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Review Article

Amines as occupational hazards for visual disturbance

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Abstract: Various amines, such as triethylamine and N,N-dimethylethylamine, have been reported to cause glaucopsia in workers employed in epoxy, foundry, and polyurethane foam industries. This symptom has been related to corneal edema and vesicular collection of fluid within the corneal subepithelial cells. Exposure to amine vapors for 30 min to several hours leads to blurring of vision, a blue-grey appearance of objects, and halos around lights, that are probably reversible. Concentration-effect relationships have been established. The visual disturbance is considered a nuisance, as it could cause onsite accidents, impair work efficiency, and create difficulties in driving back home. Occupational exposure limits have been established for some amines, but there is shortage of criteria. Volatility factors, such as vapor pressure, should be considered in industrial settings to prevent human ocular risks, while trying to reduce levels of hazardous amines in the atmosphere.

Key words: Glaucopsia, Visual disturbance, Amine, Polyurethane foam, Foundry, Catalyst

Introduction

An amine forms when one or more hydrogen atoms of ammonia are replaced by particular radicals. Aliphatic amines include alkyl and/or alkanol radicals, whereas heterocyclic amines hold nitrogen in the cyclic ring. When amines contain alcohol radicals, they are also called alkanol amines. One, two, or three nitrogen atoms can be substituted on amines, which classify them into primary, secondary, or tertiary amines, respectively. Most amines have an unpleasant fish-like odor and alkaline characteristics[1, 2].

The earliest reports describing irritation and the visual effects of various industrial amines were by Watrous *et al.*[3], and visual disturbance or glaucopsia from various amines was probably first summarized by Amor in the late 1940s[3, 4]. Glaucopsia comes from the Greek word '*glauke*' which means 'blue' or 'green[2, 5, 6] and workers suffering from these symptoms may have 'halo', 'blue haze' or 'foggy vision[6–8]. These ocular effects were induced 30–90 min after exposure to the chemicals and did not give a permanent damage to human eyes. A natural healing process might occur 4–6 h after exposure ended[7].

During the second half of the 1900s, several studies reported occurrence of ocular hazards among employees working with epoxy[9] and in foundries[10–18] that require various amine catalysts. Polyurethane (PU) foam factories, which used amines for binding catalysts, were sites where glaucopsia might be occured[19–25]. The B-side solution, which mainly consisted of polyol (one type of alcohol) contains about 1% amines, whereas the A-side solution contained isocyanate compounds, such as toluene diisocyanate (TDI) and methylene bisphenyl isocyanate (MDI)[26]. When these two solutions are mixed under cer-

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tain conditions, they undergo a urethane reaction. Amine catalysts played an important role accelerating polymerization of isocyanate monomers. In the early 2000s, the US National Institute for Occupational Safety and Health (US-NIOSH)[27–29] issued reports and a journal article that investigated several amines related to glaucopsia in a printing shop. These compounds had not been reported previously. At the same time, triethylamine (TEA) was reported to cause visual disturbances in Japanese foundry workers[30].

Glaucopsia was not considered a serious occupational disorder for workers, as it neither poisoned them, caused irreversible damage, nor led to death. However, the ocular effects resulted in physical accidents, decreased work efficiency, and impaired of task coordination. In addition, it was a workplace hazard, similar to irritation of skin or mucous membrane, and thus required control measures to restrict employees' contact with causing chemicals in the work environment[6, 7].

Dozens of occupational disorder cases were reported from a PU foam manufacturing plant in Korea[31, 32]. Workers in a passenger car seat plant experienced various visual disooders, including difficulties focusing, eye discomfort, and halo vision while driving back to home after work. Nevertheless, little information was extracted from existing workplace monitoring data or medical examination records at the plant. It was apparent that the employer was attempting to identify the cause for the problems while trying to improve the situation by installing of local ventilation systems, rotating tasks, and clinical treating affected workers. The situation was particularly aggravated during the summer and nearly all workers in the process suffered glaucopsia symptoms. The Occupational Safety and Health Research Institute (OSHRI) of the Korea Occupational Safety and Health Agency (KOSHA) tried to resolve the issue after the agency received a safety and health evaluation request from the plant. Substituting for amines in raw materials could make it possible to resolve the problem successfully. In the present study, data obtained from the literature that describes glaucopsia and its relationship to various amines are summarized.

Methods

Journal articles were retrieved from online resources, including PubMed, TOXNET, ScienceDirect, Scoup, and Google Scholar utilizing random combinations of key words, such as 'glaucopsia', 'amine', 'halo vision', blurry vision', 'blue-grey haze' and 'visual disturbance'. The National Digital Science Library (NDSL) which is operated by the Korea Institute of Science and Technology Information (KISTI), which is provides 53 million scientific English articles in SCI, SCIE, and Scoup journals, was also searched. The journal search was conducted during winter 2014 and early 2015 without a year restriction. To obtain US-NIOSH research and Health Hazard Evaluation (HHE) reports, the homepage was searched using the same keywords. Amines with occupational exposure limits (OEL) in the Documentation of Threshold Limit Values which includes about 700 chemicals' Threshold Limit Values (TLVs) with around dozens amines, published by the American Conference of Governmental Industrial Hygienists (ACGIH), were also chased. Workplace Exposure Limits (WEL) of UK Health and Safety Executive (UK-HSE) were also obtained for information. Due to the relative restriction of journal articles and reports available on visual risks, nearly all references cited by important studies were traced and obtained.

Results

Historical background and glaucopsia amine chemicals

Numerous studies have considered topics related to the negative effects of amines on vision since Amor[4] published his article illustrating the toxicity of various solvents. One of the earliest occupational cases of visual disturbance due to diisopropylamine (DIPA) in a plant was reported by Treon *et al.*[33] after exposure to dozens ppm concentrations, which had been informed to the authors personally. After this article was published, many studies have followed and discussed occupational glaucopsia related to amine compounds during the last decades. Extensive human and animal data are available on some amines, such as TEA and dimethyethylamine (DMEA), whereas others have relatively restricted and/or outdated information. Several books and review articles written by Cavender[1], Grant & Schuman[2], Albrecht[6], Ballantyne[7], and Johns & Kipling[8] contain valuable information about glaucopsia-inducing amine chemicals.

