Original article

Scand J Work Environ Health 1988;14(4):209-219

doi:10.5271/sjweh.1930

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This article in PubMed: www.ncbi.nlm.nih.gov/pubmed/3051334

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Health hazards of tertiary amine catalysts

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ALBRECHT WN, STEPHENSON RL. Health hazards of tertiary amine catalysts. *Scand J Work Environ Health* 14 (1988) 209—219. Tertiary amine catalysts are widely employed in foundry and polyurethane foam manufacture operations. These highly reactive amines have been associated with graphic disturbances in vision and systemic health effects. Prominent among the reported effects on vision are mydriasis (dilated pupils), cycloplegia (loss of accommodation), and corneal edema, which may result in hazy (looking through smoke) or blurry (out of focus) vision and halo perception. Systemic symptoms, possibly due to a release of endogenous histamine, are consistent with pharmacologic actions of amines and have also been described. These symptoms, as well as the disturbances in vision, are transient. Nevertheless, employees who work with or around machinery, or drive vehicles, may be at an increased risk of accident and injury when experiencing these symptoms.

Key terms: blue haze, corneal edema, cycloplegia, dimethylethylamine, halo vision, histamine, mydriasis, tertiary amines, triethylamine, vision disturbance.

Basic amine catalysts are extensively employed in industry to facilitate the polymerization of chemical reactions. Tertiary and ditertiary amines, such as triethylene diamine (TEDA), are reactive due to their caged structure and sterically exposed nitrogen atoms. Within the broad spectrum of tertiary amines in use, several have been under study recently because of their ability to induce disturbances in vision. A review of the literature concerning this phenomenon has also identified other distinctive health effects associated with exposure to them (table 1). Of particular interest are the widely used tertiary amines dimethylethylamine (DMEA), triethylamine (TEA), and N-methyl morpholine (NMM) and the ditertiary amines triethylene diamine (1,4-diazobicyclo(2,2,2)-octane; DABCO), trimethylpropane diamine [TMP(an)DA], trimethylpropene diamine [TMP(en)DA], and trimethylbutane diamine (TMBDA). DMEA and TEA are used in aluminum and gray-iron foundries in the manufacture of cores for metal castings. TEA, TEDA, NMM, TMP(an)DA, TMP(en)DA, and TMBDA are catalysts for the production of polyurethane foams. The National Institute for Occupational Safety and Health (NIOSH) has no estimate of the number of workers potentially exposed to tertiary amines.

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Description of the processes using tertiary amines

Core-making process

During the Second World War, it became necessary to develop new methods of coremaking to facilitate the increased demand for cast parts. Natural binders such as sugar, cereal, and sea coal were replaced with synthetic organic chemicals. Besides improving the quality of the parts, the charge increased production manifold. Now over a dozen methods are available for binding sand together as cores. The core-making processes use catalysts to increase the usual rate of reaction between a phenolic resin and an isocyanate so that a solid form is effected at room temperature in a matter of seconds (40).

Cores are solid reproductions of the hollow spaces within a desired finished casting. A phenolic urethane gas or liquid cured, no-bake (ambient conditions for catalysis) core-making process commonly employs either TEA or DMEA. The sand mold is prepared by compacting sand around a pattern. After the pattern is removed, the cores are placed within the mold, and molten metal is poured into the same mold. The metal solidifies, and, after cooling, forms the metal casting.

The sand for the core is first mixed with two liquid resin components, one a liquid phenol-formaldehyde resin and the other a liquid isocyanate, usually methylene bisphenyl-diisocyanate or toluene diisocyanate. On automated lines, the sand is either pneumatically forced or gravity-fed into the corebox, whereas on manual lines the sand is hand-packed into the corebox. Once there it is gassed with varying amounts of tertiary amine catalyst for about 0.5 to 2 s under a pressure of 15—50 pounds/square inch (104—348 kPa). The catalyst cross-links the polymer formed from the two liquid resin components and instantly hardens the resin-coated sand. Dry air is then blown through the core

Table 1. Effects of exposure to some ditertiary amines. (TMP(an)DA = trimethylpropane diamine, TMP(en)DA = trimethylpropene diamine, TMBDA = trimethylbutane diamine, TEDA = triethylene diamine)

Route	TMP(an)DA[a]	TMP(en)DA	TMBDA[b]	TEDA[c]
Cutaneous[d]	Erythema (recovery)	Erythema, yellow skin, edema, eschar, sloughing	Necrosis, median lethal dose 320 mg/kg	Marked erythema, slight necrosis, desquamation, capillary injection, eschar,[e] median lethal dose gt 3 200 mg/kg
Ocular[f]				
No rinse	Conjunctival inflammation, purulent discharge, corneal opacity (no recovery)	Conjunctival inflammation, purulent discharge, corneal opacity, (no recovery)	Severe corneal necrosis,[g] "burned eye"	Prolonged lacrimation
Rinse[h]	(recovery)	(no recovery)		
Mydriasis/ cycloplegia	Loss of reflex with large intravenous dose	.	Increased pupillary diameter, loss of accomodation, ganglionic blockade	No effect
Inhalation				
25 ppm	Eye irritation, discharge, bronchospasm	.	.	.
12 ppm	No effects	.	.	.

