Status Report

Staff Review of Five Amine Catalysts in
Spray Polyurethane Foam
09/19/2012

Staff Review of Contract with Versar, Inc (CPSC-D-07-0006)

Melanie B. Biggs, Ph.D., Toxicologist
Directorate for Health Sciences
Phone: 301-504-7858
E-mail: mbiggs@cpsc.gov

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Status Report

UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
4330 EAST WEST HIGHWAY
BETHESDA, MARYLAND 20814

Memorandum

Date: 09/19/2012

TO : Mary Ann Danello, Ph.D., Associate Executive Director, Directorate for Health Sciences

THROUGH: Lori E. Saltzman, M.S., Director, Division Toxicology and Risk Assessment

FROM : Melanie B. Biggs, Ph.D., Toxicologist, Division of Toxicology and Risk Assessment

SUBJECT : Status Report: Staff Review of Five Amine Catalysts in Spray Polyurethane Foam[1]

I. Background

Many homeowners, industries, and governments are using insulating products, such as spray foams, to increase the energy efficiency of their residences and constructed buildings. Homes can be insulated with spray polyurethane foam (SPF) by hiring a contractor to do the work or by homeowners using a do-it-yourself (DIY) kit. SPF is also used by consumers for arts and crafts projects.

The final foam product is formed by an exothermic (heat releasing) chemical reaction between approximately equal amounts of methylene diphenyl diisocyanate (MDI) or MDI-based isocyanates and a mixture of polyols and other chemicals (i.e., catalysts, blowing agents, fire retardants, or surfactants), which are referred to as the A- and the B-sides, respectively. Catalysts promote the reaction between these two sides by helping the polyurethane foam cells develop sufficient strength to maintain their structure to resist collapsing or becoming deformed and completing the reaction or "curing" the finished foam. Most catalysts used in SPF are amine-based with the B-side typically containing 1 to 5% amine catalyst. Respirators and other protective equipment are recommended to minimize exposure to vapors, aerosols, MDI particulates, and other chemicals during the spray application and subsequent operations.

Although there are energy-saving benefits of SPF, there are also significant questions about the potential health effects that this material may have on those applying the foam, as well as the occupants of the buildings treated with SPF. The U.S. Consumer Product Safety Commission (CPSC) has received 27 complaints between 2005 and 2012 from homeowners after SPF was installed by a contractor or by themselves[2]. These complaints include lingering odors in the house, respiratory-related problems (i.e., asthma, coughing), irritation (i.e., eyes, throat), and

[1] These comments are those of the CPSC staff and have not been reviewed or approved by, and may not necessarily reflect the views of, the Commission.
[2] In the U.S., SPF for sale and for export rose 22% between 2008 and 2011 (Durability and Design, 2012).

headaches. In some instances, after SPF was installed in their homes, residents moved out due to the severity of health effects they reportedly experienced.

Initially, CPSC staff focused its attention on the diisocyanates in SPF as the chemicals potentially causing these reported health effects. The constituents that make up the A-side have generally been considered to present the greatest possible health hazard due to the well-known potential of isocyanates to produce respiratory and dermal sensitization (isocyanates are believed to be a leading cause of work-related asthma (NIOSH, 2007)). However, isocyanates are very reactive. Therefore, the odors identified after SPF installation may not be due to the isocyanates but to the chemicals making up the B-side, such as amine catalysts (ACC, 2010). Exposure to airborne concentrations of amine catalysts may result in irritation of the respiratory system, skin, and eyes. Inhalation exposure may also cause a reversible effect known as glaucopsia, "blue haze," or "halovision" in the eyes. Glaucopsia is characterized by clouding or fogging of vision due to swelling of the outer layer of the cornea. Once the exposure is removed, vision is gradually restored within a few hours. In general, exposure limits are not yet established for the majority of the amine catalysts used in SPF systems.

When SPF is applied according to the manufacturer's instructions, the foam achieves a tack-free state when its surface is no longer sticky within a few minutes of application. Depending on the characteristics of the foam, such as the composition of the B-side chemicals, the heat dissipated during the exothermic reaction, and ambient conditions (temperature and humidity), it can take an additional 23 to 72 hours before the foam is fully cured and the optimum physical properties of the foam are achieved. Because some of the compounds in the A- and B-sides are expected to exist unreacted in the foam during this curing time (e.g., certain catalysts and blowing agents), they may potentially be emitted from the installed foam and cause the noted health effects. Also, an improper balance in mixing of the A- and B-sides may also lead to off-gassing of chemicals for an unknown amount of time.

It is typically recommended that entire residential and smaller commercial buildings or portions of large commercial buildings be vacated during the installation of SPF due to the potential hazards caused by these unreacted compounds. However, the consumer complaints received by the agency indicate that this cautionary information is not given to the consumers. Furthermore, SPF, like many other new building materials, can emit low levels of various chemicals for a short period of time following installation. Therefore, the time at which people reoccupy a building following the completion of SPF installation is an important consideration. The manufacturer's suggested reoccupancy times for an interior application using a DIY kit or a two-component, high-pressure SPF is commonly eight and 24 hours, respectively; however, this varies based on the variables mentioned above.

In an effort to begin assessing the available toxicological and exposure data on the amine catalysts found in most SPF formulations in the United States, CPSC staff contracted with Versar, Inc., to review the toxicity literature from the years 2000 to 2011 pertaining to five amine catalysts commonly found in these domestic formulations.