Twenty-one important amines could be listed in this review, including ethyl amine (EA)[2, 4, 8, 34–37], isopropylamine (IPA)[36–39], tert-octylamine (TOA)[2, 7, 8, 40], ethylenediamine (EDA)[2, 7, 36–42], dimethylamine (DMA)[2, 7, 8, 36, 37, 40, 43–46], diethylamine (DEA)[2, 7, 36, 37, 47, 48], DIPA[2, 7, 33, 36, 37, 49, 50], DMEA[6, 7, 10–16, 51], TEA[4, 6, 7, 10, 11, 17, 18, 23, 24, 30, 36, 37, 44, 52–58], N-ethylpiperidien (EPP)[2, 7, 8, 43, 44], 3-dimethylaminopropylamie (DMAPA)[7, 59], triethylenediamine (TEDA)[6, 7, 20, 22, 24, 25, 60], N,N,N'N'-tetrameth-

Table 1. The list of amines that may cause human glaucopsia

Chemical name	Abbreviation	CAS No.	Chemical group	Molecular form	MW	MP (°C)	BP (°C)	VP (mmHg)
Dimethylamine	DMA	124-40-3	secondary amine	$(CH_3)_2NH$	45.1	–92.2	6.8	1,520
N,N-Dimethylethylamine	DMEA	598-56-1	tertiary amine	$(CH_3)_3CH_2N$	73.1	–140	36.5	418
Triethylamine	TEA	121-44-8	tertiary amine	$(CH_3CH_2)_3N$	101.2	–114.7	89.3	57.1
Triethylenediamine	TEDA	280-57-9	tertiary diamine	$(CH_2)_6N_2$	112.2	158	174	0.742
Bis[2-dimethylaminoethyl]ether	DMAEE	3033-62-3	tertiary diamine	$O[(CH_3)_2(CH_2)_2N]_2$	160.3	NA	189	0.748
N,N,N',N'-Tetramethyl-1,6-hexandianine	TMHDA	111-18-2	tertiary diamine	$[(CH_3)_2(CH_2)_3]_2N_2$	172.3	–46	209.5	0.202
Morpholine	MP	110-91-8	heterocyclic amine	$O(CH_2)_4NH$	87.1	–4.8	128	10.1
N-Methylmorpholine	MMP	109-02-4	heterocyclic amine	$O(CH_2)_4CH_3N$	101.2	–66	115.5	18
N-Ethylmorpholine	EMP	100-74-3	heterocyclic amine	$O(CH_2)_5CH_3N$	115.2	–62.8	138.5	6.1
N,N-Dimethylaminoethanolamine	DMAEA	108-01-0	Alkanol amine	$HO(CH_3)_2(CH_2)_2N$	89.1	–70	135	100
N,N-Dimethylisopropanolamine	DMIPA	108-16-7	Alkanol amine	$HO(CH_3)_3CH_2CHN$	103.2	–85	96	8

yl-1,2-ethylenediamine (TMEDA)[2, 7, 8, 43, 44], N,N,N',N'-tetramethyl-1,3-butanedimine (TMBDA)[2, 6, 7, 20, 60], bis[2-dimethylaminoethyl]ether (DMAEE)[7, 25, 36, 37, 44, 61–64], N,N,N',N'-tetramethyl-1,6-hexandianine (TMHDA)[31, 32], morpholine (MP)[2, 6–8, 19, 20, 36, 37, 65–67], N-methylmorpholine (MMP)[2, 6–8, 19, 20, 22, 42, 44], N-ethylmorpholine (EMP)[2, 7, 8, 19, 20, 36, 37, 43, 44, 68, 69], NN,-dimethyaminoethanolamine (DMAEA)[27–29], and N,N-dimethyisopropanolamine (DMIPA)[27–29]. Among them EA, IPA, TOA, EDA, DEA, DIPA, EPP, DMAPA, TMEDA, TMBDA, and TMHDA have minimal human data and/or outdated background information published before 1970, including industry reports. Neither articles nor toxicology textbooks that have cited or recited basic original human data were considered here.

Other amines, including DMA, DMEA, TEA, TEDA, DMAEE, MP, MMP, EMP, DMAEA, and DMIPA have moderate to large quantities of background information on their glaucopsia hazards. Henceforth, this review mainly focuses on reviewing the ocular hazards of amines with significant human data, except TMHDA, which is a cases of recent workplace exposure.

Physical and chemical characteristics of important amines

Table 1 summarizes the physical and chemical properties of the important 11 amines which include chemical catalysts in various industrial processes. Except for DMA, which is a gas at normal temperature (20°C) and pressure (1 atm), many of them exist in liquid form. MP, MMP, and EMP can be categorized into a heterocyclic group, while DMIPA is an alkanol amine. Table 1 was compiled considering groups of amines, the number of amines in the molecular structure, and molecular weight (MW) of each compound. DMA has the simplest molecular structure, whereas DMAEE and TMHDA have MW of more than 160.

Vapor pressure (VP) is a very important property, as it denotes an ideal theoretical concentration in air at normal temperature and pressure (NTP), which could be a workers' exposure concentration when the air is saturated with the chemical in a confined environment without ventilation. The boiling point (BP) and melting point (MP) are critical to determine an agent's physical form (gas, liquid, or solid) at NTP. Abbreviations have been used for each amine to describe the chemicals as simply as possible.

Dimethylamine

DMA belongs to a group of secondary amines and has huge VP of 1,520 mmHg. Munn reported several ocular hazard cases resulting from industrial exposure to this chemical without detailed background information[40]. Ballantyne cited Munn's report in his study to summarize toxicity data[7]. When Mellerio & Weale decided to conduct animal experiment on several amines including DMA[43], they considered ocular hazards, and their study was cited by Grant & Schuman[2], Jones & Kipling[8] and Ballantyne[44] for studies on glaucopsia in workers. However, Hathaway & Proctor simply reported occasional dermatitis or conjunctivitis after prolonged exposure to this compound based on the 1955 MCA Inc. chemical safety data sheet[45]. ACGIH documentation indicates dermal, ocular, respiratory, and gastrointestinal track irritation caused by this compound, as evidenced in animal tests[46].

