SCOEL/REC/179
Trimethylamine

Recommendation from the
Scientific Committee on Occupational Exposure Limits

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EUROPEAN COMMISSION

Directorate-General for Employment, Social Affairs and Inclusion
Directorate B —Employment
Unit B.3 — Health and safety

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2017

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RECOMMENDATION FROM THE SCIENTIFIC COMMITTEE ON OCCUPATIONAL EXPOSURE LIMITS FOR TRIMETHYLAMINE

8-hour TWA:	2 ppm (4.9 mg/m3)
STEL:	5 ppm (12.5 mg/m3)
BLV:	None
Additional categorisation:	None
Notation:	None

The present Recommendation was accepted for public consultation.

This evaluation is based on ACGIH 2004, AIHA 2005, BIBRA 1993, Henschler 1983, Greim 2004, JCIPC 2002 and the references cited in these reviews. Further, the data bases of Toxnet and MEDLINE were evaluated till August 2014.

RECOMMENDATION EXECUTIVE SUMMARY

Trimethylamine (TMA) occurs naturally in humans. It is produced endogenously by the gut bacteria and may also be ingested with food, especially fish. The critical effects of inhalation exposure to TMA are odour annoyance and irritative effects.

Incompletely reported data have indicated moderate upper respiratory irritation during occupational exposure to TMA at 20 ppm (49 mg/m³). No effects were observed in unspecified routine medical surveillance in workers exposed to 0.1–8 ppm, most of the measurements being below 5 ppm as 8-hour TWAs (AIHA 2005). Van Thriel *et al.* (2006) reported an odour lateralisation threshold of TMA of 612 ppm (median) but stated that this might be higher than those observed in longer occupational exposure situations, and concluded that the assessment of a recommended OEL based on chemosensory thresholds is problematical. They stated that trigeminal nerve-mediated symptoms might increase with prolonged exposures duration, but did not examine this.

Animal data with repeated inhalation exposure over 2 weeks revealed a LOAEC of 75 ppm based on slight respiratory irritation, hyperaemia, epithelial degeneration and squamous metaplasia of the respiratory epithelium in a rat study (Kinney *et al* 1990). After a recovery period of 2 weeks these effects had disappeared, but at 250 and 750 ppm were irreversible.

Pathological studies in rats after inhalation exposure by Rotenberg and Mashbits (1967) demonstrated bronchopneumonia and haemorrhage in the lung tissues, with destruction of the alveolar septa, signs of passive hyperaemia, and isolated haemorrhages in the liver, kidneys, and spleen in the 75-mg/m^3 (31 ppm) group. Analogous changes, though less marked, were also observed in the animals of the 25-mg/m³ (10 ppm) group. Owing to insufficient description of the study its outcome can only be used as supportive evidence for a marginal effect level for systemic effects at 10 ppm after long-term exposure in rats.

It is also taken into account that the odour threshold is below 1 ppm and TMA has a strong, unpleasant odour.

Genotoxicity and carcinogenicity

The genotoxicity of TMA was only studied *in vitro*. Tests in bacteria yielded generally negative results. However, chromosomal aberrations have been induced in hamster cells *in vitro,* most likely due to a shift in pH. Adequate *in vivo* tests for genotoxicity are not available. There are no adequate carcinogenicity studies, but the available data do not point to a genotoxic potential of TMA. There is concern about the formation of *N*-nitroso-dimethylamines in the presence of dietary nitrites, but in view of the normally low nitrite concentration in the human stomach, the practical relevance of nitrosation is negligible, if occurring at all. However, it is not possible to evaluate the risk of *N*-nitrosamine formation at present.

Reproductive toxicity

There were no effects in an OECD-422 screening-test on fertility and developmental toxicity seen at the highest oral dose (200 mg/kg/day), though skeletal and visceral examinations of the offspring were missing (JCIPC 2002). However, a developmental study in mice showed no visceral and skeletal defects (Guest and Varma 1993), so both studies provide sufficient information on the reproductive toxicity of TMA. The NOAEL in the screening-test corresponds to an exposure of 199 ppm (490 mg/m³) TMA in humans, using correction for point of departure (7/5), an allometric scaling (UF) of 4 assuming a body weight of 70 kg and an inhalation volume of 10 m^3 per day.

Overall assessment

The study by Kinney *et al.* (1990) found a LOAEC in rats of 75 ppm for respiratory irritation. Systemic effects are expected to occur only at higher exposures. The limitation of this study is the duration of 2 weeks. Assumption of a factor of three for extrapolation from the LOAEC to the NOAEC and a factor of 6 for extrapolation from subacute to chronic exposure results in a derived value of 4 ppm. In humans a LOAEC of 20 ppm for eye, nose and throat irritation was reported, and below 5 ppm no toxic effects were seen (AHIA 2005). Furthermore, the sensory irritation (Alarie RD_{50}) mouse bioassay predicted that sensory irritation in humans would be negligible at 2 ppm. All results taken together and using the preferred value approach, an OEL of 2 ppm (4.9 mg/m³) is recommended to avoid airway pathological effects and sensory irritation, which also prevents the systemic effects observed at higher concentrations in repeated dose studies in animals.

To avoid strong odour annoyance and to take into account that the exposure-response relationship by sensory irritant is steep in general, a STEL of 5 ppm is recommended.

Other assessments

The dermal uptake of TMA is apparently low for the hydrochloride and no liquid spill can occur as the compound is a gas. A "skin" notation is therefore not necessary. There are no data concerning the sensitising properties of TMA.

Biological monitoring

As the critical effect of exposure to TMA is local irritation, biological monitoring would not provide any useful information related to toxicity. With respect to possible systemic effects, there are no appropriate data to derive a biological limit value.

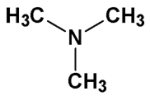
Sampling, measurement and analysis

Analytical measurement systems exist to determine the recommended levels of TMA with an appropriate level of precision and accuracy.

RECOMMENDATION FROM THE SCIENTIFIC COMMITTEE ON OCCUPATIONAL EXPOSURE LIMITS FOR 179 TRIMETHYLAMINE

RECOMMENDATION REPORT

1. CHEMICAL AGENT IDENTIFICATION AND PHYSICO-CHEMICAL PROPERTIES

Name:	Trimethylamine
Synonyms:	*N,N*-Dimethylmethanamine
Molecular formula:	C_3H_9N
Structural formula:	
EC No.:	200-875-0
CAS No.:	75-50-3
Molecular weight:	59.110 g/mol
Boiling point:	2.87 °C
Melting point:	-117 °C
Vapour pressure:	1610 mm Hg at 25 °C; 214 kPa
pKa:	9.8
Log.K_{ow}	0.16 (based on QSAR)
Density:	0.6709
Conversion factors: (20 °C, 101.3 kPa)	1 ppm = 2.42 mg/m^3; 1 mg/L = 414 ppm;

Trimethylamine (TMA) is a colourless gas with a pungent, fishy, ammoniacal odour. TMA is very soluble in water and the log P_{OW} is 0.245. The substance has a flash point of -65 °C and a density of 0.63 g/cm^3 (ACGIH 2004). Tertiary amines introduce steric factors, which may hinder the ability of the amine group to donate its lone pair. Thus trimethylamine (pK_a 9.8) is less basic than diethylamine (pK_a 10.64) or methylamine (pK_a 10.62) (Smith 2010).