II. Discussion

A. Determination of Five Amine Catalysts

To begin looking at the health effects of amine catalysts in SPF, CPSC staff chose a list of five commonly found catalysts that were obtained from an ASTM SPF working group, *WK30960 - New Practice for Spraying, Sampling, and Packaging Spray Polyurethane Foam Insulation Samples for Environmental Chamber Emissions Testing.* As part of the working group's activities, three generic SPF formulations were designed by the Center for the Polyurethane Industry (CPI) to evaluate the impact of changes in ventilation rates on the concentration of SPF chemical vapor and particulates emitted during SPF application. The generic SPF formulations were created by several experienced members of the working group who provide technical support to their clients. Other generic SPF formulations were available in the literature; however, the group concluded that those did not represent formulations currently in use today. The generic formulations do not belong to any one manufacturer/formulator but have the performance characteristics of typical 0.5 pound, 2 pound, and two component kit SPF formulations.

Therefore, based on these formulations, the following amine catalysts were chosen by CPSC staff for evaluation by Versar:

- N-[2-(dimethylamino)ethyl]-N-methylethanolamine (CASN 2212-32-0);
- N,N,N'N''-Pentamethyldiethylenetriamine (CASN 3030-47-5);
- bis(2-Dimethylaminoethyl)ether (CASN 3033-62-3);
- N-[3-(dimethylamino)propyl]-N,N',N'-trimethyl-1,3-propanediamine (CASN 3855-32-1); and
- Tetramethylimino-bis(propylamine) (TMPT; CASN 6711-48-4).

B. Steps Taken by CPSC Staff

To determine the potential health effects associated with exposure to amine catalysts, CPSC staff reviewed the five reports from Versar, Inc. Four of the five amine catalysts had very limited toxicological or exposure data to review; therefore, data relevant to amine catalyst toxicity is based on the chemical with the most information, bis(2-Dimethylaminoethyl)ether.

The final reports provided by Versar, Inc., on the five amine catalysts of interest are attached in Tab A. [3]

III. Conclusions

CPSC staff used the information provided by Versar, Inc., to determine the toxicological impacts of amine catalyst exposure. Amine catalysts are classified as being tertiary[4] and having basic[5] and nucleophilic[6] properties. Tertiary amines are generally colorless liquids with very distinct

[3] All comments and recommendations received during CPSC clearance and review were reviewed and addressed by Versar.
[4] All three hydrogen atoms are replaced by organic substituents in tertiary amines.
[5] The pH of these chemicals is greater than seven; also known as alkaline.
[6] Having or involving an affinity for a positive charge.

and strong ammonia-like odors (ACC, 2011). Tertiary amines are also more volatile and have a lower boiling point than primary and secondary amines (Albrecht and Stephenson, 1988). Although specific solubility data were not found for these five chemicals, amine catalysts are considered to be very water soluble (Albrecht and Stephenson, 1988). The American Chemistry Council (2010 and 2011) has reported that occupational exposure to amine catalysts may occur through inhalation, skin contact, eye contact, and ingestion. Although ingestion is unlikely in the workplace, the chemical may be inadvertently ingested if an individual eats, drinks, or smokes in areas where SPF chemicals are used.

No toxicity studies were found for n-[3-dimethylamino)propyl]-n,n',n'-trimethyl propanediamine. Some toxicological and exposure data were found for TMPT, n-[2-(dimethylamino)ethyl]-n-methylethanolamine, and 1,1,4,7,7-pentamethyldiethylenetriamine. These animal and human data show skin and eye irritation (Smyth, 1962; 1969; Sidorin et al, 1984, ACC, 2011; and Biosearch Inc., 1974). Bis(2-dimethylaminoethyl)ether was the only chemical with repeat dose toxicological studies; therefore, no-observed-adverse-effect level (NOAEL) and lowest-observed-adverse-effect level (LOAEL) values were determined. Also, it is the only selected amine catalyst with exposure limits established by regulatory and nonregulatory organizations.

From the Versar, Inc., report on bis(2-dimethylaminoethyl)ether, the most sensitive measures of effect in inhalation and dermal toxicity studies were observed in tissues that came in direct contact with it, namely the ocular, dermal, and respiratory tissues in animal inhalation studies and the skin in animal dermal studies. Short-term inhalation studies provided evidence for vacuolar cytoplasmic swelling in the nasal cavities of rats exposed at concentrations as low as 1 ppm for 6 hours/day, 5 days/week for 11 days (Union Carbide Corp., 1989, 1988). A subsequent subchronic-duration study (Union Carbide Corp., 1993a) was conducted over a period of 14 weeks and found vacuolar cytoplasmic swelling in the nasal cavity and swollen periocular tissue (similar to human glaucopsia) at concentrations as low as 0.22 ppm. Other histological changes to the eyes or the upper and lower respiratory tract tissues were observed at 1.25 and 5.8 ppm, respectively, after 14 weeks.

Ninety days of dermal exposure to bis(2-dimethylaminoethyl)ether at 0.7% in distilled water (approximately 2 mg/kg-day) in New Zealand white rabbits showed effects on exposed skin including slight erythema[7] and very slight edema[8]. Also, in females, a significantly increased incidence of epidermal cell vacuolization at the application site was observed. Similar, but more severe effects, were reported for rabbits exposed to the highest dose of bis(2-dimethylaminoethyl)ether (2% or approximately 5 mg/kg-day) (Ballantyne, 1986).