N,N-dimethylethylamine

DMEA is also called dimethylethylamine and is a tertiary amine. Its effects on the eye in industrial workers have been well examined. Since Schmitter investigated

Table 2. Articles describing human glaucopsia caused by DMEA

Author (s)	Year	Type	Reference
Schmitter	1977	Original	11)
Albrecht & Stephenson	1988	Review	6)
Warren & Selchan	1988	Original	10)
Ståhlbom *et al.*	1994	Original	51)
Ballantyne	2004	Review	7)
US-NIOSH	1984	Report	12)
US-NIOSH	1984	Report	13)
US-NIOSH	1986	Report	14)
US-NIOSH	1987	Report	15)
US-NIOSH	1987	Report	16)

Table 3. Articles describing human glaucopsia caused by TEA

Author (s)	Year	Type	Reference
Amor	1949	Original	4)
Schmitter	1977	Original	11)
Åkesson *et al.*	1985	Original	54)
Åkesson *et al.*	1986	Original	23)
Potts *et al.*	1986	Original	24)
Albrecht & Stephenson	1988	Review	6)
Åkesson *et al.*	1988	Original	55)
Warren Selchan	1988	Original	10)
Åkesson *et al.*	1989	Original	57)
Åkesson & Skerfving	1990	Original	58)
Reilly *et al.*	1995	Original	17)
Jävinen & Hyvärinen	1997	Original	18)
Ballantyne	1999	Review	44)
Jävinen *et al.*	1999	Original	56)
ACGIH	2001	Review	53)
Yoshida *et al.*	2001	Letter	30)
Ballantyne	2004	Review	7)
Hathaway *et al.*	2004	Review	52)

workers' hazy blue-grey vision in a Germany foundry using cold-box and shell mold casting methods in 1977[11], various studies have discussed DMEA as a catalyst and as a chemical that causes visual disturbances (Table 2). Studies that only considered sampling and analytical methods are not included in the table. Except for one review article written by Ballantyne[7] most of the studies were published before the beginning of this century.

US-NIOSH investigated several factories where glaucopsia cases had been reported in their HHE efforts[12–16], but some failed to detect amines in workplace air. Warren & Selchan[10] conducted a survey study on workers exposed to DMEA with TEA in 42 foundries. StÅhlbom *et al.*[51] conducted personal exposure experiments employing volunteers and found that glaucopsia could occur over a relatively long exposure time at low concentrations, whereas short-term exposure to high levels led to eye irritation.

Triethylamine

TEA has the most abundant data on its glaucopsia hazards. Since Amor designated the hazards of this chemical[4], visual disturbances have been reported occasionally in foundries and PU industries until the early 2000s, including a Japanese episode[30]. Studies by Hathaway & Proctor[52] and ACGIH[53] have reported detailed toxicity data on the visual disturbances caused by TEA.

Åkesson and his colleagues performed several human experiments to reveal the ocular toxicity mechanism of TEA and explained that the visual disturbance might be caused by corneal edema. They also suggested that triethylamine-N-oxide (TEAO) could be a human biological index for overexposure to the chemical, whereas alcohols such as ethanol might inhibit metabolism of TEA to TEAO[23, 55, 57, 58]. Jävinen and coworkers carried out a case-control study[18] and an intentional human exposure study[56]. Important studies that reported the ocular hazards of TEA are listed in Table 3.

Triethylenediamine

TEDA is a tertiary amine, which is occasionally called DAVCO. TEDA is a commercial PU catalyst that was used for decades. TEDA exists as a solid at NTP, with MP of 158°C and BP of 174°C. In their animal toxicity experiments of TEDS and another amine (TMBDA), Goldberg & Johnson did not fully demonstrate distinct ocular effects in mice due to low VP (0.742 mmHg)[60], whereas TMBDA (VP=1.64 mmHg) caused profound pupillary dilation and loss of accommodation. Dernehl reported visual disturbances among workers at the Union Carbide Corp. who were exposed to several amines including TEDA and constituted background for his study[20]; however, he did not definitely determine that TEDA caused the symptoms.

In a letter to the editor of the *Journal of Occupational Medicine* in 1975, Smith & Henderson commented that TEDA was an eye and respiratory system irritant but did not mention glaucopsia[70]. In another letter to the editor of same journal in 1976, Pagnotto and Wegman at the Massachusetts Division of Occupational Hygiene, following the designation of Smith & Henderson[70], carried out an investigation on a PU foam plant using TEDA[71]. They also failed to detect TEDA in the workplace atmo-

sphere due to the low sensitivity of their sampling and analytical methods (<0.4 ppm) and did not report any ocular symptoms among workers at the site. Belin *et al.* examined a PU foam factory in one health investigation of and compared exposed workers to results from an unexposed control group and concluded that MMP, which was detected at the thousand ppb level, could have been the major causative chemical for the respiratory and visual disturbance symptoms rather than TEDA[22]. They also detected this amine and isocyanates in workroom air, but the concentrations were <0.11 ppb and several ppb, respectively. Balantyne included TEDA in his list of glaucopsia-causing compounds[7] citing the Dernehl's Union Carbide case[20]. US-NIOSH and the US-Occupational Safety and Health Administration (US-OSHA) have not established any OELs for the compound until today.

Bis[2-dimethylaminoethyl]ether

Although several studies have described workplace exposure to DMAEE vapor as a causative agent of glaucopsia, few real human data are available. Boeniger *et al*. tried to verify a DMAEE air evaluation method and detected 28–208 ppm DMAEE without describing any visual disturbance effects[72]. In a case report on a PU foam factory, US-NIOSH described multiple ocular symptoms and determined DMAEE air levels but they failed to detect the compound at the site[25].

