcinomas were observed in female B6C3F1 mice, and eosinophilic foci were observed in both male and female animals (NTP 1999, 2004), which may be regarded as precursors of adenomas and these in turn as precursors of carcinomas.

The relevance of liver adenomas in B6C3F1 mice must be evaluated in the light of the high spontaneous incidence of this kind of tumour. Furthermore, there is a large discrepancy between the NTP studies of 1999 and 2004 as regards the spontaneous incidence of hepatocellular adenomas observed in the female control animals (22/50 in 1999 compared with 9/50 in 2004); therefore, the results seem questionable. For this reason, the Commission does not agree with the conclusion drawn by the NTP (2004): "some evidence of carcinogenic activity". In addition, other negative results from carcinogenicity studies with dermal application and ingestion are available, and triethanolamine did not have genotoxic effects or effects in the transgenic tumour model or in the cell transformation assay. Therefore, in the overall evaluation, triethanolamine is not considered to be carcinogenic.

6 Manifesto (MAK value/classification)

Local irritation of the upper respiratory tract proved to be the most sensitive end point of triethanolamine.

MAK value. A 28-day inhalation study in rats with aerosol exposure revealed a dose-dependent increase in the incidences of focal laryngeal inflammation in rats at the low concentration of 20 mg/m^3 and above, up to and including 100 mg/m^3; the severity was merely of grade 1 to 2. Grade 3 inflammation was observed at 400 mg/m^3 and above in the 5-day range-finding study and at 500 mg/m^3 and above in the 28-day study. This indicates that the effects on the larynx can be expected to be only slightly dependent on time, if at all.

A benchmark calculation for focal laryngeal inflammation yielded a BMDL of 14.8 mg/m^3 for male rats and 14.1 mg/m^3 for female rats (Gamer et al. 2008). On the basis of the above arguments, further extrapolation over time was not included in the calculation; therefore, the MAK value has been established at 5 mg/m^3 at half of the BMDL, taking into account the preferred value approach. Marked species differences are not to be expected.

The systemic toxicity of triethanolamine via all routes of absorption is low. In the medium-term studies, initial signs of functional kidney damage were observed at 125 mg/kg body weight and day and above in rats and at 250 mg/kg body weight and day and above in mice. Based on the 25% absorption calculated for female rats after single exposures, it can be estimated that the systemic NOAEL of 125 mg/kg body weight and day determined in female rats in the long-term dermal NTP study corresponds to a body burden of 32 mg/kg body weight. However, as skin irritation was observed in the animals at 125 mg/kg body weight and day (erosion, ulcers and erythema; NTP 1999), the amount absorbed and thus the body burden may have been higher at the NOAEL. If the MAK value is observed, uptake by inhalation (70 kg body weight, 10 m^3) is 0.7 mg/kg body weight. Therefore, the MAK value also provides protection from systemic effects caused by triethanolamine.

Peak limitation. Triethanolamine is classified in Peak Limitation Category I with an excursion factor of 4 because the effects on the larynx were observed only after prolonged exposure to 20 mg/m^3 and triethanolamine had, if at all, a very low irritative potential in studies of acute skin or eye irritation, which means that relevant irritation occurs only after repeated exposure.

Prenatal toxicity. There are no conclusive studies of developmental toxicity available. Triethanolamine has therefore been classified in Pregnancy Risk Group D.

Absorption through the skin. An in vitro study with human skin indicated poor absorption through the skin. However, this study cannot be quantitatively evaluated for exposure at the workplace because triethanolamine was formulated in an emulsion similar to that used in cosmetics. An in vivo study in mice revealed an absorption rate of 0.8 mg/cm^2 and hour after 24-hour dermal exposure to 100% triethanolamine (Knaak et al. 1997). At the same dose per skin area, the amount absorbed in rats was about one third of that in mice (NTP 2004). According to

the data in the literature, dermal absorption in rat skin is about twice as high as that for human skin (Hayes 2007; USEPA 1992). Taking these species differences into account, the dermal absorption of 266 mg triethanolamine was calculated for humans from the corrected absorption rate of 0.13 mg/cm^2 after the exposure for 1 hour of a 2000 cm^2 area of skin (3.8 mg/kg body weight). Together with inhalation exposure and assuming observance of the MAK value (see above), this results in a dose of 4.5 mg/kg body weight for a person (70 kg body weight, 100% retention and 10 m^3 respiratory volume). The estimated amount absorbed dermally and by inhalation in humans is thus 14% of the body burden at the systemic NOAEL; therefore, triethanolamine has not been designated with an "H" (for substances which can be absorbed through the skin).

Carcinogenicity. Triethanolamine did not produce genotoxic effects in vitro or in vivo; negative results were obtained in the transgenic tumour model and in the cell transformation assay, and no increased tumour incidences were found in 2 oral carcinogenicity studies. Dermal carcinogenicity studies revealed an increase in benign kidney tumours only in male F344 rats, which was not significant or dose-dependent, and liver adenomas in female B6C3F1 mice as well as eosinophilic foci in both sexes. A high spontaneous incidence of liver tumours is observed naturally in this strain of mice; moreover, the results seem questionable because the incidence differed considerably in the two NTP studies (NTP 1999, 2004). Studies of the mechanism of action showed that, like diethanolamine, triethanolamine induced a disturbance in choline homoeostasis and an imbalance in phospholipid metabolism, although to a lesser extent. However, a fundamental difference between triethanolamine and diethanolamine is that the structure of triethanolamine prevents the incorporation of triethanolamine into cell membranes, which may lead to toxic effects such as anaemia. Therefore, triethanolamine has not been classified in any of the categories for carcinogens.

Germ cell mutagenicity. The currently available genotoxicity data do not provide evidence of germ cell mutagenicity. Therefore, triethanolamine has not been classified in any of the categories for germ cell mutagens.

Sensitization. No additional relevant data have become available since the sensitizing effects of the substance were evaluated in the documentation "Triethanolamine" 2007. Triethanolamine has therefore not been designated with "Sh" or "Sa" (for substances which cause sensitization of the skin or airways).

7 References

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