Limited evidence is available for effects on white blood cells by bis(2-dimethylaminoethyl)ether exposure. Short-term inhalation studies (Union Carbide Corp., 1989, 1988) showed significant increases in total leukocyte and neutrophil counts in rats exposed over 11 days at 20 ppm. The neutrophil counts were also increased in males at 10 ppm. In a subchronic inhalation study, total leukocyte counts were unchanged from controls, but neutrophil counts were increased at 6 weeks in males and females (and at 14 weeks in females) at 5.8 ppm.

[7] Redness of skin associated with any skin injury, infection, or inflammation.
[8] Swelling caused by fluid in the body's tissues.

Rabbits that were topically administered 5% or 10% bis(2-dimethylaminoethyl)ether (about 15 or 33 mg/kg-day, respectively) over 11 days showed increased relative kidney weights and hydropic[9] degeneration and kidney tubular dilation. Increased relative kidney weight and vacuolar swelling of the collecting ducts were also found in pregnant rabbits administered 10% bis(2-dimethylaminoethyl)ether (about 24 mg/kg-day) on gestation days (GDs) 6 to 18 (Tyl et al., 1986; Union Carbide Corp., 1985). However, rats exposed via the inhalation route at up to 5.8 ppm for 14 weeks and rabbits exposed to up to 2% (about 5 mg/kg-day) for 90 days did not show signs of kidney damage (Union Carbide Corp., 1993a; Ballantyne et al., 1986; Union Carbide Corp., 1984b). Other kidney effects, such as changes in urinalysis parameters, were observed in some studies; however, they are of uncertain toxicological significance due to rat dehydration concomitant during the study (Union Carbide Corp., 1989, 1988).

No effects on implanted embryos or fetal loss were observed after topical gestational exposure of pregnant rabbits to 2-dimethylaminoethyl)ether at 10% (about 24 mg/kg-day) on GD (gestational day) 6–18. However, some fetotoxicity was indicated by significant decreases in fetal body weights (males and females combined and females alone) per litter compared to controls (Tyl et al., 1986; Union Carbide Corp., 1985). No significant effects were noted on the incidence of malformations (external, visceral, skeletal, or total) in the offspring of exposed rabbits compared to untreated or treated controls**.**

Table 1 contains NOAEL and LOAEL values for organ-specific endpoints for bis(2-dimethylaminoethyl)ether, which were derived from repeat-dose inhalation toxicity studies of Union Carbide Corp. (1988, 1989, 1993a) in rats, dermal toxicity studies of Ballantyne et al. (1986) and Union Carbide Corp. (1984b) in rabbits, and developmental toxicity studies of Tyl et al. (1986) and Union Carbide Corp. (1985) in rabbits.

For the inhalation pathway, the data identified a LOAEL of 0.22 ppm and no NOAEL based on a significantly increased incidence of cell vacuolization in the nasal cavity of male and female rats exposed for 14 weeks. For the dermal pathway, exposure to bis(2-dimethylaminoethyl)ether in these studies produced NOAEL and LOAEL values of 2.5 and 5% (8 and 15 mg/kg-day), respectively for significant signs of dermal irritation (erythema and edema), decreased body weight (males), and increased absolute and relative kidney weights. Maternal NOAEL and LOAEL values of 1 and 5% (2 and 12 mg/kg-day), respectively were identified for significantly increased incidences of dermal irritation (erythema and edema). Developmental NOAEL and LOAEL values of 5 and 10% (12 and 24 mg/kg-day), respectively were identified based on decreased mean fetal body weights (of females alone and males and females combined). No cancer bioassays or initiation/promotion studies were located. The available genotoxicity studies showed negative or equivocal results.

[9] Containing an excess of water or watery fluid.

Table 1. Summary of NOAELs/LOAELs Identified for Bis(2-dimethylaminoethyl)ether by Organ System							
Species (Gender)	**Exposure Route**	**Dose (Number of Animals per Dose Group)**	**Dose Duration**	**Effect Category**	**Toxicological Endpoint**	**Toxicological Basis**	**Citation**
Sprague-Dawley rats (M + F)	Inhalation	10/sex/group	0, 20, 40, or 90 ppm for 6 hrs/d 5 d/wk for 11 d (including 9 d of exposure)	General	NOAEL = None LOAEL = 20 ppm	Decreased food consumption (M); decreased body weights; swollen eyes	Union Carbide Corp., 1988
				Respiratory	NOAEL = None LOAEL = 20 ppm	Histopathological lesions of the upper and lower respiratory tract (vacuolar cytoplasmic swelling)	
				Hematology	NOAEL = None LOAEL = 20 ppm	Increased leukocytes and neutrophils; increased lymphocytes and monocytes (F)	
Sprague-Dawley rats (M + F)	Inhalation	10/sex/group	0, 1, 10, or 20 ppm for 6 hrs/d 5 d/wk for 11 d (including 9 d of exposure)	General	NOAEL = 10 ppm LOAEL = 20 ppm	Decreased body weight (>10%); decreased food consumption	Union Carbide Corp., 1989
				Respiratory	NOAEL = None LOAEL = 1 ppm	Epithelial cell vacuolization of the nasal cavity	
				Hematology	NOAEL = 1 ppm LOAEL = 10 ppm	Increased neutrophils and decreased platelets (M)	
				Renal	NOAEL = 10 ppm LOAEL = 20 ppm	Increased osmolality and decreased total volume and pH; increased creatinine and potassium and decreased creatinine clearance (M)	
Sprague-Dawley rats (M + F)	Inhalation	15/sex/group	0, 0.22, 1.25, or 5.8 ppm for 6 hrs/d 5 d/wk for 90 d	General	NOAEL = 1.25 ppm LOAEL = 5.8 ppm	Decreased body weight (M)	Union Carbide Corp., 1993a
				Respiratory	NOAEL = None **LOAEL = 0.22 ppm**	Epithelial cell vacuolization of the nasal cavity	
				Hematology	NOAEL = None LOAEL = 5.8 ppm	Increased neutrophils	