One scientist at the Union Carbide Corp. with the aid of other experts carried out animal studies on DMAEE and concluded that human glaucopsia could occur due to a transient increase in corneal thickness and corneal edema[61–63]. The researcher also cited relevant studies in his review article[7] and in a toxicology textbook[44]. ACGIH[64] has a current TLV of 0.005 ppm (TWA) and 0.15 ppm for STEL due to highly irritating and ocular effects of this amine.

N,N,N'N'-Tetramethyl-1,6-hexanediamine

Recent cases on human visual disturbances in a Korean PU foam factory revealed that TMHDA, a tertiary catalyst amine, was included in the B-side solution with TEDA. According to the clinical records available from the company, nearly 40 workers involved in making several types of PU foams for passenger car seats suffered relatively serious ocular symptoms, including blue-grey vision and halos around lights. The new process and the B-side solution were introduced at the site during the spring, and glaucopsia worsened in June (early summer season) when daytime temperature increased to about 30°C. The factory managers asked OSHRI of KOSHA to investigate the issue after they had attempted to and failed to resolve the problem by introducing local ventilation systems and rotating tasks. The mean air concentrations of TEDA and TMHDA were 0.060 ppm and 0.070 ppm, respectively, after confirming the identities of the chemicals by gas chromatography-mass spectrometry (GC/MS). TEDA and TMHDA are listed by the American Chemical Society (ACC) and the Center for the Polyurethanes Industry in a list of 52 amine catalysts that might be used at PU manufacturing factories[73]. The supplier of the B-side solution and the factory that had the glaucopsia problem changed amines from non-reactive to reactive foams, which could be chemically combined into PU polymers with a reduction in evaporation of amine vapors at the worksite. Substituting catalysts cut mean atmospheric levels of TEDA and TMHDA to 0.026 ppm and 0.014 ppm, which was about 60% and 80% of previous levels, respectively. Most workers did not experience symptoms in the next summer. This was the first official report on industrial glaucopsia in the country with successful resolution of an occupational issue[31, 32].

Morpholine

In 1965, Mastromatteo reported that MP could be a human glaucopsia-causing chemical in several PU foam industries in Ontario, Canada. Symptoms developed at the end of a work-shift and cleared up within hours after exposures[19]. Dernehl at the Union Carbide Corp. designated the compound as a visual disturbance hazard along with his incomplete findings on the occurrence of eye lesions at MP levels ≥40 ppm[20]. Johns & Kipling described exposure of 3 to 18 employees to a variety of amine compounds including MP in a chemical plant over several years and the complaints of workers on the presence of blue vision, grey vision, and halos with associated difficulties driving[8]. A range of amines and their intermediates were manufactured at that plant.

Ballantyne cited the afore-mentioned articles in a chemical review on glaucopsia[7]. A workplace chemical hazard book edited by Hathaway & Protor[65] summarized that workers exposed for hours to low vapor air levels of MP complain of foggy vision with halos around lights as a result of corneal edema. Actually, this information came from one of the chapters of Patty's toxicology book[66], but the data originated from Grant & Schuman's book[2]. Following this finding, ACGIH set a TLV-TWA of 20 ppm[67]. However, the eye toxicology book of Grant simply cited the work of John & Kipling[8] and Mastromatteo[19]. Skin

notation was assigned due to the potential irritation effects on the eyes, nose, and throat.

N-methylmorpholine

Mellerio & Weale prompted reports of blue and grey vision among amine plant employees by evaluating ocular effects in animal studies[43]. Mastromatteo and Dernehl reported human glaucopsia hazards of MMP when present with MP in their articles[19, 20]. When Jones & Kipling historically reviewed amine chemicals for their effect on blue-grey vision, they mentioned that one of their colleagues experienced grey haziness from intentional exposure to MMP[8]. Belin *et al.* investigated workplace exposure levels to MMP at a PU foam factory along with isocyanates and TEDA (DAVCO)[22]. Forty-two workers reported occasional eye symptoms and the presence of blue light halos. Air levels on production lines were 3.2–7.6 ppm. The concentrations were not TWA levels, instead average of several determinations. Respiratory track symptoms were also reported by workers.

In their review articles, Ballantyne and Jones & Kipling summarized occupational ophthalmic hazards of MMP[7, 8]. In a general toxicology textbook, Grant & Schuman and Ballantyne also cited the previous studies that pointed out the human ocular risks of MMP[2, 44]. ACGIH, US-OSHA, and US-NIOSH have not set any OELs for MMP.

N-ethylmorpholine

Due to chemical similarity, EMP was reported by several studies to lead to human glaucopsia. Mastromatteo demonstrated visual hazards caused by EMP in several PU industries with little comment on the onsite process or medical findings[19]. Dernehl found characteristic corneal lesions in some workers exposed to amine compounds, including EMP[20]. The workers' corneas showed diffused clouding and many obscure markings on the iris. When Mellerio & Weale considered animal studies, they reported blue or grey vision and smoky clouds among workers in chemical plants that were caused from several amines, including EMP[43]. A book edited by Hathaway & Proctor[68], toxicology books of Grant & Schuman[2] and Ballantyen[44], review articles by Ballantyne[7] and Jones & Kipling[8] have also reported occupational visual disturbances among workers exposed to EMP.

Currently, ACGIH has set a TWA-TLV of 5 ppm for the chemical by adapting references written during the 1960s[69], which are also mentioned here. In the TLVs documentation, one additional personal communication by Woewicki explained that workers exposed to 3–4 ppm, but not >11 ppm, complained of foggy vision and optical halos[69]. These results could be the basis for TLVs but the references were relatively outdated.

N,N-dimethyaminoethanolamine

US-NIOSH received a request for a HHE from a large printing shop located in Ohio, USA in January 2011. About 89% of the line division workers at the factory were suffering from blurry vision, whereas 12.5% of the employees in the prime division had the symptoms. The mean DMAEA concentration at the line division was about 0.62 ppm, which was similar to that of prime division of about 0.95 ppm. No changes in air DMAEA levels were detecting in either division after controlling the amines; however, the ocular effects among workers disappeared. The institute concluded that glaucopsia might have been caused by other amines and that DMAEA was not the culprit at the detected concentration levels[27–29].

