RISK PROFILE

Dimethyl MEA (DMAE)

CAS No.108-01-0

Date of reporting 05.06.2012

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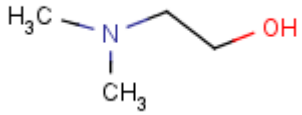
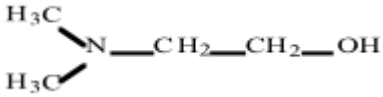
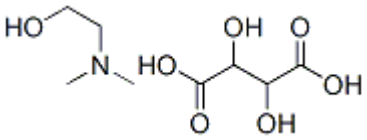
1. Identification of substance

Chemical name (IUPAC):	2-Dimethylaminoethanol; N,N-Dimethyl-2-aminoethanol
INCI	DIMETHYL MEA
Other name	“Deanol”; DMEA or DMAE (older names)
CAS No.	108-01-0
EINECS No.	203-542-8
Molecular formula	$C_4H_{11}NO$ / $(CH_3)_2NCH_2CH_2OH$
Chemical structure	
Molecular weight	89.14
Contents (if relevant))	
Physiochemical properties	Appearance: clear volatile liquid with a fishlike odor Density: 0.89 g/ml Boiling point: 135.00 °C @ 760.00 mm Hg Melting point: -59 °C Flash point: 38 °C Vapor pressure: 3.18 mm Hg (Pa at 20°C: 612)

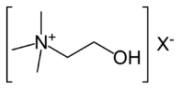
	Solubility (log $P_{ow)}$: - 0.55 (i.e. high solubility in water) pKa: 8.88 ± 0.20 References: IPCS [online]

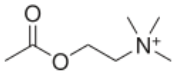
2. Uses and origin

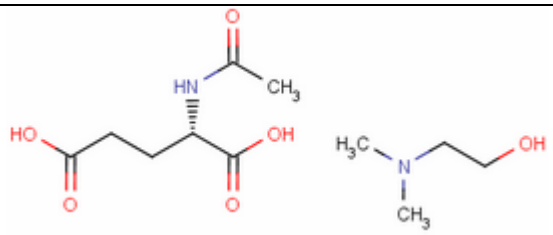
Uses	**Cosmetic products**: *Functions according to* • CosIng database: "Buffering" - stabilizes the pH of cosmetics" • Other source Anti-wrinkle & skin protection, facial moisturizer, lip balm, toners and for hair (NIEHS, 2002: pp.17; EWG's Skin Deep [online , web search). *Concentrations being applied* Example: 6% DMAE is used in a product announced on the internet (DermoPro [online]). *Frequency of use* Deanol is present in169 cosmetic products, including anti-aging, facial moisturizer /treatment, lip balm, facial cleanser (EWG's Skin Deep [online]), and in 50 products in similar categories at Codecheck.info [online] (search word: "Dimethyl MEA"). **Food** DMAE is presently marketed as a dietary supplement (as DMAE bitartrate) (NIEHS, 2002: pp.iii). Typical doses of DMAE bitartrate range from 35 – 130 mg, but may extend up to 1200 – 1800 mg daily (eHow Health [online]). DMAE may be ingested in small quantities by eating fish such as salmon, anchovies or sardines (eHow Health [online]). **Medicinal products** Deanol (DMAE) was once used as a drug for hyperactivity in children and for conditions such as neuroleptic-induced tardive dyskinesia (a trembling disorder caused by long-term anti-psychotic medication). A Cochrane review did not show any substantial effect on tardive

	dyskinesia when compared with placebo (Tammenmaa et al., 2002). "Deaner" (deanol p-acetamidobenzoate) was a U.S. prescription drug (Riker Laboratories', U.S) until 1983 when it was withdrawn from the market, not because of safety issues, but because of better alternatives. In Europe, DMAE (product name Deanol) is the main ingredient (ca.1/3 deanol) in a commonly prescribed drug, "Centrophenoxine". Manufacturers' recommended dosages and those used in clinical studies vary between 400 and 1800 mg daily. **Other products** Data not retrieved.
Origin Natural (exo /endo) Synthetic	DMAE is synthesized from equimolar amounts of ethylene oxide and dimethylamine (Budavari, 2001, cited in NIEHS, 2002).  *Biochemical precursor*: It has been suggested that DMAE is methylated to produce choline in the brain. DMAE is related to choline and may be a biochemical precursor to the neurotransmitter acetylcholine, but this has been disputed (Zahniser et al., 1977; see also NIEHS, 2002, pp.ix) [1]. *Deanol bitartrate* is a salt produced from DMAE and tartaric acid, and is marketed as a substance in food products.  *Deanol aceglutamate* is a salt produced from deanol and acetylglutamate, which is *prohibited in cosmetics* (cf. "Regulations", section 3).