Table 1. Summary of NOAELs/LOAELs Identified for Bis(2-dimethylaminoethyl)ether by Organ System							
Species (Gender)	**Exposure Route**	**Dose (Number of Animals per Dose Group)**	**Dose Duration**	**Effect Category**	**Toxicological Endpoint**	**Toxicological Basis**	**Citation**
New Zealand White rabbit (M + F)	Dermal	5/sex/group	0, 2.5, 5, or 10% in water (~0, 8, 15, or 33 mg/kg-d) for 6 hrs/d 5 d/wk for 11 d (including 9 d of exposure)	General	**NOAEL = 8 mg/kg-d** **LOAEL = 15 mg/kg-d**	Decreased food consumption and body weight loss (M)	Ballantyne et al., 1986; Union Carbide Corp., 1984b
				Dermal	**NOAEL = 8 mg/kg-d** **LOAEL = 15 mg/kg-d**	Erythema and edema	
				Renal	**NOAEL = 8 mg/kg-d** **LOAEL = 15 mg/kg-d**	Increased absolute and relative kidney weights	
New Zealand White rabbit (M + F)	Dermal	10/sex/group	0, 0.2, 0.7, or 2% in water (~0, 0.5, 2, or 5 mg/kg-d) for 6 hrs/d 5 d/wk for 90 d	General	NOAEL = 5 mg/kg-d LOAEL = None	No effects on food consumption or body weights.	Ballantyne et al., 1986; Union Carbide Corp., 1984b
				Dermal	NOAEL = None LOAEL = 2 mg/kg-d	Epidermal cell vacuolization	
New Zealand White rabbit (F)	Dermal	22/group	0, 1, 5, or 10% in water (~0, 2, 12, or 24 mg/kg-d) for 6 hrs/d 5 d/wk on GDs 6 to 18	General	NOAEL = 12 mg/kg-d LOAEL = 24 mg/kg-d	Decreased body weight gain on GDs 6 -29	Tyl et al., 1986; Union Carbide Corp., 1985
				Dermal	**NOAEL = 2 mg/kg-d** **LOAEL = 12 mg/kg-d**	Erythema and edema	
				Renal	NOAEL = 12 mg/kg-d LOAEL = 24 mg/kg-d	Increased relative kidney weight accompanied by increased vacuolar cytoplasmic swelling in the collecting ducts	
				Development	**NOAEL = 12 mg/kg-d** **LOAEL = 24 mg/kg-d**	Decreased fetal body weights (F and M+F)	

GD = gestation day
BOLD = chosen LOAELs and NOAELs for specific pathways and endpoints

In general, exposure limits in humans are not yet established for the majority of the amine catalysts used in SPF systems. Bis(2-dimethylaminoethyl)ether is one of the few polyurethane amine catalysts that has been assigned Occupational Exposure Limits (OELs) by regulatory and nonregulatory organizations (Table 2) (ACC, 2011). This includes the Ontario Ministry of Labour in Canada, which has established enforceable OELs. The U.S. Occupational Safety and Health Administration (OSHA) has also set enforceable permissible exposure limits (PELs) to protect workers. Other organizations that have established OELs include the American Conference of Government Industrial Hygienists (ACGIH), which has developed threshold limit values (TLVs). TLVs are generally provided as guidance and are not legally enforceable. The OELs, PELs, and TLVs can be provided as a time-weighted average (TWA) or short-term exposure limits (STELs). A TWA is the average exposure over a certain period of time, which may be an 8-hour day. The STEL is the average exposure over a 15-minute period that should not be exceeded during a workday even if the 8-hour TWA is within the criteria (ACC, 2011).

The ACGIH has established a TWA of 0.05 ppm (Skin) and a STEL of 0.15 ppm (Skin) (ACC, 2011) for bis(2-dimethylaminoethyl)ether. These are based on the potential, significant contribution to the overall exposure by the cutaneous route including mucous membranes and the eyes by contact with vapors, liquids, and solids (ACGIH, 2005).

Table 2. Permissible Exposure Levels and Threshold Limit Values of Some Polyurethane Amine Catalysts

Amine Catalyst	CASRN	Exposure Limit (Source)			
		PEL	STEL	TLV	TWA
Dimethylcyclohexylamine, N,N-	98-94-2	NR	5 ppm (Ontario)	NR	NR
N-ethylmorpholine	100-74-3	20 ppm Skin[2] (OSHA)	NR	NR	5 ppm Skin[1] (ACGIH)
Triethanolamine	102-71-6	NR	NR	NR	5 mg/m^3 (ACGIH)
Dimethylamino ethanol, 2-	108-01-0	NR	6 ppm (Ontario)	NR	3 ppm (Ontario)
N,N-Dimethylaminopropylamine	109-55-7	NR	NR	NR	0.5 ppm (ACGIH)
Diethanolamine	111-42-2	NR	NR	1 mg/m^3 (ACGIH)	3 ppm (ACGIH)
Triethylamine	121-44-8	25 ppm (OSHA)	3 ppm (ACGIH)	NR	NR
Triethylenediamine	280-57-9	NR	NR	NR	1 ppm Skin[1] (Ontario)
Bis (2-Dimethylaminoethyl) ether	3033-62-3	NR	0.15 ppm Skin[1] (ACGIH)	NR	0.05 ppm Skin[1] (ACGIH)

[1] Potential for significant contribution to overall exposure by skin.
[2] Substance that may be absorbed through the skin.