[a] Additional effects: eye: no structural changes evident to account for opacity; lung: vesicular/hydropic degenerative change of ciliated columnar epithelium, larynx and trachea; active inflammatory cellular inflammation with hyperemia.
[b] Additional effects: liver: dark brown with prominent acini; spleen: pale and smooth; kidney: enlarged, pale or speckled; other: some intestinal hemorrhage.
[c] No gross pathology.
[d] 0.01 ml onto shaved rabbit belly.
[e] 25 % solution of technical TEDA.
[f] 0.01 ml instilled into rabbit eye.
[g] 0.005 ml instilled into rabbit eye.
[h] Washed 4 s after instillation with 20 ml of lukewarm water.

Table 2. Some series characteristics of amines.

	Series
Volatility	3° — 2° — 1° — ammonia
Solubility	
Aqueous	ammonia — 1° — 2° — 3°
Lipid	3° — 2° — 1° — ammonia (34)

to purge any unreacted amine prior to the removal of the core from the corebox.

Polyurethane foam-making process

The chemical ingredients of a polyurethane foam are a polyfunctional isocyanate and a hydroxyl-containing polymer with the catalysts necessary to control the rate and type of reaction, along with other additives to control the surface chemistry of the process. Two general types of manufacture have been developed for producing cellular polyurethanes on a commercial basis, ie, one-shot and prepolymer processes. In the one-shot process, all the necessary ingredients for producing the foam are mixed and discharged from the mixer onto a suitable surface. The reaction begins immediately and proceeds at such a rate that expansion starts in 10 s, the entire expansion being complete in 1—2 min. Curing may take several days. In the prepolymer process, the polyhydroxy component reacts with enough polyisocyanate to form a prepolymer mixture that reacts with water to release carbon dioxide for expansion and to cross-link the matrix (17).

Chemistry of tertiary amines

A pair of nonbinding electrons imparts basic and nucleophilic properties to amines. As derivatives of ammonia, the lower molecular weight amines possess appreciable aqueous solubility. In solution, for example, TEA has a pKa of 9.78 as compared to 9.24 for ammonia. Those amines with significant volatility have odors which range from "fishy" to unpleasant to revolting. All higher molecular weight amines have the odor of ammonia.

With tertiary amines, for which N-H-:N bonding is not possible, the boiling points are much lower than those of either 1° or 2° amines and are equivalent to those of hydrocarbons of similar branching and molecular weights. The 1° and 2° amines are less volatile than their corresponding hydrocarbons, since the electronegativity of nitrogen is less than that of oxygen or fluorine, a property which thereby makes nitrogen a poor hydrogen donor. Tertiary amines are the most volatile of the series (table 2).

Basicity

The basicity of amines increases with the size and number of alkyl constituents on the nitrogen atom. For example, TEA has a pKa of 9.78 as compared to 9.24 for ammonia and 11.0 for TEDA. This value is reasonable since the conjugate acid, R_3N^+H, is likely to be stabilized by electron-donating and polarizable alkyl groups, which thereby makes R_3N a stronger base.

Solubility

Aqueous. As derivatives of ammonia, amines are generally very water soluble. In contrast, alcohols of similar molecular weight and branching are less soluble in water than their corresponding amines because of hydrogen bonding. Amines act as an hydrogen acceptor (base) with molecular water as the hydrogen

Table 3. Some physical/chemical parameters of selected tertiary amines. (DMEA = dimethylethylamine, TEA = triethylamine, TEDA = triethylenediamine, NMM = N-methyl morpholine)

	Parameter				
	Molecular weight	Vapor pressure (mm Hg[a] @ 20°C)	Boiling point (°C)	pKa	Solubility in water (ppm)
DMEA	73	414	37	10.2	inf
TEA	101	54	90	10.75	10^5
TEDA	112	..	174	11.0	..
NMM	101	17	115	..	..

[a] 1 mm Hg ≈ 0.133 kPa.

donor (acid). Tertiary amines which cannot form hydrogen bonds have boiling points similar to hydrocarbons of similar molecular weights. Although the least soluble of the series, tertiary amines still have appreciable aqueous solubility.

Lipid. Lipid solubility can be defined as the tendency of a compound to partition preferentially to octanol instead of water in a mixture of the two. Material with a high octanol : water coefficient can characteristically cross the phospholipid membrane and enter the cell. This ability to traverse the membrane is inversely related to aqueous solubility.

Other parameters

The structure of the amines described in table 3 appears in figure 1. Occupational exposures are measured from collected amines on silica gel (30). Audunsson & Mathiasson (6) describe a method for measuring tertiary amine and isocyanate concentrations simultaneously after sampling workplace air through a collection medium of 0.05M sulfuric acid at low flow rates. Sensitivity to low concentrations (micrograms per cubic meter) has been achieved by extraction of the sampling solution with basified toluene and a neat injection of toluene into a gas-liquid chromatograph (6). Isotachophoresis has been demonstrated to be an efficient method for the analysis of some tertiary amines in workplace air (18, 19).

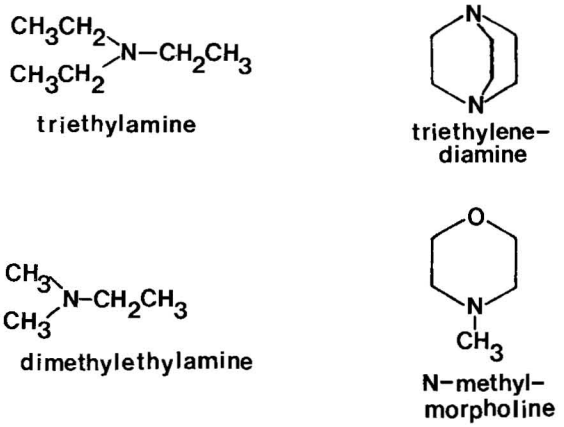

Figure 1. Structures of triethylamine (TEA), triethylene diamine (TEDA), dimethylethylamine (DMEA), and N-methyl morpholine (NMM).