[1] Choline: Acetylcholine





3. Regulation

Norway	No regulation[2]
EU	No regulation, The deanol salt, deanol aceglumate (CAS no 3342-61-8), is in the list of substances prohibited in cosmetic products; cf. CosIng Regulation (EC) No 1223/2009, annex II /Entry No 3. *Comments*: The ban of deanol aceglutamate does not extend to deanol itself. According to. e-mail 28 Jan 2008 to The Norwegian Safety Authority (Hans Jørgen Talberg) (MT) from the European Commission (Stefan Führing /Cosmetics sector Unit F3 of DG ENTER): *" the importer/producer has to be in a position to prove the safety of this ingredient, cf. Art. 7a(1)(d) Cosmetics Directive."* Besides DMAE is classified as a skin corrosive substance according the CLP part of the EU chemicals legislation (Regulation (EC) No 1272/2008)
Rest of the world	No regulation

4. Relevant toxicity studies

Absorption Skin / GI tractus	No dermal absorption data is available, and a default value of 100 % will therefore be used (SCCS, 2010).
Distribution	The chemical characteristics, metabolism, and toxicokinetics of DMAE have been described in NIEHS (2002). DMAE is absorbed and rapidly transported to the liver in male mice where much of it is metabolized (NIEHS, 2002: pp. v; 31). In humans, 33% of an injected 1 g dose of DMAE was excreted unchanged, whereas the remaining dose might have been demethylated to ethanolamine and directed towards normal metabolic pathways.
Metabolism	
Excretion	
Local toxic effects Irritation	The use of DMAE in topical creams is subject to skin irritation in some individuals. DMAE is a corrosive substance, causing dermal, eye and respiratory irritation in animal tests (OECD SIDS, 1996).

[2] The Norwegian medicinal products agency considered DMAE a medicinal remedy. Because of that up till 2008 topical products containing the substance were considered medicines – meaning a topical product containing it were automatically classified a medicine. This regime has since been lifted.

	Visual and ocular changes in production line workers were associated with exposure to two tertiary amines, including DMAE (Page et al., 2003).
Sensitization	Skin sensitization in humans has not been reported under normal handling precautions (because undiluted DMAE is corrosive, exposure is likely limited due to cautious handling). No evidence for skin sensitization found for DMAE using the guinea pig maximation procedure (Leung and Blaszcak, 1998; cited in NIEHS, 2002: pp. 57), but DMAE appears to have the *potential* to cause skin sensitization (OECD SIDS, 1996: pp.10).
Systemic toxic effects	Human data are scarce – cf. human health effects (Annex 1); therefore, the majority of toxicological data comes from animal studies. Clinical studies of DMAE have used up to 1600 mg per day with no reports of side effects, and it is therefore believed to be relatively nontoxic (Casey & Denney, 1974). However, the majority of these studies have focused on other aspects of anti-aging (e.g. mental alertness, cognitive ability), rather than skin.
Acute	Single exposure animal data indicate that DMAE is of low toxicity via the oral, dermal and inhalation routes (OECD SIDS, 1996: pp.9). (Annex 3). - Oral Toxicity (LD50): 1803 mg/kg (Oral-rat). Lowest reported. - Dermal Toxicity (LD50): 1220 mg/kg (skin-rabbit). - Inhalation Toxicity (LC50): 6.5 mg/l (inhalation-rat). Signs of toxicity included respiratory difficulties, loss of coordination and decreased motor activity.
Repeated dose	Male and female F344 rats were exposed to 8, 24, or 76 ppm (30, 88, or 280 mg/m^3; 0.3, 0.98, or 3.1 mmol/m^3) DMAE for six hours/day, five days/week for 13 weeks (Klonne et al., 1987). Repeated inhalation toxicity data in F344 rats indicate that the NOAEL is 24 ppm (88 mg/m^3) for systemic toxicity (decreased body weight gain) following 13-week exposure; NOAEL is 8 ppm (30 mg/m^3) when local effects on the eye (corneal opacity) is considered (OECD SIDS, 1996). Repeated dose *dermal* studies were not found and only a limited repeated dose oral study was identified (Smyth et al., 1951, cited in NIEHS, 2002). Therefore, toxicity by the dermal route cannot be adequately assessed.
Mutagenicity/genotoxicity	No evidence that DMAE is genotoxic in several mammalian systems, both *in vitro* and *in vivo* (See Table 9 in NIEHS, 2002: pp. 55).
Carcinogenicity	There is no evidence that DMAE is carcinogenic. (See Table 8 in NIEHS, 2002: pp. 53).
Reprotoxicity /teratogenicity	No histopathological changes were observed in the gonads after repeated exposure to DMAE in a 90-day inhalation study in rats (Davies et al., 1997, in NIEHS, 2002: pp. 49; OECD SIDS, 1996). Time-pregnant Fischer 344 rats were exposed (whole-body) to DMAE at concentrations up to 100 ppm (0, 10, 30 and 100 ppm) in a developmental study; maternal body weight was reduced at mid- and