PEL = permissible exposure limits
STEL = short-term exposure limits
OSHA = Occupational Safety and Health Administration
ACGIH = American Conference of Government Industrial Hygienists
Ontario = Ontario Ministry of Labour in Canada
NR = Not reported
TLV = threshold limit values
TWA = time-weighted average

Reference: American Chemistry Council (2011)

IV. **Staff Recommendations**

Staff finds the resulting reports sufficient in describing the toxicological and exposure effects to the five amine catalysts selected for use in SPF. Due to the lack of toxicological information for four of the amines, their properties and structures were compared to bis(2-dimethylaminoethyl)ether. This approach assumes that the structure of a molecule contains the features responsible for its physical, chemical, and biological properties. These compounds are aliphatic tertiary amines in the liquid state with low molecular weights ranging from 146–201 g/mol. Boiling points range from 128 to 210˚C and densities between 0.841 to 0.914 g/cm^3. They differ in the number of carbon and hydrogen atoms, and two of the compounds contain oxygen atoms; however, their overall structures are similar. Given the similarities in structure and properties, CPSC staff believes that it is reasonable to extrapolate the toxicity and exposure information obtained for bis(2-dimethylaminoethyl)ether to other amine catalysts. Because this report looked at only five amines from a list of many potentially used in SPF, other health effects may not be characterized here.

The toxicity of these compounds includes ocular, dermal, and respiratory tissue irritation in laboratory animals and humans. Inhalation exposure in humans may also cause a reversible effect known as glaucopsia, "blue haze," or "halovision" in the eyes. Glaucopsia is characterized by clouding or fogging of vision due to swelling of the outer layer of the cornea. The CPSC has received complaints including lingering odors in the house, respiratory-related problems (i.e., asthma, coughing), irritation (i.e., eyes, throat), and headaches after SPF was installed in consumers' homes. These effects are similar to those discussed for amine exposure in both laboratory animals and humans; and therefore, exposure to amines may be providing some of the effects from SPF exposure. However, given that SPF is a mixture of MDI or MDI-based isocyanates, polyols, catalysts, blowing agents, fire retardants, and/or surfactants, amines may not be the only chemical class producing the reported adverse health effects.

Health-based exposure limits are not available for consumers, and occupational exposure limits are not yet established for the majority of amine catalysts used in SPF. Also, using occupational exposure limits for the general population may not be protective due to factors, such as sensitive populations and exposure duration differences. In the past two years, CPSC staff, along with other members of the Federal Working Group on SPF[10], have met with members of the American Chemistry Council who have provided exposure data on some high- and low-pressure SPF systems. However, staff and other federal partners are not satisfied with the robustness of this data. To determine exposure limits for consumers, CPSC staff suggest performing exposure studies by varying exposure times and distances from spray sources with federal partners including the EPA and NIOSH. These results will provide staff with additional exposure data to make determinations of potential health effects for consumers with respect to SPF insulation.

[10] The Federal Working Group on Spray Polyurethane Foam includes CPSC, NIOSH, OSHA, and EPA. It arose from EPA's Design for the Environment Program and has been meeting regarding SPF insulation for more than three years.

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Union Carbide Corp. (1993a) Support: fourteen-week vapor inhalation study of bis (2-dimethylaminoethyl) ether (Niax catalyst a-99) on rats. Submitted under TSCA Section 8E; EPA Document No. 89931000030; NTIS No. OTS 0513398-4.

TAB A: Versar Reports on Five Amine Catalysts Commonly found in Spray Polyurethane Foam Formulations

TAB A

CASN 2212-32-0
N-[2-(dimethylamino)ethyl]-N-methylethanolamine

REVISED DRAFT

TOXICITY REVIEW FOR N-[2-(DIMETHYLAMINO)ETHYL]-N-METHYLETHANOLAMINE (CASRN 2212-32-0)

Contract No. CPSC-D-06-0006
Task Order 015

Prepared by:

Versar Inc.
6850 Versar Center
Springfield, VA 22151

and

SRC, Inc.
7502 Round Pond Road
North Syracuse, NY 13212

Prepared for:

Melanie B. Biggs, Ph.D.
U.S. Consumer Product Safety Commission
4330 East West Highway
Bethesda, MD 20814

June 15, 2012

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TOXICITY REVIEW FOR N-[2-(DIMETHYLAMINO)ETHYL]-N-METHYLETHANOLAMINE (CASRN 2212-32-0)

LIST OF ABBREVIATIONS AND ACRONYMS

ACC	American Chemistry Council
ACGIH	American Conference of Government Industrial Hygienists
CPSC	Consumer Product Safety Commission
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
MDI	methylene diphenyl diisocyanate
NOAEL	no-observed-adverse-effect level
OEL	occupational exposure limit
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
SPF	spray polyurethane foam
STEL	short-term exposure limit
TDI	toluene diisocyanate
TLV	threshold limit value
TWA	time-weighted average

TOXICITY REVIEW FOR
N-[2-(DIMETHYLAMINO)ETHYL]-N-METHYLETHANOLAMINE
(CASRN 2212-32-0)

1. INTRODUCTION

This report summarizes available data on the identity, physicochemical properties, manufacture, supply, use, toxicity, and exposure information on n-[2-(dimethylamino)ethyl]-n-methylethanolamine. This assessment was prepared from several review articles (ACC, 2010; ACC, 2011; PubChem, 2005).