Table 4. Odor thresholds for some tertiary amines and ammonia.

Compound	Odor Threshold (ppm)		
	Normal	Anosmic	Defect steps
Ammonia	23.9	81.6	1.77
Triethylamine	2.21	36.4	4.04
Dimethylethylamine (DMEA)	$7.6 \cdot 10^{-3}$	4.01	9.04
N-methylpiperidine	1.2	41.7	5.16

Toxicology

General effects

Being very basic compounds, tertiary amines have primary irritant properties. Thus dermal exposure to the undiluted liquid can have a corrosive effect on the skin. Vapors may act on the mucous membrane of the eye and cause lacrimation, conjunctivitis, and corneal edema, while exposure of the mucous membrane of the nose or throat can result in irritation, cough, and respiratory distress. Systemic symptoms reported from exposure include headache, nausea, faintness, and anxiety. These systemic symptoms (those affecting the body generally, due to exposure via the lungs or skin, or from ingestion, followed by absorption and a toxic effect) may be related to the pharmacological action of amines, and they are usually transient. It is known that some amines may cause histamine to be liberated, and histamine can bring about a decrease in blood pressure, tachycardia (rapid heart rate), itching, erythema (reddening of the skin), urticaria (hives), and facial edema (swelling) (10, 11, 14, 23, 29, 33).

Odor thresholds and anosmia

The odor threshold for tertiary amines is very low (table 4). Approximately 7 % of the population is specifically anosmic to trimethylamine. According to Amoore & Forrester (4) anosmia is very pronounced for tertiary amines as a class, especially for the low-molecular weight members. These amines exhibit much lower thresholds than the isomeric or homologous

primary or secondary amines. Anosmia to tertiary amines is thought to result from a defect in the human olfactory organ and, if so, could indicate that they function as human pheromones.

Effects on vision

Brieger & Hodes (9) found that 50 ppm of vapors of ethylamine, diethylamine, or TEA caused corneal edema and multiple punctate erosions of the corneal epithelium. Rockhold et al (36) noted that a dog injected with a large dose of TMP(en)DA showed a loss of eye reflex, while Goldberg & Johnson (15), using a classic nictitating membrane preparation, found that exposure to a concentrated vapor of the ditertiary amine TMBDA produced marked mydriasis and loss of accommodation after only 15 min. A 5-h exposure to TEDA had no effects on vision.

The mechanism for TMBDA-induced effects was found to be a selective blockade of autonomic ganglia without any involvement of peripheral sites. No blockade was observed with TEDA.

Reports of blue or grey vision among workers in amine plants prompted Mellerio & Weale (28) to study the effects of N-ethyl piperidine, NMM, N- ethylmorpholine, tetramethyl ethylenediamine, and dimethylamine on rabbit corneas. All the amines attacked the cornea and caused "haziness," irregularities, sloughing of the surface, and the general appearance associated with violent desiccation. They surmised that the amines act directly upon the eye, producing the blue-vision effect. This conclusion was based on the fact that the author was not aware of any reports which included the description of systemic symptoms associated with disturbances in vision.

Typically, vision becomes misty, and halos have appeared, several hours after workmen have been exposed to vapors of amines at concentrations sometimes too low to cause discomfort during the workday. Generally, the corneal edema clears up spontaneously by the next day. However, after very intense exposures, edema and blurring have taken several days to clear and have been accompanied by photophobia and discomfort due to roughness of the corneal surface (16).

Akesson et al (3) subjected two volunteers to increasing concentrations (0, 10, 18, 34, and 48 mg/m^3) of TEA in an exposure chamber. At 48 mg/m^3 prominent vision disturbances began 1 h after the onset of exposure. Lights were surrounded by bluish halos, and outlines of objects and the general field of vision were hazy. Both subjects complained of some discomfort in their eyes without definite irritation. Their visual acuity was only slightly decreased, but pronounced corneal edema (as determined by slit-lamp microscopy and Haag-Streit pachometry, which measured an 18 % increase in corneal thickness in one of the two subjects) and conjunctival injection confined to palpebral tissue was found. The effect faded and had disappeared after about 4 h. Both subjects had base-line evaluations the next day.

At 34 mg/m^3, similar effects were found, but the effects on vision began after 2 h of exposure instead of after 1 h. Foggy, blurry, and halo vision was distinctly present without discomfort, but corneal edema was only moderate, as was the increase in corneal thickness.

A concentration of 18 mg/m^3 elicited a slight disturbance in vision only after 4—6 h of exposure. Eight hours at this exposure level was necessary to induce a slight corneal edema with no decrease in visual acuity.

There were no effects at 10 mg/m^3.

Systemic effects

Rabbits exposed to either 50 or 100 ppm of TEA 7 h a day, 5 d a week for six weeks survived (9). Histopathology showed parenchymous degeneration of the liver and kidneys at both doses and a striking parenchymous degeneration of the myocardium in animals exposed to 100 ppm. The lungs showed evidence of hyperemia and edema, hemorrhage, and a moderate peribronchitis with vascular thickening.