	high concentrations, whereas transient ocular changes were observed also in low-dose groups. There were no consistent treatment-related effects on fetal development, although delayed ossification was reported for some skeletal elements. (Leung et al., 1996, cited in NIEHS, 2002). Thus, NOAELs for maternal toxicity and teratogenicity were estimated to be 10 ppm (40 mg/m^3) and 100 ppm (370 mg/m^3), respectively (Leung et al., 1996; IUCLID, 1997; both cited in NIEHS, 2002). (See Table 7 in NIEHS, 2002: pp. 50).
Other effects	In 2007, an *in vitro* study in the British Journal of Dermatology reported that the anti-wrinkle effect of topical DMAE involves a vacuolar cytopathology, raising concerns that topical application of DMAE may actually cause skin damage (Morissette et al., 2007).

5. Exposure estimate and critical NOAEL / NOEL

NOAEL, critical value	Embryonic toxicity: no evidence of embryonic toxicity, including teratogenicity, at any exposure level. -> NOAEL (embryonic toxicity/teratogenicity): ≥ 100 ppm (370 mg/m^3) Maternal toxicity: at 30 ppm and 100 ppm (with transient ocular changes at 10 ppm). -> NOAEL (maternal toxicity): 10 ppm (40 mg/m^3)
Adjusted NOAEL value (mg/kg bw/day) based on daily intake of DMAE[3]	Embryonic toxicity: Whole-body exposure DMAE vapor (exposure level): 370 mg/m^3 Inhalation rate (rat): 20.5 l/h = 0.0205 m^3/h (Sanner et al., 2001) Exposure time: 6 h/day Default body weight (rat): 0.350 kg Daily intake of DMAE corresponding to NOAEL = (370 mg/m^3) X (0.0205 m^3/h) X (6 h/day) X (0.350 kg)$^{-1}$ =130 mg/kg bw/day Maternal toxicity: Whole-body exposure DMAE vapor (exposure level): 40 mg/m^3 Daily intake corresponding to NOAEL = (40 mg/m^3) X (0.0205 m^3/h) X (6 h/day) X (0.350 kg)$^{-1}$ =14.1 mg/kg bw/day
Exposure cosmetic products	**Systemic exposure dose (SED) for DMAE in humans.** [4] SED = **A** (mg/kg bw/day) x **DA$_p$** (%)/100 x **C** (%)/100 *Face cream*[5]: 24.14 mg/kg bw/day x 1 x 0.06 = 1.45 mg/kg bw/day *Body lotion*[6]: 123.20 mg/kg bw/day x 1 x 0.06 = 7.4 mg/kg bw/day *Hand cream*[7]: 32.70 mg/kg bw/day x 1 x 0.06 = 2.0 mg/kg bw/day Overall SED (total body): 1.45 + 7.4 + 2.0 = 10.85 mg/kg bw/day
Margin of safety (MoS)	Embryonic toxicity: NOAEL: 130 mg/kg bw/day MoS (face cream): 130/1.45 = **89.7** MoS (body lotion): 130/7.4 = **17.6** MoS (hand cream): 130/2.0 = **65.0** MoS (overall exposure to DMAE from cosmetics): 130/10.85 = **12.0** Maternal toxicity: NOAEL: 14.1 mg/kg bw/day MoS (face cream): 14.1/1.45 = **9.7** MoS (body lotion): 14.1/7.4 = **1.9** MoS (hand cream): 14.1/2.0 = **7.1** MoS (overall exposure to DMAE from cosmetics): 14.1/10.85 = **1.3**