N-[2-(dimethylamino)ethyl]-N-methylethanolamine is an amine catalyst primarily used in the production of spray polyurethane foam (SPF). SPF is an insulation or sealant product, which is formed via an exothermic chemical reaction between the A-side and B-side chemicals (ACC, 2010). The A-side consists of chemicals such as methylene diphenyl diisocyanate (MDI) or toluene diissocyante (TDI). Polyols are part of the B-side chemicals, which also include amine and/or metal catalysts, blowing agents, surfactants, and flame retardants. Amine and/or metal catalysts are used to promote the reaction between polyols and A-side chemicals, which help polyurethane foam cells develop sufficient strength to maintain their structure and resist collapsing (ACC, 2010). Recent concerns have emerged regarding potential health effects of amine catalysts in SPF due to their potential to cause respiratory-related problems, irritation to skin and eyes, temporary vision problems, and headaches (ACC, 2010).

2. IDENTITY and PHYSICOCHEMICAL CHARACTERISTICS

This section highlights the available identity and key physicochemical properties of n-[2-(dimethylamino)ethyl]-n-methylethanolamine. Amine catalysts are a derivative of ammonia and are primary, secondary, or tertiary amines depending if one or more of the three hydrogen atoms of ammonia are replaced with hydrocarbon groups. N-[2-(dimethylamino)ethyl]-N-methylethanolamine is classified as being tertiary and has basic and nucleophilic properties.

Tertiary amines are generally colorless liquids with very distinct and strong ammonia-like odors (ACC, 2011). Tertiary amines are also more volatile and have a lower boiling point than primary and secondary amines (Albrecht and Stephenson, 1988). Although specific solubility data were not found for n-[2-(dimethylamino)ethyl]-n-methylethanolamine, amine catalysts are considered to be very water soluble (Albrecht and Stephenson, 1988).

The identity and physicochemical properties of n-[2-(dimethylamino)ethyl]-n-methylethanolamine are provided in Tables 1 and 2.

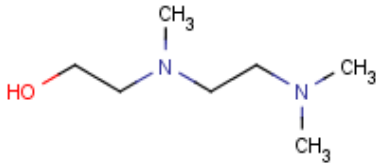
Table 1. Names, Structural Descriptors, and Molecular Formulas of N-[2-(Dimethylamino)ethyl]-N-methylethanolamine (ACC, 2011; PubChem, 2005)	
CAS Number	2212-32-0
Chemical Name	N-[2-(Dimethylamino)ethyl]-N-methylethanolamine
Trade Name	DABCO T; TOYOCAT RX55
Molecular Formula	C7H18N2O
Structural Formula	
Molecular Weight	146.23062 g/mol
Synonyms	2-((2-(Dimethylamino)ethyl)methylamino)-ethanol Ethanol, 2-((2-(dimethylamino)ethyl)methylamino)-
Purity/Impurities/Additives	No data

Table 2. Physicochemical Properties of N-[2-(Dimethylamino)ethyl]-N-methylethanolamine	
Property	**Value**
Physical state	Colorless to yellow liquid with amine-like odor (BASF, 2010)
Melting point	<-70°C (BASF, 2010)
Boiling point	210°C (BASF, 2010); 207°C (Sigma-Aldrich, 2010)
Density	0.914 g/cm^3 (15°C; BASF, 2010); 0.908 g/cm^3 (20°C; BASF, 2010); 0.904 g/cm^3 (25°C; Sigma-Aldrich, 2010)
Vapor pressure	1.3 mbar (21°C; BASF 2010)
Water solubility	No data
Partition coefficient n-octanol/water (log Kow)	<0 (25°C; BASF, 2010)
Henry's law constant	No data
Flash point (open cup)	85°C (BASF, 2010); 87 °C (Sigma-Aldrich, 2010)

3. MANUFACTURE, SUPPLY, AND USE

Manufacture

Amine catalysts are produced from ammonia by replacing one or more hydrogen atoms with alkyl groups or nonacidic radicals containing hydrogen and carbon atoms (ACC, 2011). An Internet search was performed to identify companies that manufacture n-[2-(dimethylamino)ethyl]-n-methylethanolamine. A search performed on the Alibaba Group website (2011) listed Jiangdu Dajiang Chemical Industrial Co. Ltd as a manufacturer of n-[2-(dimethylamino)ethyl]-n-methylethanolamine in China. BASF (2011) was also listed as a

manufacturer of n-[2-(dimethylamino)ethyl]-n-methylethanolamine in Germany and the USA under the brand name Lupragen® N400. However, Jiangdu Dajiang stated on their company profile that they supply n-[2-(dimethylamino)ethyl]-n-methylethanolamine to several chemical companies such as DOW, Huntsman, BASF and Momentive ECT. Therefore, it is unclear whether BASF actually manufactures n-[2-(dimethylamino)ethyl]-n-methylethanolamin or if they purchase this amine catalyst from a manufacturing company like Jiangdu Dajiang Chemical.

Additional manufacturing data specific to n-[2-(dimethylamino)ethyl]-n-methylethanolamine were not found.

Supply

Based on information found on the Alibaba website (2011), it appears that companies such as DOW, Huntsman, BASF and Momentive ECT may be suppliers of n-[2-(dimethylamino)ethyl]-n-methylethanolamine. However, this information has not been confirmed.

Additional supply data specific to n-[2-(dimethylamino)ethyl]-n-methylethanolamine were not found.