N,N-dimethyisopropanolamine

DMIPA was the other amine at the Ohio printing factory mentioned in the previous DMAEA section, which has a VP of 100 mmHg, whereas that of DMAEA is 8 mmHg. The prime division used DMAEA and the pH adjuster in the line division contained DMIPA[27–29]. The mean DMIPA concentration at the line division was 1.83 ppm and that for the prime division was 0.49 ppm before introducing control measures. By eliminating DMIPA in the line division, it was possible to dramatically reduce the concentration, and visual disturbances among workers disappeared. The institution suspected that the high air levels of DMIPA before introducing the control measures might be caused by the high VP of this substance, as shown in Table 1. Acute irritation toxicity of this chemical was reported by Ballantyne[74] in an animal study; however, additional data on human glaucopsia could not be found for this particular alkylalkanol amine.

Discussion

Amine processes related to glaucopsia

Amines have been used extensively as starting materials for chemical syntheses, as intermediates, and as solvents in numerous industrial processes. Amines are used intensively in catalysts, poultry feed, corrosion inhibitors, drugs, bactericides, and herbicides[1]. Considering the glaucopsia hazards due to various amines, the processes employing such compounds were relatively restricted. Early visual disturbance cases originated from some chemical

Table 4. Industrial processes for glaucopsia and irritation hazards

Process	Amines	References (glaucopsia)	References (irritation)
PU foam	TEA, TEDA, DMAEE, TMHDA, MP, MMP, EMP, DEtA*	7, 19–25, 31, 32, 60)	61, 71, 75, 76)
Foundry	DMEA, TEA, HMTA**	10, 14, 20, 26, 30–32)	15, 77–80)
Epoxy	Other amines#	9)	81, 82)
Printing	DMAEA, DMIPA,	27–29)	
Others	DMA, MMP, EMP	43)	3, 43)

*DEtA: diethanolamine

**HMTA: hexamethylenetetramine

#Other amines include m-phenylenediamine, triethylenetetramine, dimethylethanolamine, diethylenetriamine, dimethylaminopropylamine, diethylaminopropylamine, and benzyldimethylamine

factories[33, 59]; however, two major reported industrial sites were foundries and PU foam factories (Table 4).

The chemicals that can cause glaucopsia and those that may be occupational irritation hazards are included in Table 4 to warn occupational health practitioners. Also, several special amines that are not listed in Table 1 have been included in Table 4 following the same intention. Eight amines used in PU foam factories were appropriate to the list, including diethanolamine (DEtA), which could not be traced in Table 1. MP, MMP, and EMP had long history of PU industry use since the 1960s, whereas other amines have been used since 1980. DMEA, TEA, and hexamethylenetetramine (HMTA) have been employed in foundries as cold-box curing catalysts and workers might be exposed to the vapor when the injecting amines into sand molds for hardening. Several amines not listed in Table 1 were used as epoxy resin binders but their effects were mainly irritations rather than visual disturbances. Other processes described in Table 4 include chemical plants and pharmacological factories, and glaucopsia has been associated with exposure to DMA, MMP, and EMP[43]. Irritation symptoms in workers exposed to DMA could be due to chlorinated DMA but this has not been clearly explained[6]. Recently, DMAEA and DMIPA that caused ocular hazards were reported to be used in a US printing shop[27–29], which previously was not included in processes causing a visual disturbance.

Workers exposure levels to amines

The exposure levels of workers to amines that could cause occupational glaucopsia have been reported with relevance to previous studies (Table 5). Air levels of amines causing irritation were not considered to construct the table. Among the amines in Table 1, TEA, DMEA, TEDA, DMAEA, DMIPA, TMHDA, DMAEE, and MMP have sufficient data to be summarized. There are only limited monitoring data for the other amines. A good number of data are available for TEA and DMEA, whereas information on the other compounds is too restrictive to construct meaningful OELs.

Warren & Selchan did not report glaucopsia hazard at TEA concentrations ≤5 ppm[10] and Reilly *et al.* found that ≤2.5 ppm was a possible threshold level[17]. According to several intentional human experiments performed by Åkesson and coworkers[23, 54, 55, 57, 58] and Jävinen & Hyvärinen[18], visual disturbances did not occur when air exposure levels were ≤1 ppm. ACGIH is currently trying to change a TWA-TLV from 1 to 0.5 ppm with a STEL of 1 ppm as per the Notice of Intended Changes (NIC) and this measure should protect workers against glaucopsia[36].

Warren & Selchan reported no ocular hazards at DMEA levels ≤5 ppm[10]. Schmitter and several studies done by NIOSH found that mean levels of several ppm of DMEA were related to glaucopsia[11, 13, 14], but one NIOSH study reported that 0.4–0.8 ppm was a possible cause of hazard[12]. Another NIOSH report described that DMEA concentrations of 2 ppm (TWA) and 9.7 ppm (STEL) might have caused human visual disturbances in an aluminum casting foundry[15]. In their human experimental studies, StÅhlbom *et al.* reported that ≤6.6 ppm did not cause glaucopsia[51]. Minimal data are available to consider occupational threshold values for TEDA. Also, additional data for DMAEA, DMIPA, TMHDA, and MMP are required to set the OELs.