Rockhold et al (36) conducted basic toxicity studies, including the determination of the approximate median lethal dose and the cutaneous and ocular toxicities, of two ditertiary amines, tetramethylpropanediamine and tetramethylpropenediamine. Human volunteers were able to detect concentrations as low as 2 ppm upon repeated trials. At 5 ppm, slight nasal and eye irritation was reported, and at 8 ppm definite irritation appeared.

In response to industry reports of "ocular hazard," Goldberg & Johnson (15) studied the basic pharmacology of the ditertiary amines TMBDA and TEDA. TMBDA can block autonomic ganglia. The prominent depressor/pressor effects of TEDA were found to be a combination of cholinomimetic and ganglion stimulating properties, with the quarternized derivative being inactive. TEDA was found to be spasmogenic in isolated rabbit intestine.

Unfortunately, animal experiments do not provide information on any but the most graphic toxic effects of exposure. Therefore, it is truly unusual that work which used human volunteers to explore the systemic effects of amine exposure was located. Lecomte (24, 25) studied the reaction of histamine liberators in man in detail. A tertiary, substituted butylamine L-1935 [2-hydroxy-4-dimethylaminobenzyldimethylamine; Registry of Toxic Effects of Chemical Substances (RTECS) # G06839000 (31)], caused itching, flushing, and tachycardia at a low dose (0.1 mg/kg). At an intermediate dose (0.3 mg/kg) more intense itching, flushing of the face, tachycardia, a drop [20—40 mm Hg (2.7—5.3 kPa)] in blood pressure, and some headache was seen. His high dose (0.5 mg/kg) caused immediate itching and a generalized feeling of warmth. Blood pressure fell by 40—60 mm Hg (5.3—

8.0 kPa) with a firm but accelerated pulse and severe headache. Five minutes later, blood pressure rose above normal, and there was colic (intestinal cramping), nausea, acid vomit, and swelling of the face and eyes.

Occupational case reports

Since their introduction into general use over 40 years ago, tertiary amines have been linked with sporadic cases of toxic effects among exposed workers. Vision or systemic effects, or a combination of the two, are commonly reported.

The earliest report that could be found was one by Watrous et al (44), who described four cases of acute intoxication from suspected exposures to DMEA and TEA. These compounds were used to make their chloroethyl analogues via ethanolamine and chlorination with thionyl chloride for use in the manufacturing of pharmaceutical intermediates. It is unclear if the starting material (DMEA or TEA) or the final product (chloro-DMEA or chloro-TEA) was responsible for the exposures. The symptoms identified in workers involved in the TEA process included severe irritation of the mucous membranes of the eyes, nose, and throat and mild pulmonary edema. DMEA at an estimated concentration of 50—500 mg/m^3 had an irritant and necrotizing effect on the skin. Both processes were associated with nausea, vomiting, and prolonged mydriasis. No circulatory effects were reported.

Although cyclohexylamine is not a tertiary amine, the 1950 report of Watrous & Schulz (45) described potent systemic effects demonstrated by amine catalysts. Two chemical operators and one supervisor were exposed to substantial (but not measured) amounts in separate incidents. One operator reported a burning sensation in the throat, faintness, and "great anxiety" after a hose carrying the material near him broke. Another operator was splashed in the face with cyclohexylamine. He reported to the plant physician with "burned skin" and widely dilated pupils that showed a weak reaction to light. His pulse and blood pressure were normal. He vomited twice in 20 min after his exposure. However, he was normal by the next day. A supervisor in the department told the physician that he regularly experienced nausea when working near the process, but had never vomited.

In a general report on health hazards associated with the new technology of epoxy resins and catalysts, Savitt (38) said organic mono- and polyamines used as curing agents were frequently responsible for severe irritant contact dermatitis among workers. He also remarked that continuous exposure to "slight concentrations" of amines in the air were able to produce an asthma-like reaction. Bourne et al (8) mentioned that the health problems of exposure to epoxy resins and amine-curing agents included complaints of an inability to focus and a halo effect around objects focused upon.

A summary article by Mastrometteo (27) on occupational health hazards encountered in Ontario describes eight workers who reported seeing halos around lights in connection with exposure to recently foamed polyurethane. The disturbance occurred at the end of the shift and cleared within hours after the end of the shift. The author stated that the disorder was experienced at levels below that which causes eye or respiratory irritation.

Dernehl (12) noted that amine curing agents can be present in curing rooms of polyurethane foam manufacturing plants at high concentrations even though toluene diisocyanate (which reacts almost completely) is not. In his article on health hazards he described some effects (he had observed) of exposure to some alipathic amines in their manufacture and use in polyurethane foam making, among them NMM, TEDA, and TMBDA. Besides throat irritation, a characteristic lesion of the cornea resulting in visions of blue haze and refractile rings (halos) around point light sources was noted. He reported that the condition is self-limiting and clears within 3—4 h after exposure. The condition had been experienced by workers at the end of the day for many days in a row without any identified persistent harmful effect. Upon examination under slit-lamp microscopy, the cornea showed diffuse edema with tiny vesicular collections of fluid within the corneal stroma. He mentioned that some workmen exposed to TMBDA reported prolonged blurring of vision in addition to symptoms of corneal edema. At the beginning of the workday, the cornea appeared to be clear, but the pupils were mydriatic and failed to contract when exposed to light. In another study, people exposed to amine vapors and given an ophthalmologic examination a few hours after the onset of hazy vision did not show any striking changes in the eye (28).