Use

Amine catalysts are primarily used in the production of polyurethane foam to promote the reaction between polyols and A-side chemicals. The American Chemistry Council (2010) reported that this reaction helps polyurethane foam cells develop sufficient strength to maintain their structure to resist collapsing or becoming deformed, and also helps with the completion of the reaction or “cure” in the finished foam. Amine catalysts are typically 0.1 to 5.0 percent of a polyurethane formulation (ACC, 2011). Although metal catalysts are also used in polyurethane foam, most catalysts used in SPF are amine based. N-[2-(dimethylamino)ethyl]-N-methylethanolamine is a highly efficient amine blowing catalyst and has been used in flexible and rigid polyurethane systems (Dajiang Chemical, 2011). It readily reacts into the urethane network due to its reactive hydroxyl group, which provides the added benefit of low residual odor (Dajiang Chemical, 2011).

4. TOXICOKINETICS

No toxicokinetic studies were located for n-[2-(dimethylamino)ethyl]-n-methylethanolamine.

5. HAZARD INFORMATION

Exposure to the B-side chemicals can cause irritation of the respiratory tract, causing cough, sore throat, difficulty breathing, and runny nose (ACC, 2010). Inhalation of some amine catalyst vapors can temporarily cause vision to become foggy or blurry, and halos may appear around bright objects such as lights (ACC, 2010). Skin contact may cause moderate to severe irritation and burns, from redness and swelling to painful blistering, ulceration, and chemical burns (ACC, 2010). Amine catalysts can also irritate the eyes and may cause the following symptoms at low concentrations: corneal swelling without pain; blurred or "foggy" vision with a blue tint; and a halo phenomenon effect around lights. Higher vapor concentrations or direct contact with the liquid amines may result in severe irritation and tissue injury (ACC, 2011). If amines are ingested, this may result in severe irritation, ulceration, or burns of the mouth, throat, esophagus, and gastrointestinal tract. Other serious symptoms may include pain in the chest or abdomen, nausea, bleeding of the throat and gastrointestinal tract, diarrhea, dizziness, thirst, circulatory collapse, coma, and even death (ACC, 2011).

ACUTE DOSE TOXICITY

5.1. Acute Oral Toxicity

A brief summary of acute toxicity information for n-[2-(dimethylamino)ethyl]-n-methylethanolamine reported that the oral LD_{50} in rats ranged from 1580 to 2520 mg/kg (ACC, 2011). No further information was provided.

5.2. Acute Dermal Toxicity

ACC (2011) reported that the dermal LD_{50} for n-[2-(dimethylamino)ethyl]-n-methylethanolamine in the rabbit was >1800 mg/kg. No further information was provided.

5.3. Acute Inhalation Toxicity

ACC (2011) reported a 1-hour inhalation LC_{50} of 1670 ppm for n-[2-(dimethylamino)ethyl]-n-methylethanolamine in rats. No further information was provided.

5.4. Primary Skin Irritation

N-[2-(dimethylamino)ethyl]-N-methylethanolamine was reported to be a severe skin irritant (ACC, 2011). No further information was provided.

5.5. Primary Eye Irritation

Instillation of 0.1 ml of n-[2-(dimethylamino)ethyl]-n-methylethanolamine (purity not reported) into the right eyes of six young adult albino rabbits (the left eyes served as untreated controls) produced severe ocular irritation, based on ocular examinations of the unwashed eyes at 1, 24, 48, and 72 hours, and 5 and 7 days after instillation of the chemical (Biosearch Inc., 1974). The chemical was also reported to be a severe eye irritant by ACC (2011), although no further information was provided.

REPEAT DOSE TOXICITY

No repeat dose toxicity studies were located for n-[2-(dimethylamino)ethyl]-n-methylethanolamine.

6. EXPOSURE

The American Chemistry Council (2010 and 2011) has reported that occupational exposure to amine catalysts may occur through inhalation, skin contact, eye contact, and ingestion. Although ingestion is unlikely in the workplace, the chemical may be inadvertently ingested if an individual eats, drinks, or smokes in areas where SPF chemicals are used.

In general, exposure limits are not yet established for the majority of the amine catalysts used in SPF systems. Only a few polyurethane amine catalysts have been assigned Occupational Exposure Limits (OELs) by regulatory and non-regulatory organizations (ACC, 2011) (Table 3). This includes the Ontario Ministry of Labour in Canada, which has established enforceable OELs. The U.S. Occupational Safety and Health Administration (OSHA) has also set enforceable permissible exposure limits (PELs) to protect workers. Other organizations that have

established OELs include the American Conference of Government Industrial Hygienists (ACGIH), which has developed threshold limit values (TLVs). TLVs are generally provided as guidance and are not legally enforceable. The OELs, PELs, and TLVs can be provided as a time-weighted average (TWA) or short-term exposure limits (STELs). A TWA is the average exposure over a certain period of time, which may be an 8-hour day. The STEL is the average exposure over a 15 minute period that should not be exceeded during a workday even if the 8-hour TWA is within the criteria (ACC, 2011).