2. EU HARMONISED CLASSIFICATION AND LABELLING

Information about the EU harmonised classification and labelling for trimethylamine is provided by ECHA (2016), as summarised in Table 1.

Table 1: Classification according to Regulation (EC) No 1272/2008, Annex VI, Table 3.1 "List of harmonised classification and labelling of hazardous substances" [#]

Index no.	CAS no.	EC / List no.	EC / List name	IUPAC Name
612-001-00-9	75-50-3	200-875-0	Trimethylamine	N,N-dimethylmethanamine

Classification		Labelling		Specific Concentration Limits, M-factors	Notes
Hazard Class & Category Codes	Hazard Statement Codes*	Hazard Statement Codes*	Pictograms, Signal Word Codes		
Press. Gas			GHS02 GHS04 GHS05 GHS07 Dgr**	Skin Irrit. 2; H315: C ≥ 5% Eye Dam. 1; H318: C ≥ 5% Eye Irrit. 2; H319: 0,5% ≤ C < 5% STOT SE 3; H335: C ≥ 5%	Note 5 Note U
Flam. Gas 1	H220	H220			
Skin Irrit. 2	H315	H315			
Eye Dam. 1	H318	H318			
Acute Tox. 4	H332	H332			
STOT SE 3	H335	H335			

[#] Explanations: H220 - *Extremely flammable gas;* H315 - *Causes skin irritation;* H318 - *Causes serious eye damage;* H332 - *Harmful if inhaled;* H335 - *May cause respiratory irritation;* 'Dgr' *for 'Danger;* Note 5 - *The concentration limits for gaseous mixtures are expressed as volume per volume percentage;* Note U - *When put on the market gases have to be classified as 'Gases under pressure', in one of the groups compressed gas, liquefied gas, refrigerated liquefied gas or dissolved gas. The group depends on the physical state in which the gas is packaged and therefore has to be assigned case by case.*

3. CHEMICAL AGENT AND SCOPE OF LEGISLATION

Trimethylamine (TMA) is a hazardous chemical agent in accordance with Article 2 (b) of Directive 98/24/EC and falls within the scope of this legislation.

Trimethylamine (TMA) is not a carcinogen or mutagen for humans in accordance with Article 2(a) and (b) of Directive 2004/37/EC and does not fall within the scope of this legislation.

4. EXISTING OCCUPATIONAL EXPOSURE LIMITS

At EU level, no *OEL* has been adopted yet for trimethylamine. However, OEL's do exist in various EU Member States as well as outside the EU. These OEL's are presented in Table 2 as examples and the list should not be considered as exhaustive.

No *BLV* (Biological Limit Value) has been adopted yet for trimethylamine either in the EU or any EU Member State or in any other country outside the EU.

Table 2: An overview of existing OELs for trimethylamine in EU MS's and elsewhere:

EU	**TWA * (8 hrs)**		**STEL # (15 min)**		**References**
	ppm	mg/m³	ppm	mg/m³	
Belgium	5	12	15	37	BE KB (2014)
Denmark	5	12	10	24	DK BEK (2011)
Germany	2	4.9	4	9.8	DE DFG (2012)
Finland	5	12	15	37	FI MSAH (2012
France			10	25	FR INRF (2012)
Hungary		12.3		36.9	HU MHSFA (2000)
Ireland	5				IE HSA (2011)
Spain	5	12	15	37	ES INSHT (2011)
United Kingdom[&]	[10]	[25]	[15]	[37]	GB HSE (2002)
Non-EU					
Australia	10	24	15	36	AU SWA (2011)
Canada (Ontario)	5		15		CA OML (2013)
Canada (Québec)	5	12	15	36	CA IRSST (2010)
New Zealand	10	24	15	36	NZ HS (2013)
Singapore	5	12	15	36	IFA (2015)
South Korea	5	13.2	15	36	IFA (2015)
Switzerland	2	4.9	4	9.8	CH SUVA (2016)
USA (NIOSH)	10	24	15	36	US NIOSH (2016)
USA (ACGIH)		5		15	USA ACGIH (2012)

[*] Occupational Exposure Limit (e.g. MAK, TRK, TLV, PEL, REL)

[#] Short Term OEL (e.g. STEL)

[&] The UK Advisory Committee on Toxic Substances has expressed concern that, for the OELs shown in parentheses, health may not be adequately protected because of doubts that the limit was soundly-based. These OELs were included in the published UK 2002 list and its 2003 supplement, but are omitted from the published 2005 list.

5. OCCURRENCE, USE AND OCCUPATIONAL EXPOSURE

5.1. Occurrence and use

Trimethylamine occurs as a natural microbial degradation product of nitrogenous macromolecules such as choline and betaine in plant and animal tissues, and is formed by bacterial reduction of trimethylamine N-oxide, a common excretion product of aquatic organisms (Clayton et al. 1994; Graedel 1978; O'Neil 2006; ACGIH 2004).

Release to the environment of this substance is likely to occur from its production, use as an intermediate, formulation in materials, in processing aids, and in the production of articles and for thermoplastics (ECHA Website, 2016).

Trimethylamine is degraded atmospherically by reaction with photochemically-produced hydroxyl radicals. In soil, adsorption of trimethylamine is favoured over volatilization as, because of the high pKa, cationic trimethylamine is the predominant form over the neutral volatile form (TOXNET HSDB).

Degradation products formed under aerobic conditions include dimethylamine, formaldehyde, formate, and carbon dioxide, while products formed under anaerobic conditions include dimethylamine, ammonium cation, and methane (TOXNET HSDB).

5.2. Production and use

Methylamines are produced by the exothermic reaction of methanol with ammonia over amorphous silica - alumina catalyst at 390 - 430 °C. All three possible methylamines are produced. The reaction proceeds to thermodynamic equilibrium, whose position is governed by the temperature and the nitrogen:carbon ratio. The crude reaction mixture consists essentially of excess ammonia, mono-, di-, and trimethylamines, reaction water and unconverted methanol. Purification is generally effected in a train of four to five distillation columns or through azeotropic or extractive distillation. Another method for the preparation of trimethylamine involves the use of paraformaldehyde and ammonium chloride by the reaction of formaldehyde and formic acid with ammonia (TOXNET HSDB).

Trimethylamine is manufactured and/or imported in the European Economic Area in 10 - 100 tonnes per year (ECHA Brief Profile) but this seems a gross underestimate when compared to historical data from US and the European Economic Area (EEA) unless there has been a dramatic shift in trade volume to non-EEA countries. Based on the production of vitamin B4 that starts from trimethylamine and which happens mostly in North America and Europa, in 2004, the total annual trade volume of trimethylamine in the EEA was estimated to be about 40000 tonnes (EC 2004).