Pagnotto & Wegman (32), in a letter to the editor, claimed they had observed that toluene diisocyanate was responsible for respiratory sensitization in a polyurethane foam manufacturing operation since it and TEDA were present in the workplace, but the TEDA concentration was measured to be zero. Their sampling and analytic methodology was faulty, and, although the conclusion that toluene diisocyanate was the sensitizer has merit, the level of detection for TEDA sampling did not enable them to conclude that ambient concentrations were zero. No disturbances in vision were mentioned.

Hazy blue-gray vision and trigeminal neuralgia (tic douloureux) were reported by Schmitter (39) in his study of foundry hazards. These symptoms were representative of exposure to DMEA and TEA. Interestingly, he demonstrated that DMEA can be deposited on respirable dust in foundries. Respirable dust, along with vapor phase exposure, may contribute to bronchial reactivity and overall exposure to amine catalysts. An increase in blood pressure in the exposed group was also noted.

A health hazard evaluation performed in a gray-iron foundry where DMEA was used in the Isocure® core-making process found that three of 30 exposed employees reported blurry vision that lasted for 1—4 h after they left work (20). Headache and irritation of the ears, nose, and throat were also prominent symptoms. Head operator exposures averaged 15.5 mg/m³ over the range of 5.3—26.5 mg/m³.

Belin et al (7) found that workers who were exposed to toluene diisocyanate, NMM, and TEDA in the manufacture of polyurethane foam and reported symptoms of vision disturbance (light objects seemed to have hazy contours and were surrounded by halos of blue light) were found to have increased methacholine reactivity. On the basis of the amine concentration being 1 000 to 10 000 times higher than the toluene diisocyanate concentrations, the authors concluded that amines, as well as isocyanates, may be responsible for the obstructive respiratory symptoms experienced by the exposed workers, as evidenced by increased bronchial reactivity to methacholine.

In their study of various sand-binder systems used in an Australian steel foundry, Low & Mitchell (26) recorded symptoms of nasal, eye, and respiratory irritation, and some evidence of possible hypersensitivity or obstructive airway disease (wheezing). These symptoms were prominent in workers in the core-making process which used DMEA as a catalyst. No disturbances in vision were noted, nor were the exposure levels given.

A field evaluation of TEA exposure followed the chamber study by Akesson et al (3). Forty-seven incidents of eye irritation followed by the workers seeing blue haze were reported over an 11-week period (2). Workers exposed to TEA in a polyurethane foam manufacturing plant experienced foggy, blurry, and halo vision at time-weighted averages of 12—13 mg/m³ for jobs associated with the disturbances in vision. Peak levels as high as 24 mg/m³ were measured. The authors concluded that at least some of the disturbance in vision was caused by these peak exposures.

Another health hazard evaluation, on this occasion at an aluminum foundry (43) using DMEA, found that, over the past year, episodes of hazy vision were reported by 91 % (117 of 129 persons) of the coreroom workers. Other symptoms related to "disturbances in vision" were also prominent, including blurry vision (72 %), halo perception (64 %), lacrimation (72 %), and eye irritation (48 %). Many systemic symptoms, including nausea and vomiting, were mentioned as well. The authors presented evidence to substantiate their contention that peak exposures are probably responsible for many of the symptoms reported.

Of six foundries where NIOSH conducted health hazard evaluations (20, 34, 37, 41, 42, 43) and two polyurethane foam manufacturing plants that were studied (2, 7), all used tertiary amine catalysts and isocyanates. In seven of the eight facilities, isocyanates were detected (measured in concentrations greater than zero). Occupational asthma (determined by pulmonary function testing and interpretation of the results by the individual investigator) was judged to be present in two of the eight factories. Three of the eight made no attempt to determine whether occupational asthma was present in exposed workers. Disturbances in vision were mentioned in five studies.

Table 5. Sympathetic and parasympathetic innervation and effects of tertiary amines.

Muscle	Response	
	Sympathetic	Parasympathetic
Radial (iris)	Contraction (mydriasis)	.
Sphincter (iris)	.	Contraction (miosis)
Ciliary (lens)	Relaxation (far vision)	Contraction (near vision)

Discussion

Effects on vision

A review of animal data and occupational reports indicates that exposure to tertiary amines is capable of disturbing vision by two distinct mechanisms. The first mechanism is mydriasis and cycloplegia. It has been reported to occur in both animals (15) and workers (12, 44, 45) after exposure to tertiary amines and has been plausibly demonstrated to be a result of pharmacological activity of some tertiary amines on parasympathetic ganglia (15). Corneal edema, the second mechanism, was observed in rabbits exposed to TEA vapors by Brieger & Hodes (9) and under closely controlled and elaborately evaluated experimental conditions in humans (3). This phenomenon appears to occur as a consequence of a direct action of amines on the corneal epithelium. In order to understand the underlying mechanism of the effect better, each will be discussed separately.