[3] Calculation of daily intake based on exposure inhalation, see example in Annex 4.
[4] Systemic exposure dose (SED) based on calculated relative daily exposure (mg/kg bw/day), cf. SCCS, 2010, table 3, pp. 70.
[5] 1/2 area head female = 565 cm^2
[6] The area exposed to body lotion: total area – area head (female) = 15670 cm^2
[7] Area hands = 860 cm^2

6. Other sources of exposure than cosmetic products

Food stuffs	The main source of DMAE is from dietary supplements, with the predominant form when specified being DMAE bitartrate. Recommended intake is up to *600 mg daily two to three times a day*, according to some nutritional "experts" (eHow™ Health [online]). Small quantities of DMAE may be ingested through the consumption of salmon roe, mollusks (squid), and fish such as salmon and anchovies (NIEHS, 2002: pp.iii).
Pharmaceuticals	Deanol is a cholinergic drug – also known as the prescription drug "Deaner", which was withdrawn from the US market in 1983. Deanol is a major ingredient in a commonly prescribed drug in Europe, called "Centrophenoxine" (see section 2: Uses and origin).
Other sources	DMAE is used in consumer products such as flexible and rigid polyurethane foams ("cold-box"), building materials or furnishings that might contribute to indoor air pollution.
Adverse side effects apart from cosmetics	DMAE is regarded as safe as ingredient in food /flavoring agent, according to FEMA (Flavor and Extract Manufacturers Association) – Generally Recognized as Safe as an ingredient – GRAS 19 (3960). JECFA (The Joint FAO/WHO Expert Committee on Food Additives) concluded that the substance does not present a safety concern at current levels of intake when used as a flavoring agent (736). According to a French database on pharmaceutical products (biam2.org), some reported side effects of deanol bitartrate are headache, constipation, insomnia, itch and weight decrease (biam2.org [online]). DMAE is a corrosive substance that may cause asthma and permanent eye injury in humans (NIEHS, 2002: pp.iv). Heavy inhalation exposure of DMAE may cause pulmonary edema and asthma (Haz-Map [online]). A case study reports that inhalation of DMAE caused asthma in a spray painter (Vallieres et al., 1977). DMAE may cause confusion, drowsiness, and elevated blood pressure (Fisman et al., 1981), headache and muscle tension (Haug & Holzgraefe, 1991), weight loss and insomnia (Sergio, 1988) and tardive dyskinesia (TD) (Haug & Holzgraefe, 1991). DMAE supplementation is contraindicated during pregnancy, lactation, and for treatment of people with symptoms of schizophrenia, epilepsy, or a history of convulsions. DMAE antagonizes the depressant effects of barbiturates (NIEHS, 2002, pp. iv). Maximum safe dosages for young children, pregnant or nursing women, or people with severe liver or kidney disease have not been established.

7. Assessment

General toxicity
Very little human toxicity data are available. The majority of clinical trials have not focused on skin, but rather on anti-aging as it relates to mental alertness and cognitive abilities. Therefore, the data used to calculate NOAEL and MoS comes from animal studies.

Animal data indicate that DMAE is of low single exposure toxicity via the oral, dermal and inhalation routes, but it has corrosive properties that might cause skin burns or eye damage on direct contact.

DMAE is not genotoxic or toxic to development of the gonads (OECD SIDS, 1996). However, DMAE induced *maternal* toxicity in pregnant rats as demonstrated by changes in body weight gain and ocular changes, whereas alterations in other gestational parameters were not significant. Consistent *fetal* toxicity was not demonstrated even at the highest dose of DMAE (100 ppm) (Leung et al, 1996; NIEHS, 2002: pp. vii). Thus, NOAEL values of ≥ 100 ppm (370 mg/m^3) and 10 ppm (40 mg/m^3) were set for *embryonic* toxicity / teratogenicity and *maternal* toxicity, respectively, based on a prediction of the NOAEL for inhalation exposure in pregnant rats.