The production volumes in the US varied between 22500 - 45400 tonnes in 2002 (TOXNET HSDB).

Trimethylamine is a good nucleophile and a nitrogenous base (pKa 9.4) that can be readily protonated to give trimethylammonium cation, this reaction being the basis of most of its applications.

It is used in organic synthesis, especially of choline salts (e.g. choline chloride: vitamin B4), as a warning agent for natural gas and photochemicals, in the manufacture of cationic starches, intense sweeteners and strongly basic anion exchange resins, in the production of disinfectants, flotation agents, insect attractants and in manufacturing quaternary ammonium compounds (i.e. tetramethylammonium hydroxide) and plastics (TOXNET HSDB, EC 2004).

It is also used as an acid scavenger for nylon and benzyl ester production, as a corrosion inhibitor and as a synthetic (fish and seafood) flavour ingredient (TOXNET HSDB). Trimethylamine is also used in the synthesis of plant growth regulators and herbicides, dye levelling agents and a number of basic dyes (ACGIH 2004).

5.3. Occupational Exposure

According to an estimate by NIOSH and based on a statistical approach, in the US, 5261 workers were potentially exposed to trimethylamine (TOXNET HSDB).

The exposure of workers to trimethylamine was measured by a manufacturer and found at concentrations of 0.1 to 8 ppm (8-hour average value below 5 ppm). Routine medical examinations did not reveal any toxic effects. At concentrations in the air of above 20 ppm, trimethylamine has irritative effects on mucous membranes and eyes. Even low concentrations are a nuisance because of their unpleasant fishy odour (DFG 1983).

5.4. ***Routes of exposure and uptake***

Following its boiling point and vapour pressure, occupational exposure to trimethylamine may occur through inhalation and via dermal contact (TOXNET HSDB).

Monitoring data indicate that the general population may be exposed to trimethylamine via inhalation of tobacco smoke, and ingestion of trimethylamine-containing foods (TOXNET HSDB).

6. MONITORING EXPOSURE

6.1. *External exposure*

Trimethylamine can be monitored in the air of the workplace by applying the partially evaluated OSHA method PV2060 (OSHA 1993; NIOSH 2011): trimethylamine is sampled from workplace air by adsorption onto a solid sorbent, followed by solvent extraction, and separation/determination by GC-FID. Details of the method are shown in Table 3.

Table 3: Sampling and analytical method for monitoring airborne trimethylamine.

Method	Sorbent	Desorption solution	Analysis	Desorption efficiency (%)	LOD/LOQ	Air volume/ sampling rate	Ref.
OSHA Method PV2060	10% phosphoric acid coated XAD-7 tube	Methanol: deionized water (1:1)	GC-FID	98.9	LOD=0.05 mg/m^3 LOQ=0.2 mg/m^3	10 L at 0.1 L/min (Maximum 20 L at a 0.2 L/min)	OSHA 1993
BGIA-Method 7853	Activated carbontubes ORBO 77, sulfuric acid	Deionized water	Ion-chromatography	97.0	LOD=0.05 mg/m^3 LOQ=0.2 mg/m^3	40 L at 0.3 L/min	BGIA 7853

6.2. *Internal exposure/biomonitoring of exposure*

BLVs have not been developed or implemented yet, nor are biomonitoring methods available at present for trimethylamine.

7. HEALTH EFFECTS

7.1. *Toxicokinetics (absporption, distribution, metabolism, excretion)*

7.1.1. Human data

TMA occurs naturally in human body fluids. It can be produced in the body during the metabolism of e.g. choline or L-carnitine by the gut flora and can also be ingested with food (especially by consumption of fish) (Bain et al. 2005, Greim 2004).

After external exposure, the absorption of TMA by the oral route is almost complete, based on the amount of the compound excreted in the urine of volunteers (Al-Waiz et al. 1987, Lundh et al. 1995). The major route of metabolism is N-oxidation to TMA oxide. At higher doses, low amounts of TMA may be demethylated to dimethylamine (DMA) (Greim 2004). After single oral doses of up to 970 mg/kg bw of TMA hydrochloride (600 mg/kg bw of TMA) to humans, the compound was almost quantitatively excreted in the urine (Al-Waiz et al. 1987). TMA is readily absorbed from the gastrointestinal tract and excreted in urine within 24 hours (TMA 86%). The main metabolic pathway is N-oxygenation by a flavin-containing mono-oxygenase and excretion as trimethylamine-N-oxide (TMAO; Lundh et al., 1995). Moreover, some evidence suggests formation of endogenous TMA.

Passage across human skin has been investigated employing excised skin circles in an in vitro diffusion cell apparatus (applied concentrations corresponding to 0.1, 1 and 10 mg per 0.32 cm^2 free base, applied as the hydrochloride). The in vitro penetration rate of TMA in excised human skin was 0.98, 9.21 and 92.7 µg/cm^2/hour, respectively. Within

24 hours, 5 % of all applied doses penetrated the skin. Small but detectable amounts of TMA oxide were formed during the percutaneous passage (Kenyon et al. 2004).

7.1.2. Animal data

The toxicokinetics of TMA in animals are similar to those in humans. The substance is efficiently absorbed after oral exposure and metabolised to TMA oxide and traces of DMA. TMA is cleared from the blood more rapidly than TMA oxide (Nnane and Damani 2001). After a single oral administration of TMA (15 mg/kg bw TMA hydrochloride) to various strains of rats, 80–86 % was excreted in urine and 4–6 % in faeces within 24 hours. The urine contained about 50 % unchanged compound, 45 % TMA oxide (N-oxidation) and 3 % DMA. Faeces contained mostly unchanged TMA and only traces of TMA oxide (Al-Waiz and Mitchell 1991).

The in vitro penetration rate of TMA in excised rat skin (applied concentrations corresponding to 0.1, 1 and 10 mg per 0.32 cm2 of free base, applied as the hydrochloride) was 3.4, 58.3 and 265.0 µg/cm2/hour, respectively. Within 24 hours, 21 % of the applied dose penetrated the skin at all doses. Small amounts of TMA oxide were formed during the percutaneous passage (Kenyon et al. 2004).

7.1.3. In vitro data

7.1.4. Toxicokinetic modelling

7.1.5. Biological monitoring

Among the general population (n = 9–12), the mean TMA background concentrations in gastric juice, saliva, blood and urine have been found to be 118 µg/l, 183 µg/l, 745 µg/l and 715 µg/l, respectively (Zeisel et al. 1988). People with hyperthyroidism have restricted TMA oxidation capacity, so their TMA concentration in blood and urine is higher than in healthy subjects. Patients with uraemia have elevated TMA levels in blood (2–18 mg/l) and in urine. Elevated urine levels (and excretion of TMA via respiration and sweat) have also been found in subjects with trimethylaminuria, a condition caused by reduced capacity for oxidation of TMA to TMA oxide due to an autosomal recessive defect in the flavin-containing monooxygenase form 3 (FMO3) or secondary mechanisms (Bain et al. 2005, Cashman et al. 2003). No adequate data on correlations between external exposure and internal burden were available.