Occupational exposure limits

OELs are critical baselines for chemical specific risk assessments and constructing control options to protect workers from many hazardous substances. Relatively well-accepted criteria include TLVs of ACGIH, Recommended Exposure Limits (RELs) of US-NIOSH, Permissible Exposure Limits (PELs) of US-OSHA, Maximum

Table 5. Amine exposure levels causing glaucopsia in workers

Reference	Amines	Process	Type	Samples	Exposure range	Glaucopsia	Additional findings
Warren & Selchan[10]	TEA	Foundry	Onsite	31 (TWA)	2.6–3.6 ppm* (GM: 3.1 ppm)	+	No glaucopsia at less than 5 ppm
		Foundry	Onsite	69 (STEL)	4.5–5.9 ppm* (GM: 2.7 ppm)	+	
Schmitter[11]		Foundry	Onsite	38	0.1–11.8 ppm (mean: 3.3 ppm)	+	
Reilly *et al.*[17]		Foundry	Onsite	17	0.1–4.9 ppm (mean: 1.9 ppm)	+	Common symptom at >2.5 ppm
Jävinen & Hyvärinen[18]		Foundry	Onsite	NA	0.1–14.5 ppm (median: 6.4 ppm)	+	
Åkesson *et al.*[23]		PU	Onsite	5 (TWA)	1.2–8.0 ppm (mean: 3.2 ppm)	+	2.4–3.6 ppm (TWA) may cause glaucopsia
				NA (STEL)	ND-5.8 ppm (mean : NA)		
Åkesson *et al.*[54]		Chamber experiment		2	2.4/4.4/8.2/11.6 ppm	+/–	Glaucopsia at 4.4 ppm and higher
Åkesson *et al.*[55]		Chamber experiment		5	2.4/4.8/8.5/12.8	+/–	Glaucopsia at 4.8 ppm and higher
Jävinen *et al.*[56]		Chamber experiment		4	0.72/1.58/9.8 ppm	+/–	Glaucopsia at 1.58 ppm and higher
Åkesson *et al.*[58]		Chamber experiment		4	4.8 ppm	+	Occurrence of glaucopsia
Warren & Selchan[10]	DMEA	Foundry	Onsite	54 (TWA)	5.7–6.9 ppm* (GM: 6.3 ppm)	+	No glaucopsia at less than 5 ppm
		Foundry	Onsite	151 (STEL)	10.2–11.2.9 ppm* (GM: 10.7 ppm)	+	
Schmitter[11]		Foundry	Onsite	26	0.001–12.3 ppm (mean: 2.6 ppm)	+	
US-NIOSH[12]		Foundry	Onsite	4	0.4–0.8 ppm (mean: 0.6 ppm)	+	
US-NIOSH[13]		Foundry	Onsite	9	1.8–8.8 ppm (mean: 4.4 ppm)	+	
US-NIOSH[15]		Foundry	Onsite	NA	NA	+	Glaucopsis at 2 ppm (TWA) or higher, 9.7 ppm (STEL) or higher
US-NIOSH[16]		Foundry	Onsite	63 (TWA)	ND-8.0 ppm (mean: 2.3 ppm)	+	
				30 (STEL)	ND-9.7 ppm (mean: 1.6 ppm)		
Ståhlbom *et al.*[51]		Chamber experiment		4 (TWA)	3.3/6.6/13.3/16.6 ppm	+/–	No glaucopsia at less than 6.6 ppm
		Chamber experiment		30 (STEL)	26.7/53.3 ppm	-	No glaucopsia with eye irritation
		Foundry	Onsite	12	0.16–9.3 ppm (mean: 1.2 ppm)	+	Glaucopsis at 7.6–9.3 ppm
Belin *et al.*[22]	TEDA	PU	Onsite	7	0.017–0.11 ppm (mean: 0.08 ppm)	+	
US-NIOSH[25]		PU	Onsite	NA	NA	+	Failed to detect amines in the air
Jang *et al.*[31]		PU	Onsite (Pre)	29	ND-0.26 ppm (mean: 0.06 ppm)	+	Isocyanate and aldehydes detected
Jang & Park[32]		PU	Onsite (Post)	29	ND-0.08 ppm (mean: 0.03 ppm)	-	Aldehyde levels also reduced
US-NIOSH[27]	DMAEA	Printing	Onsite (Pre)	110	0.05–1.24 ppm (mean: 0.66 ppm)	+/–	
US-NIOSH[28]		Printing	Onsite (Post)	64	0.01–1.37 ppm (mean: 0.76 ppm)	-	DMAEA was not related to glaucopsia
US-NIOSH[27]	DMIPA	Printing	Onsite (Pre)	110	0.16–4.0 ppm (mean: 1.65 ppm)	+/–	Mean DMIPA (1.83 ppm, N=96) caused glaucopsia
US-NIOSH[28]		Printing	Onsite (Post)	64	0.01–0.09 ppm (mean: 0.02 ppm)	-	DMIPA related to glaucopsia
Jang *et al.*[31]	TMHDA	PU	Onsite (Pre)	29	ND-0.29 ppm (mean: 0.07 ppm)	+	Isocyanate and aldehydes detected
Jang & Park[32]		PU	Onsite (Post)	29	ND-0.002 ppm (mean: 0.01 ppm)	-	Aldehyde levels also reduced
US-NIOSH[25]	DMAEE	PU	Onsite	NA	NA	+	Failed to detect amines in the air
Belin *et al.*[22]	MMP	PU	Onsite	7	3.2–7.6 ppm (median: 6.9 ppm)	+	MMP might cause glaucopsia

* Upper and lower 95% confidence limits of the GM

Table 6. Occupational exposure limits of amines for glaucopsia

Chemical name	ACGIH-TLVs[73]		OSHA-PELs[74]		NIOSH-RELs[74]		AIHA-WEEL[74]		UK HSL-WEL[86]		German-MAKs[74]		Skin notation
	TLV	STEL	TLV	STEL	TLV	STEL	TLV	STEL	TLV	STEL	TLV	STEL	
Ethylamine	5	15	10	-	10	-	-	-	2	6	5	C10	ACGIH
Isopropylamine	5	10	5	-	-	-	-	-	-	-	5	C10	
Ethylenediamine	10	-	10	-	10	-	-	-	-	-	-	-	ACGIH
Dimethylamine*	5	15	10	-	10	-	1	3	2	6	2	-	
Diethylamine	5	15	25	-	10	25	-	-	5	10	5	C10	ACGIH
Diisopropylamine	5	-	5	-	5	-	-	-	5	-	-	-	ACGIH/OSHA/NIOSH
Triethylamine	1**	3*	25	-	-	-	-	-	2	4	1		ACGIH/HSL
Bis (2-dimethylaminoethyl) ether*	0.005	0.15	-	-	-	-	-	-			-	-	ACGIH
Morpholine*	20	-	20	-	20	30	10	-	10	20	-	-	ACGIH/OSHA/NIOSH/HSL
N-Ethylmorpholine*	5	-	20	-	5	-	-	-	5	20	-	-	ACGIH/OSHA/NIOSH/HSL