Cosmetics
The lowest critical NOAEL for *maternal* toxicity is 14.1 mg /kg /day based on animal experiments. Systemic exposure dosage (SED) was calculated for different parts of the body (face, body, hands), using a cream containing 6% DMAE for illustrative purposes (Examples, Annex 5). At this use level, MoS values were in the range of 17-6 - 89.7 (overall 12.0) for embryonic toxicity, and 1.9 – 9.7 (overall 1.3) in relation to maternal toxicity. Because the NOAEL is based on animal data, a MoS of 100 is generally considered to represent a sufficient margin of safety. Thus, these results suggest that both maternal and embryonic toxicity are of potential concern for consumer health, with the lowest safe use levels governed by maternal toxicity.

Medicinal products
DMAE as a drug was discontinued from the US market in 1983, not because of safety issues, but because more efficient drugs became available. In Europe, DMAE is a main ingredient in a commonly prescribed drug, “Centrophenoxine”. Manufacturers' recommended dosages and those used in clinical studies vary between 400 - 1800 mg daily. This corresponds to a SED of 6.7 – 30 mg DMAE/kg bw/day, with the premise that bioavailability is 100% (equals a MoS of less than 2.1 for maternal toxicity).

Most clinical studies have reported that DMAE did not cause serious side effects, but there is enough evidence for adverse effects to suggest that caution is prudent ((cf. section 3; Annex 1; Biam2.org [online]). The use of DMAE in drug formulations is contraindicated for people with epilepsy or a history of convulsions (Biam2.org [online]).

Food supplements
The recommended intake of DMAE in the form of the salt DMAE bitartrate (the predominant form in dietary supplements) is up to 600 mg daily two to three times a day (eHow^{TM} Health [online]). Conversion to SED for a person weighing 60 kg, yields 10 – 30 mg/kg bw/day, resulting in a MoS < 2 for maternal toxicity.

Other
Deanol aceglutamate, a salt of deanol, is classified as a prohibited substance in cosmetics[8]. The ban of this substance does not extend to deanol itsel (*inter alia*)

.

[8] According to CosIng Regulation (EC) No 1223/2009; cf. annex II (List of substances prohibited in cosmetic products)/Entry no 3.

8. Conclusion

The following maximum usage limits (%) were calculated[9] for DMAE, corresponding to an acceptable margin of safety (MoS) of 100 (based on animal data):

- Face cream: (6% x 9.7) / 100 =0.6% {(6% x 9.7) / 100 = 0.6%}
- Body lotion: (6% x 1.9) / 100 = 0.11%
- Hand cream: (6% x 7.1) / 100 = 0.43%
- Total body (overall exposure to DMAE from cosmetics): (6% x 1.3) / 100 = 0.08%

Thus, the following upper use level is proposed for DMAE in all sorts of cosmetic products: 0.1 %

[9] C2 (%) [SED2] = (C1 (%) [SED1] x MoS1) / MoS2, where C2 is the concentration (%) of the ingredient corresponding to a MoS = 100 (i.e. MoS2). C1 in this example is 6% used to calculate MoS in section 5 (i.e. MoS1).

9. References

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10. Annexes:

Annex 1: Excerpts from 'Toxline' (NLM)

Human Health Effects:

Human Toxicity Excerpts:
- Doses as high as 1200 mg daily produce no serious side effects; & single 2500 mg dose taken in a suicide attempt had no adverse effects. [Gosselin, R.E., H.C. Hodge, R.P. Smith, and M.N. Gleason. Clinical Toxicology of Commercial Products. 4th ed. Baltimore: Williams and Wilkins, 1976., p. II-240] **PEER REVIEWED**

- Reported side effects incl occipital headache, constipation, muscle tenseness, restlessness, incr irritability, insomnia, pruritis, skin rash, postural hypotension, & weight loss. /**deanol** acetamidobenzoate/ [American Hospital Formulary Service. Volumes I and II. Washington, DC: American Society of Hospital Pharmacists, to 1984., p. 28:20] **PEER REVIEWED**