7.2. *Acute toxicity*

7.2.1. Human data

The majority of human data cited in summaries are older case reports which revealed no toxic effects following single or repeated oral doses of up to 2.3 g TMA hydrochloride (ca. 20 mg/kg bw of TMA) administered to volunteers or patients. At higher doses, subjects complained of a fish-like odour of the breath, sweat and urine (ACGIH 2004, BIBRA 1993). One study reported the occurrence of gastric pain, vomiting, diarrhoea and excitation after oral administration of 300–600 mg TMA (Lewin 1929), but this is in conflict with the results of other case studies. Another study documented the occurrence of nausea in a volunteer after ingestion of 15 mg/kg bw (NOAEL 2.5 mg/kg bw) (Calvert 1973).

7.2.2. Animal data

The 4-hour LC50 for rats was determined to be more than 5900 mg/m³ (>2400 ml/m³;) and 3500 ml/m3, respectively (Kinney et al.1990), and for mice 10 300 mg/m3 (4 187 ppm) after 4 hour exposure (Koch et al, 1980). Oral LD50 values were in the range of 397–820 mg/kg for rats (JCIPC 2002, ECHA Registration Dossier 2014). In mice, the oral LD50 was 1 039 mg/kg bw, given as 1 680 mg/kg bw TMA hydrochloride. The dermal LD50 in rats of a 45 % solution of TMA was > 5 000 mg/kg bw (AIHA 2005). Toxic symptoms at high concentrations were laboured breathing, inactivity, convulsions, irritation of mucous membranes, nasal and oral discharge, lack of auditory response and central nervous excitability (BIBRA 1993, Henschler 1983).

Oral application of 1 000 mg/kg bw produced vomiting and diarrhoea in dogs. The same dose caused vomiting, paralysis and death in pigs. Loss of appetite, anorexia, salivation, hypothermia and accelerated heart rate were reported in dogs exposed to single oral doses of 100 or 200 mg/kg bw of TMA (BIBRA 1993).

The effects of single and repeated exposures to TMA were investigated in rats (Kinney et al. 1990) (see also Section 7.3.2). In the acute exposure study, male Crl:CD(SD)BR-rats were exposed for single 4-hour periods to 2 000 or 3 500 ppm TMA. The rats were observed daily for 14 days, at which time the surviving rats were sacrificed (without pathologic examination). Three of six rats died following exposure to 3 500 ppm while no deaths occurred following exposure to 2 000 ppm. All groups exhibited red nasal discharge and irritation of the nasal cavity and turbinates.

7.2.3. In vitro data

7.3. *Specific Target Organ Toxicity/Repeated Exposure*

7.3.1. Human data

Inhalation exposure of workers, usually exposed below 5 ppm (8-hour TWAs, range 0.1–8 ppm; 0.25–19.7 mg/m^3) produced no toxic effects observable by routine medical examinations (See also Section 7.4.1). No additional details were provided (AIHA 2005). High TMA concentrations of 940 ppm and more than 2 000 ppm (together with DMA) have been measured in former times during the unloading of fishing boats. The fishermen frequently complained about discomfort of the eyes, eczema and nervous disorders. Eye contact to liquid or gases from putrefying fish produced irritation, reddening and greyish corneal opacity. The occurrence of nervous disorders in this context is attributed not only to TMA but also to concurrent exposure to other toxic substances (Greim 2004). Nonetheless, cases of diseases, which result in elevated TMA levels in blood (uraemia, hyperthyroidism), are known to be associated with neurotoxic symptoms (Henschler 1983).

The most sensitive endpoint associated with some structurally related tertiary ethyl amines is visual disturbance, including blurred vision after exposures to TEA and N,N-dimethylethylamine, but this has not been looked for in the studies of TMA exposure (Greim 2004). This effect has not been reported for TMA.

7.3.2. Animal data

7.3.2.1. Inhalation

Groups of Sprague-Dawley rats (10/sex) exposed whole-body for 4 hours to 2 440 ppm TMA (2 570 ppm nominal) had irregular respiration and nasal discharge during and one day after treatment (BASF AG 1979). None died during the 14-day study. No effects were seen on animal body weight, measured on study days 0, 7 and 14, and necropsy of all animals revealed no toxic effects. Further study details were not available. These study results were inconsistent with the body of the TMA data, i.e. much lower toxicity was seen at the given test concentration than in other studies.

Rotenberg and Mashbits (1967) studied TMA inhalation exposure in a 7-month chronic experiment. Two groups of animals (12 male white rats/group) were exposed 5 hours/day to TMA at 10.4 ppm (25.0 mg/m3) or 31.0 ppm (75.0 mg/m3). Male rats from a third group were used as control. During exposure, air samples were taken 3–4 times a day and TMA levels determined. Excitation and aggressiveness were manifested for 3–4 weeks after the beginning of the experiment. During the first exposure month, diarrhoea was observed the first 2–3 hours of each exposure. Lymphocyte counts decreased and the number of neutrophils increased in rats from the 31-ppm group beginning from the 4th exposure month onwards. No statistically significant differences between experimental and control groups were revealed when the following data were analysed: body weight, oxygen consumption, emission of carbon dioxide, protein fractions in the blood, antitoxic function of the liver (Quick's – Pytel's Test), and the threshold for nervous and muscular excitability. Patho-morphological studies showed that animals from the 31-ppm group exhibited bronchopneumonia and haemorrhage in the pulmonary tissue with destruction of interalveolar *septa*, and isolated haemorrhage in the liver, kidneys and spleen. Analogous, though less marked, changes were also observed in the animals of the 25-mg/m³ (10 ppm) group. Further details of the study are not available.

The effects of single (Section 7.2.2) and repeated exposures to TMA were investigated in rats (Kinney et al. 1990). In the repeated exposure studies, male Crl:CD(SD)BR rats were exposed to 75, 250 or 750 ppm TMA for 6 hours per day, 5 days per week for 2 weeks and were sacrificed after exposure or after a 14-day recovery period. Determinations were made regarding body weight, clinical pathology (urine and blood samples), and histopathology. Rats exposed to 750 ppm exhibited significantly reduced body weights; significantly increased blood erythrocytes and neutrophils; significantly reduced lymphocyte, leukocyte, and platelet numbers; significantly increased serum urea nitrogen, protein and creatinine; distended alveoli; inflamed or necrotic tracheae; and reduced auditory response. The nasal irritation was characterised by oedema, and focal degeneration/regeneration in the olfactory and respiratory epithelium was related to exposure concentration; this was not reversible within the 14-day recovery period allowed. Irritation was also found in other sections of the respiratory tract of rats exposed to 750 ppm since the trachea was inflamed and necrotic, and mild emphysematous changes were noted in the lung immediately after ten exposures. These findings in the trachea and the lungs were not seen after 14 days of recovery with no additional exposures. At 250 ppm, erythrocyte counts were significantly increased, returning to normal in the recovery period. The other haematological and serum parameters were similar to those in the control group. The irritancy at 75 and 250 ppm was less marked and was restricted to the nasal mucosa. Degenerative changes in the nasal olfactory and respiratory mucosa were reversible at 75 ppm by the end of the 2-week recovery period, but not at 250 or 750 ppm. A no-observed-effect level for TMA under these test conditions was not determined, although the nasal effects seen at 75 ppm were minimal and not seen after a recovery period of 14 days with no additional exposures.