*Amines listed in Table 1 as glaucopsia chemicals, **Notice of intended change in 2014 TLVs

Concentrations at the Workplace (MAKs) in Germany, and WELs in the United Kingdom. OELs for amines are quite restrictive, as summarized in Table 6, in which only 10 compounds have exposure limits, including four substances listed in Table 1[36, 37, 83]. All 21 amine chemicals listed in the Introduction section were considered to enlist OELs for occupational health professional instructional purposes.

As mentioned previously, fundamental information to develop OELs is relatively restricted due to limited studies available to criteria-setting organizations. In some cases, only one or two human studies are available to set limits and some are outdated[33, 38, 39, 49]. As it is well known that the reaction between isocyanates and alcohols, such as polyol, follows second-order kinetics, catalyst amines play an important role in the PU reaction[75]. When the numbers of amino groups in a molecule increases, catalytic activities tend to increase[76]. Therefore, while uses for tetraamines and triamines have increased, the possibility of occupational exposure to di and monoamines has decreased, which could result in little additional field exposure data for low molecular weight amine compounds in the PU industry.

ACGIH proposed a 0.5 ppm (TWA) NIC for TEA, and the German MAK for the compound is 1 ppm (TWA), whereas the PEL of US-OSHA is 25 ppm (TWA) and the WEL of the UK-HSL is 2 ppm (TWA)[36, 37, 83]. Despite some valuable DMEA data, none of the organizations has currently set OELs for this compound.

New OELs have been suggested. Ballantyne proposed a 5 ppm OEL for MMP as a EMP homolog[7]. Most amines are alkali and may induce skin, mucous membrane, and respiratory tract irritation. Considering these symptoms may be more useful than glaucopsia for constructing OELs for amine compounds in the future. Following the data in Table 6, a DMEA TWA-OEL of ≤2 ppm could be a safe level to prevent glaucopsia among workers. Visual disturbances can also occur in the presence of low air levels when exposure time is prolonged to hours before the onset of eye and skin irritations, and the consequences depend on the nature of the amine compound[51]. Korean workers complained of visual disturbances caused by TMHDA, but they were not suffering from irritation hazards in a PU foam factory[31, 32].

Amine sampling and analytical methods

Determining airborne amine levels in the workplace atmosphere is relatively complex compared to that for organic solvents, such as toluene, xylene, and acetone. The sampling and analytical methods taken from various studies are listed in Table 7, and include recommended methods from US-OSHA, US-NIOSH, and UK-HSL. In constructing the table, authors, publication year, and method number are considered.

During the 1980s, acid-filled impinges containing hydrochloric or sulfuric acid were widely used to capture amine compounds, as these chemicals had alkali characteristics[72, 84, 86, 87, 91, 95]. Subsequently, charcoal tubes were used for low molecular weight aliphatic amines[88], XAD-2[88, 89] or XAD-7[96–98] was used for cyclic and long chain amines, silica gel[92–94, 99] and acid-coated glass fiber filter were used with Tenax[100], and Thermosorb/A[72, 90] has been introduced in past decades. Acid-coated XAD tubes could effectively capture alkali and polar amine compounds. Thus, it is very difficult to recommend one versatile sampling medium for impregnating all types of

Table 7. Sampling and analytical methods for glaucopsia amines

Reference	Year	Amines	Sampling	Analysis*	Findings
Audursson & Mathiasson[84]	1983	MMP, DMAEE	Acid-filled impinger	GC/TSD	Testing for sampling/ analytical measure
Audunsson & Mathiasson[85]	1984	DMA, TEA, MMP	-	GC/TSD	Testing for analytical measure
Hansén *et al.*[86]	1985	DMEA	Acid-filled impinger/Silica gel	Isotachophoresis	Comparing sampling/ analytical measure
Hansén *et al.*[87]	1986	MMP	Acid-filled impinger	Isotachophoresis	Testing for sampling/ analytical measure
Boeniger *et al.*[72]	1987	TEDA	Acid-filled impinger	GC/TEA	Impinger method could be complementary
			Thermosorb/A		
Andersson & Andersson[88]	1989	DMEA, TEA	Char coal tube	GC/NPD & FID	Charcoal for methyl/ ethyl aliphatic amines
		EMP	Aberlite XAD-2		XAD-2 for long chain amines
Andersson & Andersson[89]	1991	TEDA	Aberlite XAD-2	GC/NPD	XAD-2 is recommended for TEDA
Foley *et al.*[90]	1991	TEA, DMAEE, EMP	Thermosorb/A	GC/NPD	Thermosorb/A be use with caution
Rampel *et al.*[91]	2008	TEA	H_3PO_4 impregnated sampler	LC/MS	Testing for sampling/ analytical measure
US-NIOSH NMAM 2010[92]	1994	Aliphatic amines	Silica gel	GC/FID	Recommended method
US-NIOSH NMAM 2002[93]	1994	Aromatic amines	Silica gel	GC/FID	Recommended method
US-NIOSH NMAM 2007[94]	1994	Aminoethanol compounds I	Silica gel	GC/FID	Recommended method
US-NIOSH NMAM 3509[95]	1994	Aminoethanol compounds II	Impinger with hexanesulfonic acid	IC	Recommended method
US-OSHA 34[96]	1982	DMA	10% NBD chloride coated XAD-7	HPLC/Fl or Vis	Recommended method
US-OSHA PV 2060[97]	1993	TEA	10% H_3PO_4 coated XAD-7	GC/FID	Recommended method
US-OSHA PV 2123[98]	2003	MP	10% H_3PO_4 coated XAD-7	GC/FID	Recommended method
US-OSHA IMIS 1225[99]	NA	NMP	Silica gel	GC/FID	Recommended method
UK-HSL MDHS75/2[100]	NA	Aromatic amines	Acid-coated GF filter with Tenax	HPLC/UV	Recommended method