- Severe sneezing, rhinorrhea, cough, wheezing, & dyspnea developed in spraypainter upon exposure to particular spray paint. under lab conditions, asthmatic responses resulted on exposure to dimethylethanolamine soln (2%). [vallieres m et al; dimethyl ethanolamine-induced asthma; am rev respir dis 115(5) 867 (1977)] **peer reviewed**

- Deanol appears to have a relatively/ low order of toxicity.
d**eanol** acetamidobenzoate/ [American Hospital Formulary Service. Volumes I and II. Washington, DC: American Society of Hospital Pharmacists, to 1984., p. 28:20] **PEER REVIEWED**

Drug Warnings:
- Principal contraindication to its use is grand mal epilepsy. [Gosselin, R.E., H.C. Hodge, R.P. Smith, and M.N. Gleason. Clinical Toxicology of Commercial Products. 4th ed. Baltimore: Williams and Wilkins, 1976., p. II-240] **PEER REVIEWED**

- Deanol (400-6000 mg/day for 1-4 mo) admin to pt with involuntary movement disorders produced mood changes (depression or hypomania) only in those pt with tardive dyskinesia with a past history of psychiatric disorders.
[casey de; mood alterations during deanol therapy; psychopharmacology (berlin) 62(2) 187 (1979)] **peer reviewed**

Annex 2: Selected health effect abstracts:

Am Rev Respir Dis. 1977 May;115(5):867-71.

Dimethyl ethanolamine-induced asthma.

Vallieres M, Cockcroft DW, Taylor DM, Dolovich J, Hargreave FE.

Abstract

Progressively severe sneezing, rhinorrhea, cough, wheezing, and dyspnea developed in a spray-painter, apparently in relation to exposure to a particular spray paint. A monitoring of exposure at work revealed the development of symptoms and a decrease in peak flow rates. Subsequent challenges in the laboratory performed under conditions resembling occupational exposure resulted in dual asthmatic responses on exposure to the whole paint (98 per cent methyl methacrylate emulsion and 2 per cent dimethyl ethanolamine solution) and to dimethyl ethanolamine solution (2 per cent) alone. Water, methyl methacrylate emulsion, and 1,4 dioxane (0.6 per cent) used as a thinner in the dimethyl ethanolamine did not produce a response in the airways. Allergy skin tests with dimethyl ethanolamine and a mixture of dimethyl ethanolamine and human serum albumin were negative. To our knowledge, this is the first report of asthma and/or rhinitis induced specifically by dimethyl ethanolamine. The mechanism of the specific reactivity is not known.

PMID: 857720 [PubMed - indexed for MEDLINE]

ORIGINAL ARTICLE

Visual and ocular changes associated with exposure to two tertiary amines

E H Page, C K Cook, M A Hater, C A Mueller, A A Grote, V D Mortimer

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See end of article for authors' affiliations

Correspondence to: Dr E H Page, Division of Surveillance, Hazard Evaluations, and Field Studies, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, 4676 Columbia Parkway, MS R-10, Cincinnati, Ohio 45226-1998, USA; email:edp7@cdc.gov

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Aims: To determine if exposure to dimethylisopropanolamine (DMIPA) and dimethylaminoethanol (DMAE) in a label printing plant was associated with visual disturbances and/or ocular changes.
Methods: Questionnaires, eye examinations (visual acuity, contrast sensitivity at 2.5% and 1.25% contrast, slit lamp biomicroscopy, and pachymetry), and industrial hygiene monitoring for DMIPA and DMAE were performed over a two week period.
Results: Eighty nine per cent of line workers reported having experienced blurry vision while at work in the past 12 months, compared to 12.5% of prime workers. A total of 108 full shift personal breathing zone (PBZ) air samples for the amines were collected. The mean time weighted average (TWA) concentration of DMIPA was significantly higher in the line division than in the prime division, as was the mean TWA concentration for total amines. The mean TWA concentration of DMAE was higher in the prime division than the line division. Higher levels of total amines were associated with increased risk of reporting blurry vision, halo vision, and blue-grey vision. The risk of corneal opacity rose with increasing exposure to total amines. The prevalence of corneal opacity also increased with increasing concentration of total amines. Median corneal thickness increased with increasing grades of corneal opacity. There was a statistically significant relation between total amine concentration and increased risk of reduced bilateral visual acuity and 2.5% contrast sensitivity.
Conclusions: Exposure to tertiary amines was associated with blurry, halo, and blue-grey vision, corneal opacity, and decrements in visual acuity and contrast sensitivity at 2.5% contrast.