A limited reported study (Trubko and Tepliakova 1981, cited in ACGIH 2004, Henschler 1983) found effects after inhalation exposure of rats to 10 or 31 ppm TMA (25 or 75 mg/m^3, 5 hours/day, 7 months). During the first months of exposure, the animals

were aggressive and had diarrhoea. At the end of the study, they showed damage to lungs, liver, kidneys and spleens. (ACGIH 2004, Henschler 1983).

7.3.2.2. Oral exposure

In a brief summary (details not provided) (JCIPC 2002), an unpublished rat screening test on reproductive/developmental toxicity (according to OECD guideline 422) is described. Rats (13 of each sex) were orally exposed to 8, 40 or 200 mg/kg bw/day for 42 days (males) or from 14 days before mating to day 4 of lactation (females). There were no effects in the F0 generation after oral exposure to doses up to 40 mg/kg bw/day for 42 days. Doses of 200 mg/kg bw/day caused clinical signs of toxicity (stridor, temporary salivation), increased mortality (two males and one female died in the 200-mg/kg bw group), decreased body weights and decreased food consumption. Pathological examination, reported with no further details described, revealed inflammation, ulceration and hyperplasia of the gastrointestinal tract. No other organs were affected. The no observed adverse effect level (NOAEL) for systemic toxicity of TMA was considered to be 40 mg/kg bw/day in males and females.

Amoore et al. (1978) exposed rats to TMA in the diet at doses of about 250, 480 and 1000 mg/kg bw/day for up to 84 days. After 84 days of exposure to 1000 mg/kg bw/day, there were gross and microscopic changes in seminal vesicles and prostate. Fourteen days of exposure to 480 mg/kg bw/day caused reduced growth. No effects on haematology, urinalysis and no histological alterations were found in rats given about 250 mg/kg bw/ day TMA by feed for up to 84 days. Incomplete data reporting makes this study unsuitable for risk assessment (Greim 2004).

7.3.2.3. Dermal exposure

No studies of repeated dermal exposure were available.

7.3.3. In vitro data

7.4. *Irritancy and corrosivity*

7.4.1. Human data

Reported odour thresholds of TMA are in a broad range of 0.00011–0.87 ppm (0.00026–2.1 mg/m3). Amoore and Hautala (1983) reported a geometric mean of existing odour thresholds (omitting extreme values) of 0.00044 ppm (0.0011 mg/m3) with a wide standard deviation. None of the values was considered acceptable by AIHA (2005) due to unclear experimental protocols.

Odour and nasal lateralisation thresholds of several substances including TMA were determined by van Thriel et al. (2006) using single sniff exposures of varying concentrations. Series of twenty 280 ml glass bottles were filled with the chemicals by different, ascending dilution steps. By sniffing the headspaces from two bottles simultaneously, subjects were confronted with different concentrations of the respective chemicals. The sequence of the presentation of the substances was randomised across the subjects and the odour threshold was always measured before the lateralisation threshold in a separate run. Data were derived from 144 non-smoking subjects (male and female). The experiment demonstrated a median odour threshold of 0.26 ppm (0.16 ppm for males, 0.36 ppm, for females, $p = 0.03$), with a 25th percentile of 0.04 ppm. The median lateralisation threshold was 612 ppm and the 25th percentile

284 ppm. All sniffing bottle concentrations were verified by different analytical techniques.

TMA is irritating to the human respiratory tract, skin and eyes. AIHA (2005) reported that TMA concentrations in the range 0.1–8 ppm were measured in industrial rooms during 8-hour workdays, with most 8-hour TWAs < 5 ppm. "Routine medical and biological monitoring" (not described) revealed no toxic effects in these workers. In this limited report, it was not stated whether any irritation occurred at 0.1–8 ppm, but "moderate" upper respiratory irritation occurred at ≥ 20 ppm (exposure time not specified). No additional details were provided.

A concentrated solution produced severe burning and reddening of the human skin. Petechial haemorrhages under the skin developed even when this solution was washed off within minutes after application. The exposed area remained tender for 1–2 hours, and slight desquamation occurred (ACGIH 2004, BIBRA 1993).

Two daily occlusive exposures (30 min each) on 4 consecutive days to 1.5 % TMA did not irritate the skin of 20 volunteers (Fluhr et al. 2005).

A probably minimal exposure of the human eye to TMA during an accident caused corneal epithelial sloughing. Healing followed within 4–5 days (ACGIH 2001, BIBRA 1993).

7.4.2. Animal data

7.4.2.1. Skin

TMA as a 45 % solution caused severe burns to rabbit skin (BASF 1979).

7.4.2.2. Eyes

The application of 1 % TMA (one drop every 2 hours, 4 times) to the rabbit eye produced severe conjunctivitis, keratitis and corneal opacity. One drop of 5 % TMA caused haemorrhagic conjunctivitis and oedema of the cornea with opacity of the parenchyma (Friemann et al. 1959).

7.4.2.3 Respiratory tract

The RD50 (concentration that reduce the respiratory rate by 50 %) values derived from animal bioassays may be used for scaling the irritating properties of airborne chemicals with sensory irritation as the critical effect. The bioassay is termed the Alarie test. Shaper et al. (1993) found a strong correlation ($R^2 = 0.78$) between the TLV and RD50 for 89 chemicals and the relationship writes: TLV~0.03 x RD50. Gagnaire et al. (1989) exposed male Swiss-OF1 mice to a series of aliphatic amines and reported similar RD50 values for TMA and DMA (61 and 70 ppm, respectively), whereas the RD50 of triethylamine (TEA), DEA, methylamine and ethylamine were higher (156, 202, 141 and 151 ppm, respectively). It also has to be taken into account that sensory irritation, in general, has a steep concentration-response relationship (Nielsen et al. 2007).

Kinney et al. (1990) reported irritation of the respiratory tract of rats (hyperaemia, epithelial degeneration and squamous metaplasia), following repeated exposure by inhalation to concentrations of 75 ppm (185 mg/m3) (see also Section 7.3.2).

7.4.3. In vitro data

There are no *in vitro* data on irritancy and corrosivity.