Mydriasis and cycloplegia. Mydriasis (widely dilated pupils that are not responsive to light) is primarily associated with the blockade of postganglionic muscarinic cholinergic stimulation which prevents the pupillary constrictor (sphincter) muscle from acting (table 5). This phenomenon leads to unopposed sympathetic dilator activity by the radial muscle of the iris. Cycloplegia, or loss of accommodation, is a paralysis of the ciliary muscle which results in an inability to move the lens and focus on an object in the visual field. Goldberg & Johnson (15) reported that the pupillary dilation observed by them in experimental animals was due to blockade at parasympathetic ganglia which direct innervation to the sphincter muscle of the iris. Ciliary muscles also receive parasympathetic innervation, but via the ciliary ganglion. Since the pupil receives both sympathetic and parasympathetic inner-

vation, action resulting from general ganglionic blockade is not always predictable, although parasympathetic tone is dominant and moderate miosis will usually occur. A peripheral effect noticed by patients receiving antimuscarinic drugs is a complaint of a sand-in-the-eye feeling due to a decrease in lacrimal secretion (22).

Corneal edema or "halo vision." Probably first reported by Amor in 1949 (5), the disturbance in vision colloquially called "halo vision" has never been adequately characterized. Although a few secondary amines such as piperazine and morpholine have been cited as causing vision disturbances (16) similar to those caused by tertiary amines, no reports could be directly retrieved from the literature. Similarly, none were found which identified ammonia or primary amines as causing a disturbance in vision of the nature caused by tertiary amines. Data on some studies concerning exposure to tertiary amines and halo vision are presented in table 6.

The basic pathophysiology of halo vision is purported to be a degradation of the visual image falling on the retina due to corneal edema. The degree of edema is thought to result in a continuum of vision disturbance from haziness to halo perception. A case of "halo vision" can be defined as hazy or blurry vision which may progress to the perception of primarily blue halos around lights 15 min to 1 h after appropriate vapor phase exposure to primarily tertiary amines. The disturbance usually lasts for 1—4 h after the cessation of exposure. Vision can be so impaired that working around machinery or driving vehicles becomes hazardous because the affected worker cannot see. Usually, the condition spontaneously reverses itself shortly after the cessation of exposure.

This explanation may be more fully appreciated after a brief review and summary of corneal anatomy, physiology, and toxicology. The cornea is the anterior part of the supporting layer of the eye. It is transparent, nonvascular, and permeable. For example, carbon dioxide is eliminated through the corneal epithelium. The diffusion phenomenon on which its cells depend must be very efficient, for corneal epithelium, upon injury, regenerates rapidly. The layer immediately beneath the corneal epithelium is called Bowman's membrane, and, although resistant to trauma and bacterial injury, once damaged, it does not regenerate.

The cornea has five cell layers altogether; the outermost one being a nonkeratizing, stratified squamous epithelium, five to six cells in thickness. Because the connective tissue beneath the cornea has no capillaries, the epithelium of the cornea is a comparatively long way from a source of nutrition.

It is the spherical shape of the cornea and the tear-cornea interface that accounts for about 80 % of the refractive power of the eye. Refractivity is also dependent upon proper transparency and hydration. Proper hydration results from the layers of tear film. Proper tear flow, absence of deposits or blood vessels, and proper nutrition are other factors important to vision. Any distortion, as well as any opacity, will scatter light and degrade the optical image (13).

There are several reasons why tertiary amines cause the effect and have been the prominent amines reported to have caused the effect in humans. Basicity alone is not a sufficient reason, since ammonia exposures are common, often at high concentrations. As described in the section on the chemistry of tertiary amines, volatility and solubility are useful in ascribing why tertiary amines can preferentially cause halo vision.

It is understood that the corneal epithelium becomes edematous (swollen) when it is exposed to tertiary amines. We speculate that a combination of appreciable aqueous solubility and excellent lipid solubility allows tertiary amines to enter corneal epithelial cells. For example, as a liquid, an amine with a substantial vapor pressure such as DMEA [414 mm Hg (55.1 kPa)] readily enters the vapor phase. Once in the air, it is at least moderately soluble in tears. From this "reservoir," it can cross the membrane of the epithelial cell in the nonionized or highly lipid-soluble form. Equilibrium is favorable toward the inside of the cell. Either increased pressure (turgor) or a direct corrosive action of the amine then causes the cells to swell. If concentrations are sufficient, they may swell to the point of lysis and ultimately burst.

When cells of the spherical central cornea have burst, cellular debris, dentured protein, and cytoplasm may act to scatter incident light and produce halo perception when point light sources are viewed. Perhaps a similar phenomenon occurs in nature. A circle or ring around the sun (the light source) is seen when ice crystals (the refractile material) are present at high altitudes. We propose that halo perception may occur when cells and contents are spilled onto the cornea. The perception of color is hypothesized to occur as incident light is separated prismatically into its spectral colors by droplets of fluid on the corneal epithelium, similar to the way that light passing through droplets of rain forms a rainbow (1).

It is unknown why the halos have been primarily reported to be blue in color, although blue light is not dispersed as much as longer wavelengths. The sky is an example. In addition the potential contribution of ganglionic blockade to the symptoms of hazy and/or blurry vision noticed during "halo vision" has not been investigated.