*GC/FID: Gas Chromatograph/Flame Ionization Detector, GC/MS: Gas Chromatograph/Mass Spectrometer, GC/NPD: Gas Chromatograph/Nitrogen Phosphorous Detector, GC/TEA: Gas Chromatograph/Thermal Energy Analyzer, 4GC/TSD: Gas Chromatograph/Thermionic Specific Detector, HPLC/Fl or Vis: High Performance Liquid Chromatograph/Florescence or Visible detector, HPLC/UV: High Performance Liquid Chromatograph/ Ultraviolet detector, IC: Ion Chromatograph, LC/MS: Liquid Chromatograph/Mass Spectrometer.

amines; rather researchers should conduct laboratory tests for media that would be useful for their workplace monitoring program and target compounds.

For the instrumentations of amines, Gas Chromatograph has been widely adopted coupled with Flame Ionization Detector (FID), Nitrogen Phosphorous Detector (NPD), Thermal Energy Analyzer (TED) with nitrogen selective detector, Thermionic Specific Detector (TSD), and Mass Spectrometer (MS). Today High Performance Liquid Chromatography (HPLC) with Ultra Violet (UV) detector, fluorescence detector, visible light detector, Mass Selective Detector (MSD) are also commercially available in advanced laboratories. US-NIOSH recommends Ion Chromatography (IC) for some alkanol compounds[95] and they have also tested HPLC for aromatic amines[100]. Although Hansén *et al.* suggested using isotachophoresis for analysis, it is not well accepted to analyze amine compounds, currently[86, 87].

Mechanism of visual disturbances

Several researchers have attempted to identify the pathophysiology and mechanism of glaucopsia in animal and human experiments. Dernehl found diffuse corneal edema with vesicular fluid collections using slit-lamp microscopy in several Union Carbide workers who had been exposed to excessive levels of amine catalysts[20].

In their animal study, Mellerio & Weale reported that glaucopsia might be related to the Tyndall effect caused by denaturation of proteins in corneal epithelium[43]. Albrecht & Stephenson summarized that two distinct mechanisms, corneal edema and mydriasis with cycloplegia, could be the major reasons for the visual disturbances in response to some amines[6]. Brieger & Hodes, Belin *et al.* Akesson *et al.*, and Järvinen *et al.* supported the occurrences of transient corneal edema[22, 54–56, 101]. Mydriasis and cycloplegia were reported by Watrous *et al.*[3], Dernehel[20], Goldberg & Johnson[60] mainly before the 1960s; however, additional studies did not fully demonstrate the autonomous ganglion effects. Recently, Ballantyne reviewed occupational glaucopsia and concluded that local diffusion of amine vapors into the corneal surface caused epithelial edema with subepithelial microcysts and the water accumulation in the superficial cornea[7]. He also found that the systematic contribution to visual disturbances was small or negligible and that glaucopsia caused by exposure to amines did not cause chronic corneal damage.

Other health effects

These chemicals have demonstrated various effects on human health in addition to glaucopsia due to their chemical and physical characteristics. Some symptoms in humans include eye and respiratory track irritation, asthma, and headache[80, 102–106]. Amines may be causative agents in bronchial hyper-reactivity in PU factory workers. Belin *et al.* argued that isocyanates and amines might be responsible for respiratory symptoms among workers[22]. When the levels of other chemicals, such as isocyanate or formaldehyde, were relatively high during the 1970s and 1980s, apprehension about amines did not attract much attention in some scientific articles[77, 78, 107].

Many studies have demonstrated the irritation effects of amines through human experience and animal testing[77, 78, 108–110]. Among them, some amines may not be found in the 21 names listed for this review due to relatively restricted information. The reference listing from this review may help occupational health researchers conducting studies on these topics (either human occupational studies or animal experiments). The articles referred in this section for animal experiments were also cited by other human glaucopsia studies referenced in this article.

Limitations and future

Despite the enormous effort to gather all articles and reports referenced in important studies, some valuable studies, such as case reports in factories in 1950s to the 1970s, could not be retrieved. Although this kind of limitation does not impart serious restrictions on this review, some information, such as process and hazardous level data, should have been obtained. Another limitation includes that some studies published in other languages, such as German, French, and Japanese might not be reviewed fully. Whether it was a inevitable publication bias for every scientist, some local data may be valuable, particularly if the information came from an advanced country with long-standing foundries and PU foam factories. The full text of some US-NIOSH studies[15, 79, 107] could not be obtained, although abstracts were available. Although the human glaucopsia hazard is a relatively acute hazard and on-site follow-up studies may not be available, long-term epidemiological studies are necessary to detect sequelae from amine exposure and to prevent future risk.

Conclusion

Following the expansion of amine use during the past dozens of years, knowledge about occupational glaucopsia among workers engaged in the epoxy, foundry, and PU foam industries is valuable. Various amines, including TEA and DMEA, are reported to cause ocular hazards mainly creating conditions of diffused corneal edema and vesicular collection of fluid within subepithelial cells of the cornea. These visual effects occur 30 min to several hours after exposure to amines and the symptom last for several hours after termination of vapor exposure. Nevertheless, glaucopsia does not lead to permanent eye damage. The concentration-effect relationships have been established, from which it was inferred that concentration levels at worksites were critical to prevent the hazard. Visual disturbances may be a nuisance and not a life-threatening risk; however, they could predispose workers to occupational accidents, reduce coordinate performance, and impair work efficiency. While chemical manufacturers have been warning about visual disturbance from amines, occupational exposure criteria for many compounds are lacking. Volatility characteristics, such as VP, should be considered when new complex amines are introduced to industrial processes, such as printing shops, to prevent human ocular hazards including irritation effects.

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