7.5. *Sensitisation*

7.5.1. Human data

There are no data on sensitisation in humans.

7.5.2. Animal data

Sensitisation tests in animals are not available.

7.5.3. In vitro data

There are no *in vitro* data on sensitisation.

7.6. *Genotoxicity*

7.6.1. Human data

Human data on genotoxic effects are not available.

7.6.2. Animal data

Animal data on genotoxic effects are lacking.

7.6.3. In vitro

TMA was not mutagenic when tested in *Salmonella typhimurium* (TA97, TA98, TA100, TA1535 and TA1537) with or without metabolic activation (AIHA 2005). Another study confirmed these negative results in various strains of *Salmonella* and also in *Escherichia coli* WP2 (JCIPC 2002). However, chromosomal aberrations were induced in Chinese hamster lung cells *in vitro* with or without metabolic activation (JCIPC 2002). The effective concentrations (≥ 296 µg/ml without and ≥ 473 µg/ml with metabolic activation) caused a shift of the pH of the culture medium to values > 8, so that the increase in chromosomal aberrations might have been evoked by this change in pH (Greim 2004).

7.7. *Carcinogenicity*

7.7.1. Human data

Human data on the carcinogenic effects of TMA are not available, although there is some concern about the formation of carcinogenic nitrosamines resulting from a reaction of TMA, TMA oxide or DMA with nitrite (Bain *et al.* 2005, Greim 2004). *In vitro* and *in vivo* studies showed the conversion of DMA to *N*-nitrosodimethylamine in gastric juice in the presence of nitrite (Choi *et al.* 2002, Zeisel *et al.* 1988). However, the endogenous demethylation of TMA to DMA, which is the relevant substance for the formation of nitrosoamines is quite small. Nevertheless, owing to the influence of varying exposures to nitrite and other factors in food (e.g. vegetables, fruits or green tea) (Choi *et al.* 2002), a possible risk of this effect cannot be evaluated at present.

7.7.2. Animal data

No data on carcinogenic effects in animals are available.

7.8. Reproductive toxicity

7.8.1. Human data

No human data on reproductive or developmental effects are available.

7.8.2. Animal data

7.7.2.1. Fertility

No effects on reproduction in rats were found after oral exposure to doses up to 200 mg/kg bw/day in an unpublished screening test on reproductive/developmental toxicity (according to OECD guideline 422) (JCIPC 2002) (see Section 7.3.2).

After oral exposure of rats to about 1 000 mg/kg bw/day of TMA by feed for 84 days, gross and microscopic changes in seminal vesicles and prostate were evident, but not at lower doses of 480 mg/kg bw/day for 14 days or 250 mg/kg bw/day for 84 days (Amoore *et al.* 1978).

7.7.2.2. Developmental toxicity

No developmental effects were found in the offspring of rats exposed orally to doses up to 200 mg/kg bw/day in an unpublished screening test on reproductive/developmental toxicity (according to OECD guideline 422) (JCIPC 2002) (see Section 7.3.2).

TMA was administered intraperitoneally at doses of 0, 60, 150, 300 and 450 mg/kg bw/day to mice on days 6–15 of gestation. No signs of toxicity were seen in the mice given TMA at doses up to 150 mg/kg bw/day. At 300 mg/kg bw/day, there was a decrease in foetal body weight and postnatal body weight gain was reduced. At 450 mg/kg bw/day, the body weight of dams and the litter size were reduced. Postnatal reductions of brain DNA and protein content as well as decreased serum testosterone levels were evident in the offspring of the high dose group (Guest and Varma 1993).

In another mouse study by the same authors (Guest and Varma 1993), TMA was administered intraperitoneally at 0, 15, 60, 150 and 300 mg/kg b.w./day to pregnant animals on days 1-17 of gestation; the group sizes comprised 4-11 dams. The dams and foetuses were examined on day 18 of gestation. There was no decrease in body weight of the dams at 300 mg/kg b.w./day, but 5 dams died. The foetal body weight decreased at ≥150 mg/kg b.w./day and a decrease in foetal survival was observed at 300 mg/kg b.w./day. However, no visceral or skeletal anomalies were observed.

7.7.2.3. Inhalation

No data on reproductive toxicity by inhalation studies are available.

7.7.2.4. Oral

See 7.7.2.1 and 7.7.2.2

7.7.2.5. Dermal

7.7.2.6. Other routes

7.8.3. In vitro data

There are no further *in vitro* data available.

7.9. Mode of action and adverse outcome pathway considerations

Trimethylamine stimulates the sensory trigeminal nerve endings, causing facial and eye irritation, and also causes respiratory tract epithelial damage from a direct toxic effect.

7.10. Lack of specific scientific information

8. GROUPS AT EXTRA RISK

No group at extra risk has been identified.

9. REFERENCES

ACGIH [American Conference of Governmental Industrial Hygienists] (2004). Trimethylamine. In: Threshold limit values for chemical substances and physical agents and biological exposure indices. American Conference of Governmental Industrial Hygienists, 2004, Cincinnati, OH.

ACGIH [American Conference of Governmental Industrial Hygienists] (2012). Appendix B. ACGIH Threshold Limit Values (TLVs) and Biological Exposure Indices (BEIs). Based on the Documentation of the Threshold Limit Values for Chemical Substances and Physical Agents & Biological Exposure Indices.

AIHA, American Industrial Hygiene Association (2005). Trimethylamine. In: Workplace environmental exposure level (WEEL). American Industrial Hygiene Association, Fairfax, VA.

Al-Waiz M, Mitchell SC, Idle JR, Smith RL (1987 d) The relative importance of N-oxidation and N-demethylation in the metabolism of trimethylamine in man. Toxicology 43: 117–121.

Al-Waiz M, Mitchell SC (1991). The fate of trimethylamine in the rat. Drug Metabol Drug Interact 9:41-48.

Amoore JE, Gumbmann MR, Booth AN, Gould DH (1978). Synthetic flavors: efficiency and safety factors for sweaty and fishy odorants. Chemical Senses 3:307-317, cited in BIBRA 1993.

Amoore JE, Hautala E (1983). Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J Appl Toxicol 3:272-290.

Bain MA, Fornasini G, Evans AM (2005). Trimethylamine: metabolic, pharmacokinetic and safety aspects. Curr Drug Metab 6:227-240.

BASF AG (1979). Bericht über die Bestimmung der akuten Inhalationtoxizität (LC50) von Trimethylamin als Gas. Data obtained from IUCLID 2004 for trimethylamine.

BEK (2011) Bekendtgørelse om ændring af bekendtgørelse om grænseværdier for stoffer og materialer, BEK nr 1134 af 01/12/2011 (Gældende), Ministerium: Beskæftigelsesministeriet Journalnummer: Beskæftigelsesmin, Arbejdstilsynet, j.nr. 2011007144, Denmark. https://www.retsinformation.dk/pdfPrint.aspx?id=139131

BGFA, Berufsgenossenschaftliches Forschungsinstitut für Arbeitsmedizin (2004). BGFA-Jahresbericht 2004. Institut der Ruhr-Universität Bochum. www.bgfa.ruhr-uni-bochum.de/pdf/jabe0401.pdf.