Systemic effects

Ganglionic blockade. Compounds that produce blockade of parasympathetic and sympathetic ganglia act as competitive inhibitors of acetylcholine and similar agonists. All ganglion-blocking drugs of interest are synthetic amines. They have many undesirable side-effects and are only employed for blood-pressure control (22). The pressor/depressor effect of TEDA seen

Table 6. Halo vision from dimethylethylamine (DMEA), triethylamine (TEA), and other tertiary amines. (LOD = limit of detection, NMM = methylmorpholine, $FEV_{1.0}$ = forced expiratory volume in 1 s, FVC = forced vital capacity, MMF = maximum midexpiratory flow)

Reference	Exposure and type of plant	Job	Exposure range	Sample collection method and LOD	Halo vision[a]	Primary symptoms	Other findings
Hansen et al (18)	DMEA in gray-iron foundry	Head operator (N = 3)	5.3—26.5 mg/m³ (mean 15.5)	Silica gel tube, LOD 0.08 mg/sample	+	Headache (in 16 of 30); ear (in 14 of 30), nose (in 13 of 30) and throat (in 7 of 30) irritation; blurry vision (in 3 of 30)	Isocyanates present, isocyanates detected, no occupational asthma detected; hazy/halo vision lasting for 1—4 h after work
		Sm blower operator (N = 5)	4.2—18.8 mg/m³ (mean 11.6)				
Shreve & Brink (40)	DMEA in gray-iron foundry	Coremaker (N = 2)	1.2—2.3 mg/m³	Silica gel tube, LOD 0.01 mg/sample	+/—	Headache (in 7 of 13), nosebleed (in 6 of 13), blurry vision (in 5 of 13), dizziness and nausea (in 2 of 13)	Isocyanates present, isocyanates detected, no occupational asthma detected
Rockhold et al (36)	DMEA in gray-iron foundry	Isocure operator (N = 2)	2.1—36.8 mg/m³	Silica gel tube, LOD 0.01 mg/sample	—	Eye irritation (in 4 of 10), headache (in 4 of 10), dizziness (in 3 of 10), stomach pain (in 2 of 10)	Isocyanates present, isocyanates detected, occupational asthma not evaluated; breathlessness/choking during DMEA transfer
Savitt (38)	DMEA and TEA in gray-iron foundry				+	Hazy blue-grey vision, trigeminal neuralgia	52 % of the exposed had an increase in blood pressure versus 19 % of the referents
	DMEA	Exposed workers (N = 26)	0.1—11.8 ppm (mean 3.3 ppm, peaks to 100 ppm)	..			
	TEA	Exposed workers (N = 38)	0.01—12.3 ppm (mean 2.6 ppm, peaks to 30 ppm)	..			
	Volatile compounds on foundry dust (N = 3)		VC-25 dust collector				
	DMEA	..	111—239 ppm (mean 158 ppm)				
	TEA	..	7—95 ppm (mean 55 ppm)				
Stephenson (41)	TEA in gray-iron foundry	Workers in core-mold area (N = 18)	Not detected	Silica gel tube, LOD 0.01 mg/sample	—	Multiple symptoms	Isocyanates present, isocyanates detected; occupational asthma detected
Akesson et al (2)	TEA in polyurethane foam	Circulating workers (N = 8)	.. (mean 6 mg/m³, peak to 12 mg/m)	0.1N hydrogen chloride/impinger	+	47 incidents of eye irritation followed by blue haze, sometimes halo vision, over 11-week period	Eyes returned to normal after 3 days off work; isocyanates present, isocyanates detected; occupational asthma not evaluated
		Trimmers (N = 4)	.. (mean 13 mg/m³)				
Audunsson & Mathiasson (6)	NMM and TEDA in polyurethane manufacture			Alkalinized 0.1N sulfuric acid/ impinger	+	Light objects had hazy contours and were surrounded by halos of blue light	Isocyanates present, isocyanates detected, occupational asthma detected
		Molding (N = 3)					
		NMM	200 ppb				
		TEDA	17 ppb				
		Cell crush (N = 7)					
		NMM	600 ppb				
		TEDA	46 ppb				
		Foam removal		..			
		NMM	600 ppb[b]				
		TEDA	110 ppb[b]				
Akesson et al (3)	TEA in experimental exposure	(N = 2)	48 mg/m³ for 4 h	Infrared analyzer	+	Slight eye discomfort, no eye irritation, no decreased visual acuity, both returned to the base line after 24 h, hazy vision, lights surrounded by blue halos, no symptoms 4.5 h after exposure	Corneal edema, increased corneal thickness, no pathology
		(N = 2)	18 mg/m³			No symptoms/slight subjective effects after 4—6 h of exposure	
		(N = 2)	10 mg/m³			No effects after 8 h of exposure	

(continued)

Table 6. Continued.

Reference	Exposure and type of plant	Job	Exposure range	Sample collection method and LOD	Halo vision[a]	Primary symptoms	Other findings
Paton (33)	DMEA in aluminum foundry	Corebox operator (N = 13)	Not detected-15.6 ppm, (mean 2.64, SD 4.08)	Charcoal tube, LOD 0.02 ppm	+/—	Headache (in 15 of 34), ear (in 14 of 34), nose (in 6 of 34), and throat (in 6 of 34) irritation, nausea (in 6 of 34), dyspnea (in 5 of 34), chest pain (in 5 of 34)	In 6 of 23 decreased eosinophil count in pre- versus postshift; no decrease in $FEV_{1.0}$, FVC or MMF; isocyanates present, isocyanates detected, no occupational asthma detected
		Trimmer (N = 4)	Not detected-0.06 ppm, (mean 0.4)				
Stephenson (42)	DMEA in aluminum foundry	Core-machine operator (N = 34)	3.1—24 mg/m³ (mean 8.3, SD 4.6)	Silica gel tube, LOD 0.05 mg/sample	+	Hazy vision in 91 %, blurry vision in 79 %, halos in 67 %, colored halos in 64 %, watery eyes in 72 %, itchy eyes in 48 %, headache in 81 %	13 workers sent to hospital emergency room during two incidents of large releases of DMEA; many symptoms indicative of endogenous histamine release; isocyanates present, isocyanates detected, occupational asthma not evaluated
		Core-finisher (N = 22)	1.6—19 mg/m³ (mean 5.5, SD 4.2)				
		Utility person (N = 3)	3.1—4.6 mg/m³ (mean 4.0)				
		Core-sand mixer (N = 3)	trace-1.9 mg/m³ (mean 1.2)				
		Prototype operator (N = 4)	8.5—24 mg/m³ (mean 14)				