Annex 3: Acute toxicity

Organism	Test Type	Route	Reported Dose (Normalized Dose)	Effect	Source
guinea pig	LDLo	intraperitoneal	450mg/kg (450mg/kg)		Proceedings of the Society for Experimental Biology and Medicine. Vol. 85, Pg. 642, 1954. Link to PubMed
mouse	LC50	inhalation	3250mg/m3 (3250mg/m3)	BRAIN AND COVERINGS: RECORDINGS FROM SPECIFIC AREAS OF CNS SENSE ORGANS AND SPECIAL SENSES: CONJUNCTIVE IRRITATION: EYE BEHAVIORAL: CONVULSIONS OR EFFECT ON SEIZURE THRESHOLD	Gigiena Truda i Professional'nye Zabolevaniya. Labor Hygiene and Occupational Diseases. Vol. 14(11), Pg. 52, 1970.
mouse	LD50	intraperitoneal	234mg/kg (234mg/kg)	BEHAVIORAL: ATAXIA	Journal of Pharmacology and Experimental Therapeutics. Vol. 94, Pg. 249, 1948.
mouse	LD50	subcutaneous	961mg/kg (961mg/kg)	BEHAVIORAL: TREMOR BEHAVIORAL: COMA LUNGS, THORAX, OR RESPIRATION: OTHER CHANGES	Naunyn-Schmiedeberg's Archiv fuer Experimentelle Pathologie und Pharmakologie. Vol. 225, Pg. 428, 1955. Link to PubMed
rabbit	LD50	skin	1370uL/kg (1.37mL/kg)		AMA Archives of Industrial Hygiene and Occupational Medicine. Vol. 4, Pg. 119, 1951.
rat	LC50	inhalation	1641ppm/4H (1641ppm)	SENSE ORGANS AND SPECIAL SENSES: LACRIMATION: EYE BEHAVIORAL: ATAXIA LUNGS, THORAX, OR RESPIRATION: DYSPNEA	Fundamental and Applied Toxicology. Vol. 9, Pg. 512, 1987.
rat	LD50	intraperitoneal	1080mg/kg (1080mg/kg)		Toxicology and Applied Pharmacology. Vol. 12, Pg. 486, 1968.
rat	LD50	oral	2gm/kg (2000mg/kg)		Zeitschrift fuer die Gesamte Hygiene und Ihre Grenzgebiete. Vol. 20, Pg. 393, 1974. Link to PubMed

Annex 4: Calculations – exposure inhalation

Appendix 3. Occupational exposure with the worst case scenario and risk assessment

Based on the highest air concentration (0.38 mg/m^3) at a production site, and the maximal exposure period (1 hr/day), the daily intake (EHE) is calculated to be 0.0068 mg/kg/day as follows;

$$EHE = Cair \times IHair \times period \times BW^{-1}$$

Where	Cair	concentration at a production site	:	0.38 mg/m^3
	Ihair	inhalation rate	:	1.25 m^3/hr
	Period	exposure period	:	1 hr/day
	BW	adult body weight (default)	:	70 kg

Thus

$$EHE = 0.38 \text{ mg/m}^3 \times 1.25 \text{ m}^3/\text{hr} \times 1 \text{ hr/day} \times 70 \text{ kg}^{-1} = 0.0068 \text{ mg/kg/day}$$

Based on the daily intake (EHE) calculated in the worst case scenario, the margin of safety (MOS) for occupational exposure was estimated as follows;

$$MOS = NOAEL / EHE$$

where	NOAEL :	12.5 mg/kg/day	based on 53-day oral dose toxicity test
	EHE :	0.008 mg/kg/day	worst case daily intake

Thus

$$MOS = 12.5 / 0.0068 = 1800$$

The MOS of 1500 is based on the worst case scenario. Actual MOS is expected to be higher and normally workers wear respiratory protective equipment (mask) during the operation.