BIBRA, The British Industrial Biological Research Association (1993). Toxicity profile trimethylamine and its hydrochloride. BIBRA Toxicology International, Great Britain.

Calvert GD (1973). Trimethylaminuria and inherited Noonan's syndrome. Lancet I:320-321, cited in BIBRA 1993.

Cashman JR, Camp K, Fakharzadeh SS, Fennessey PV, Hines RN, Mamer OV, Mitchell SC, Preti G, Schlenk D, Smith RL, Tjoa SS, Williams DE, Yannicelli S (2003). Biochemical and clinical aspects of the human flavin-containing monooxygenase form 3 (FMO3) related to trimethylaminuria. Curr Drug Metab 4:151-170.

Choi SY, Chung MJ, Sung NJ (2002). Volatile N-nitrosamine inhibition after intake Korean green tea and Maesil (Prunus mume SIEB. et ZACC.) extracts with an amine-rich diet in subjects ingesting nitrate. Food Chem Toxicol 40:949-957.

Clayton G.B., Clayton F.E., eds (1994) Patty's Industrial Hygiene and Toxicology. Toxicology. 4th ed. NY, NY: John Wiley and Sons Inc., 1993-1994. p. 1115

DFG [Deutsche Forschungsgemeinschaft] (2016) MAK- und BAT-Werte-Liste. MAK Value Documentation for Trimethylamine in German language, 2016

http://onlinelibrary.wiley.com/doi/10.1002/3527600418.mb7550d0060/pdf Accessed 2016.03.15

DFG [Deutsche Forschungsgemeinschaft] The MAK Collection for Occupational Health and Safety. MAK Value Documentation for Trimethylamine, 1983. Trimethylamine http://onlinelibrary.wiley.com/doi/10.1002/3527600418.mb7550e0914/pdf Accessed 2016.04.13

EC [European Commission] 2004 Commission Decision relating to a proceeding under Article 81 of the EC Treaty and Article 53 of the EEA Agreement (Case COMP / E-2 / 37.533 - Choline Chloride). Commission of the European Communities. Brussels, 9.12.2004. http://ec.europa.eu/competition/antitrust/cases/dec_docs/37533/37533_43_1.pdf Accessed 2016.04.12.

ECHA Brief Profile. Accessed 2016.04.12.

ECHA Website. Accessed 2016.03.16. http://echa.europa.eu/substance-information/-/substanceinfo/100.000.796

ECHA, European Chemical Agency (2014). http://echa.europa.eu/information-on-chemicals/registered-substances (accessed October 9, 2015).

Fluhr JW, Kelterer D, Fuchs S, Kaatz M, Grieshaber R, Kleesz P, Elsner P (2005). Additive impairment of the barrier function and irritation by biogenic amines and sodium lauryl sulphate: a controlled in vivo tandem irritation study. Skin Pharmacol Physiol 18:88-97.

Friemann W, Overhoff W, Wolter JR (1959). [Eye diseases in the fishing industry.] Arch Gewerbepathol Gewerbehyg 17:1-56, cited in Henschler 1983.

Gagnaire F, Azim S, Bonnet P, Simon P, Guenier JP, de Ceaurriz J (1989). Nasal irritation and pulmonary toxicity of aliphatic amines in mice. J Appl Toxicol 9:301-304.

Graedel T.E. (1978) Chemical Compound in the Atmopshere. NY, NY: Academic Press

Greim H (1996). Gesundheitsschädliche Arbeitsstoffe, Toxikologisch-arbeitsmedizinische Begründungen von MAK-Werten, Loseblattsammlung, 22. Lfg. DFG, Deutsche Forschungsgemeinschaft, VCH Verlag Weinheim.

Greim H (2002). Gesundheitsschädliche Arbeitsstoffe, Toxikologisch-arbeitsmedizinische Begründungen von MAK-Werten, Loseblattsammlung, 34. Lfg. DFG, Deutsche Forschungsgemeinschaft, Wiley-VCH Verlag, Weinheim.

Greim H (2004). Gesundheitsschädliche Arbeitsstoffe, Toxikologisch-arbeitsmedizinische Begründungen von MAK-Werten, Loseblattsammlung, 38. Lfg. DFG, Deutsche Forschungsgemeinschaft, Wiley-VCH Verlag, Weinheim.

Guest I, Varma DR (1993). Selective growth inhibition of the male progeny of mice treated with trimethylamine during pregnancy. Can J Physiol Pharmacol 71:185-187, cited in Greim 2004 and ECB 2000.

Henschler D (1983). Gesundheitsschädliche Arbeitsstoffe, Toxikologisch-arbeits-medizinische Begründungen von MAK-Werten, Loseblattsammlung, 9. Lfg. DFG, Deutsche Forschungsgemeinschaft, VCH Verlag Weinheim.

HS [Health and Safety] (2013) Workplace Exposure Standards and Biological exposure Indices Effective from February 2013 7th Edition. The Ministry of Business, Innovation and Employment, New Zealand. http://www.business.govt.nz/worksafe/information-guidance/all-guidance-items/workplace-exposure-standards-and-biological-exposure-indices/workplace-exposure-standards-and-biological-indices-2013.pdf

HSA [Health and Safety Authority] (2011) 2011 Code of Practice for the Safety, Health and Welfare at Work (Chemical Agents) Regulations 2001 (S.I. No. 619 of 2001), Health and Safety Authority, Ireland

http://www.hsa.ie/eng/Publications_and_Forms/Publications/Chemical_and_Hazardous_Substances/Code_of_Practice_Chemical_Agent_Regulations_2011.pdf

HSE [Health and Safety Executive] (2002) EH40 (Second edition, Health and Safety Executive (HSE), UK. http://a-a.co.kr/downloads/ION/ionscience.pdf

HSE, Health and Safety Executive (2000). Control of substances hazardous to health regulations 1999. Proposal for maximum exposure limits, and occupational exposure standards. http://hse.gov.uk/consult/condocs/cd157.pdf (accessed April 2006).

IFA, Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung (2015) GESTIS - International limit values for chemical agents, DGUV, IFA, Sankt Augustin, Germany. http://limitvalue.ifa.dguv.de/. Accessed 2016.03.15

INRS (2012) Valeurs limites d'exposition professionnelle aux agents chimiques en France, Institut National de Recherche et de Sécurité (INRS), France, http://www.inrs.fr/media.html?refINRS=ED%20984

INSHT [Instituto Nacional de Seguridad e Higiene en el Trabajo] (2011). Limites de Exposicion profesional para agentes quimicos en Espana, Spain. http://www.insht.es/InshtWeb/Contenidos/Documentacion/TextosOnline/Valores_Limite/limites2011/Limites2011web.pdf

IRSST [Institut de Recherche Robert Sauvé en Santé et en Sécurité du Travail] (2010) Québec, Canada. http://www.irsst.qc.ca/en/laboratories/references-tools/workplace-air-contaminant/substance/i/555

Järvinen P, Engström Riihimäki V, Ruusuvaara P, Setälä K (1999). Effects of experimental exposure to triethylamine on vision and the eye. Occup Environ Med 56:1-5.