[a] + = experienced by worker, — = not experienced by worker.
[b] Not personal samples — approximate values.

in dogs (15) was observed in humans (24) after the administration of a high dose of a tertiary amine histamine liberator, L-1935. It is not known if this effect in humans is due to ganglionic blockade, but it is suggested that these effects are seen at high exposure levels that are achieved in industrial situations.

Histamine release. Among the many known pharmacologic effects of the amines is their ability to liberate histamine (14). Histamine is an important autacoid (local hormone) whose myriad functions within the body are still being determined (table 7). Every mammalian tissue that contains histamine is capable of synthesizing it from the amino acid histidine, by virtue of its content of *l*-histidine decarboxylase, an inducible enzyme. In most tissue, the chief site of histamine storage is the mast cell or its circulating counterpart, the basophil. These cells store histamine in secretory granules. The turnover rate is slow, and, when tissues rich in mast cells are depleted of their stores of histamine, it may take weeks before concentrations return to normal.

The range of compounds which can cause the release of preformed histamine (and other biologically active mediators) from mast cells and basophils is lengthy. Enzymes, lectins, polysaccharides, anaphylactoxins (C3a and C5a), venoms, calcium, and poly- and paucibasic amines, as well as several therapeutic drugs such as morphine, curare, and others, are all capable of liberating histamine. The release may occur from stimuli which are cyto- or noncytotoxic, and it can be independent of any immune-mediated response.

Table 7. Some histaminic actions and possible symptoms of intoxication.

Action of histamine	Possible symptom
Constriction of bronchiolar smooth muscle	Tight feeling in chest, difficulty breathing
Constriction of gut smooth muscle	Nausea/vomiting, cramps/diarrhea
Vasodilatation	Flushed face, headache, dizziness or faintness, increased heart rate
In dermal tissue	Itching
Unexplained but unique action	Metallic taste

A mechanism behind the systemic effects reported has yet to be clearly identified. However, ammonia, as well as structurally simple monoamines, can liberate endogenous histamine from mast cells.

Many of the symptoms postulated in table 7 were documented by Lecomte (24) when he administered a histamine liberator to experimental subjects. In addition many of these symptoms were also described by workers exposed to various tertiary amines during the course of health hazard evaluations conducted by the National Institute for Occupational Safety and Health. A wide variety of distinct physiological effects may occur when histamine is released into tissues or into circulation. Two classes of histamine receptors, called H_1 and H_2 receptors, are known from studies which have classified them according to the actions of specific agonist and antagonist compounds at the receptor. The H_1 receptors are primarily located in the bronchi and gut, where stimulation causes smooth muscle to con-

tract, and in vasculature, where stimulation causes smooth muscle to relax. H_2 receptors are found in the stomach, where stimulation causes gastric secretion, and the heart, where stimulation causes an increase in heart rate. Histamine has also been identified as a putative neurotransmitter in areas of the brain.

Chronic effects

Vision. An excellent review of corneal healing after forms of chemically-induced injury has been presented by Chan & Hayes (21). The cornea is an active tissue, and a wound to the epithelium is usually quickly repaired. The degree of injury will of course dictate the duration of healing. Healing has been observed to begin as soon as 1 h after exposure with epithelial cells migrating by amoeboid movement across the area of injury until it is completely covered. Acute exposures to TEA have produced measurable (by Haag-Streit pachometry) corneal edema (3). Exposure to amines producing halo vision has not been documented to produce chronic damage to the cornea.

Systemic. The ganglionic blockade observed in experimental animals and possibly in man has been reversible. Histamine is readily metabolized and tissue becomes refractory to further release once stores have been depleted. Histidine decarboxylase and histamine 4-methyltransferase (imidazole N-methyltransferase) are inducible enzymes, and elevated levels may be indicative of increased synthesis. With the increasing involvement and importance histamine has been shown to play as both a local hormone and central neurotransmitter, radical tissue depletion may exert chronic effects still to be determined.

Concluding remarks

Occupational exposure to tertiary amines may produce health effects that are not commonly encountered. Vision disturbances characterized by either mydriasis and cycloplegia or corneal edema present safety hazards due to a decrement in vigilance and vision. Systemic effects, although transient, are incapacitating and could create anxiety in workers who are not informed of their etiology.

Employees working with tertiary amines should be educated by management and instructed to recognize the potential health effects that these compounds may cause. Worker-reported symptoms might serve as an administrative control of exposure levels. Graphic symptoms produced by exposures to these compounds serve as a warning that engineering controls are inadequate. The lack of identifiable chronic effects should not deter control of exposures.

Acknowledgments

The authors would like to acknowledge the careful review provided by TR Norton, PhD.

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Received for publication: 9 September 1987