JCIPC, Japanese Chemicals Investigation Promoting Council (2002). Chemical toxicity database. http://dra4.nihs.go.jp/mhlw_data/home/file/file75-50-3.html (accessed February 2014).

KB (2002) [Koninklijk Besluit - Royal Decision] (2002) Revised version valid for after July 2014. Koninklijk besluit van 11 maart 2002 betreffende de bescherming van de gezondheid en de veiligheid van de werknemers tegen de risico's van chemische agentia op het werk, Belgium. https://www.google.it/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0ahUKEwj7hoam8f7LAhWBORoKHcMgAp4QFggcMAA&url=http%3A%2F%2Fwww.werk.belgie.be%2FDownloadAsset.aspx%3Fid%3D2162&usg=AFQjCNGhKN3FmC8o8vps9iLtBYFpdxEBXg&sig2=R62PTd6ymNQtN9MW1tgqZw&bvm=bv.119028448,d.d2s&cad=rja

Kenyon S, Carmichael PL, Khalaque S, Panchal S, Waring R, Harris R, Smith RL, Mitchell SC (2004). The passage of trimethylamine across rat and human skin. Food Chem Toxicol 42:1619-1628.

Kinney LA, Burgess BA, Chen HC, Kennedy GL (1990). Inhalation toxicology of trimethylamine (TMA). Inhal Toxicol 2:41-51.

Koch F , Mehlhorn G , Kliche R , Lang R (1980) Wiss. Z. Karl-Marx-Univ. Leipzig, Math.-Naturwiss. Reihe 29: 463

Lewin L (1929). Gifte und Vergiftungen. Georg Stilke-Verlag Berlin p. 477.

Lundh T, Åkesson B, Skerfving S (1995). Effect of dietary intake of trimethylamine on human metabolism of the industrial catalyst dimethylethylamine. Occup Environ Med 52:478-483.

MHSFA [Ministry of Health, Social and Ministry of Family Affairs] (2000) 25/2000. (IX. 30.) EüM-SzCsM együttes rendelet a munkahelyek kémiai biztonságáról, Hungary. http://net.jogtar.hu/jr/gen/hjegy_doc.cgi?docid=A0000025.EUM

MSAH [Ministry of Social Affairs and Health] (2012) HTP-värden 2012. Koncentrationer som befunnits skadliga. Social- och halso vardsministeriets publikationer 2012:6,

Finland. http://www.ttk.fi/files/2610/STM_2012_6_HTP_SWE_web.pdf. Accessed 2016.03.15.

Nielsen GD, Wolkoff P, Alarie Y. Sensory irritation: Risk assessment approaches. Regul Toxicol Pharmacol 2007; 48: 6-18.

NIOSH [National Institute for Occupational Safety and Health] (2011) Pocket guide to chemical hazards Trimethylamine http://www.cdc.gov/niosh/npg/npgd0636.html Accessed 2016.03.16

NIOSH [US National Institute for Occupational Safety and Health] (2016) NIOSH Publications & Products. Immediately Dangerous To Life or Health (IDLH). Chemical Listing and Documentation. Immediately Dangerous to Life or Health Concentrations (IDLH). Trimethylamine. http://www.cdc.gov/niosh/npg/npgd0636.html Accessed 2016.02.10

Nnane IP, Damani LA (2001). Pharmacokinetics of trimethylamine in rats, including the effects of a synthetic diet. Xenobiotica 31:749-755.

OML [Ontario Ministry of Labour] (2013) Current Occupational Exposure Limits for Ontario Workplaces Required under Regulation 833, Canada. http://www.labour.gov.on.ca/english/hs/pubs/oel_table.php

O'Neil, M.J. ed. (2006) The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse Station, NJ: Merck and Co., Inc., p. 1668

OSHA [Occupational Safety and Health Administration] (1993) OSHA method PV2060 for Triethylamine, https://www.osha.gov/dts/sltc/methods/partial/pv2060/2060.htmlTrimethylamine

OSHA, Occupational Safety and Health administration (1993). Method PV 2060 https://www.osha.gov/dts/sltc/methods/partial/pv2060/2060.html (accessed February 2014).

Rotenberg YS, Mashbits FD (1967). On the toxic action of trimethylamine at low concentrations. Gig Tr Prof Zabol 11:26-30.

Smith DA (ed.) (2010). Metabolism, pharmacokinetics, and toxicity of functional groups: impact of the building blocks of medicinal chemistry in ADMET. Royal society of chemistry. Royal society of chemistry.

Sutton W (1959). As cited in Patty's Industrial Hygiene and Toxicology, 2nd Ed. 1963, cited in AIHA 2005.

SUVA [Schweizerische Unfallversicherungsanstalt] (2016) Grenzwerte am Arbeitsplatz 2015. MAK-Werte, BAT-Werte, Grenzwerte für physikalische Einwirkungen Switzerland https://extra.suva.ch/suva/b2c/download/(layout=7.01-15_1_71_68_6_125&uiarea=1&carea=50328D134DA837E0E10080000A630358&citem=50328D134DA837E0E10080000A6303584BE36A0936148016E10080000A630387)/.do;jsessionid=Ax9Bf-vMX-vSaIHzG4I9HPMom4f1UwFzkRoe_SAPW5jysT93Gt3nXMIRx2HFbmCH;saplb_*=(J2EE505057620)505057651?doctype=pdf&docid=0000000000000004490&file=1903_F.pdf

SWA [Safe Work Australia] (2011) Workplace exposure standards for airborne contaminants date of effect: 22 December 2011, Australia. http://www.safeworkaustralia.gov.au/sites/SWA/about/Publications/Documents/639/Workplace_Exposure_Standards_for_Airborne_Contaminants.pdf

TOXNET HSDB [TOXicology Data NETwork - Hazardous Substances Databank] National Institutes of Health https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@DOCNO+808

Trubko EI, Tepliakova EV (1981). [Hygienic standardization of trimethylamine in reservoir water] [Article in Russian] Gig Sanit 8:79-80.

Van Thriel C, Schäper M, Kiesswetter E, Kleinbeck S, Juran S, Blaszkewicz M, Fricke H-H, Altmann L, Berresheim H, Brüning T (2006). From chemosensory thresholds to whole body exposures-experimental approaches evaluating chemosensory effects of chemicals. Int Arch Occup Environ Health 79:308-321.

Zeisel SH, da Costa KA, LaMont JT (1988). Mono-, di- and trimethylamine in human gastric fluid: potential substrates for nitrosodimethylamine formation. Carcinogenesis 9:179-181.

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