Table 3. Permissible Exposure Levels and Threshold Limit Values of Some Polyurethane Amine Catalysts

Amine Catalyst	CASRN	Exposure Limit (Source)			
		PEL	STEL	TLV	TWA
Dimethylcyclohexylamine, N,N-	98-94-2	NR	5 ppm (Ontario)	NR	NR
N-ethylmorpholine	100-74-3	20 ppm Skin[2] (OSHA)	NR	NR	5 ppm Skin[1] (ACGIH)
Triethanolamine	102-71-6	NR	NR	NR	5 mg/m^3 (ACGIH)
Dimethylamino ethanol, 2-	108-01-0	NR	6 ppm (Ontario)	NR	3 ppm (Ontario)
N,N-Dimethylaminopropylamine	109-55-7	NR	NR	NR	0.5 ppm (ACGIH)
Diethanolamine	111-42-2	NR	NR	1 mg/m^3 (ACGIH)	3 ppm (ACGIH)
Triethylamine	121-44-8	25 ppm (OSHA)	3 ppm (ACGIH)	NR	NR
Triethylenediamine	280-57-9	NR	NR	NR	1 ppm Skin[1] (Ontario)
Bis (2-Dimethylaminoethyl) ether	3033-62-3	NR	0.15 ppm Skin[1] (ACGIH)	NR	0.05 ppm Skin[1] (ACGIH)

[1] Potential for significant contribution to overall exposure by skin.
[2] Substance which may be absorbed through the skin.

PEL = permissible exposure limit
STEL = short-term exposure limit
TLV = threshold limit value
TWA = time-weighted average
OSHA = Occupational Safety and Health Administration
ACGIH = American Conference of Government Industrial Hygienists
Ontario = Ontario Ministry of Labour in Canada
NR = Not reported

Reference: American Chemistry Council (2011)

Exposure data specific to n-[2-(dimethylamino)ethyl]-n-methylethanolamine were not found for consumer or general populations.

7. DISCUSSION

Overall, very few toxicological and exposure studies on n-[2-(dimethylamino)ethyl]-n-methylethanolamine were found during this assessment. The current literature is also limited on physicochemical, manufacture, supply, and use information.

Toxicity data associated with n-[2-(dimethylamino)ethyl]-n-methylethanolamine are limited to a single primary eye irritation study, which identified this compound as a severe ocular irritant, and a summary table that also identified the chemical as a severe skin irritant. This summary table reported lethal dose levels for acute oral, dermal, and inhalation exposures without providing any supporting information. Absence of any repeat dose toxicity studies precludes the identification of no-observed-adverse-effect level (NOAEL) or lowest-observed-adverse-effect level (LOAEL) values for reproductive, developmental, or repeated-dose systemic toxicity.

Only general occupational hazard and exposure data were found on amine catalysts. However, no exposure data associated with n-[2-(dimethylamino)ethyl]-n-methylethanolamine were found for consumer or general populations.

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CASN 3030-47-5
N,N,N’N’N’’-Pentamethyldiethylenetriamine

DRAFT

TOXICITY REVIEW FOR 1,1,4,7,7-PENTAMETHYLDIETHYLENETRIAMINE (CASRN 3030-47-5)

Contract No. CPSC-D-06-0006
Task Order 015

Prepared by:

Versar Inc.
6850 Versar Center
Springfield, VA 22151

and

SRC, Inc.
7502 Round Pond Road
North Syracuse, NY 13212

Prepared for:

Melanie B. Biggs, Ph.D.
U.S. Consumer Product Safety Commission
4330 East West Highway
Bethesda, MD 20814

June 15, 2012

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LIST OF ABBREVIATIONS AND ACRONYMS

ACC	American Chemistry Council
ACGIH	American Conference of Government Industrial Hygienists
CI	confidence interval
CPSC	Consumer Product Safety Commission
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
MDI	methylene diphenyl diisocyanate
NOAEL	no-observed-adverse-effect level
OEL	occupational exposure limit
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
SPF	spray polyurethane foam
STEL	short-term exposure limit
TDI	toluene diisocyanate
TLV	threshold limit value
TWA	time-weighted average

TOXICITY REVIEW FOR 1,1,4,7,7-PENTAMETHYLDIETHYLENETRIAMINE (CASRN 3030-47-5)

1. INTRODUCTION

This report summarizes available data on the identity, physicochemical properties, manufacture, supply, use, toxicity, and exposure information on 1,1,4,7,7-pentamethyldiethylenetriamine. This assessment was prepared from several review articles (ACC, 2010; ACC, 2011; PubChem, 2005).

1,1,4,7,7-Pentamethyldiethylenetriamine is an amine catalyst primarily used in the production of spray polyurethane foam (SPF). SPF is an insulation or sealant product, which is formed via an exothermic chemical reaction between the A-side and B-side chemicals (ACC, 2010). The A-side consists of chemicals such as methylene diphenyl diisocyanate (MDI) or toluene diissocyante (TDI). Polyols are part of the B-side chemicals, which also include amine and/or metal catalysts, blowing agents, surfactants, and flame retardants. Amine and/or metal catalysts are used to promote the reaction between polyols and A-side chemicals, which help polyurethane foam cells develop sufficient strength to maintain their structure and resist collapsing (ACC, 2010). Recent concerns have emerged regarding potential health effects of amine catalysts in SPF due to their potential to cause respiratory-related problems, irritation to skin and eyes, temporary vision problems, and headaches (ACC, 2010).

2. IDENTITY and PHYSICOCHEMICAL CHARACTERISTICS

This section highlights the available identity and key physicochemical properties of 1,1,4,7,7-pentamethyldiethylenetriamine. Amine catalysts are a derivative of ammonia and are primary, secondary, or tertiary amines depending if one or more of the three hydrogen atoms of ammonia are replaced with hydrocarbon groups. 1,1,4,7,7-Pentamethyldiethylenetriamine is classified as tertiary and has basic and nucleophilic properties.

Tertiary amines are generally colorless liquids with very distinct and strong ammonia-like odors (ACC, 2011). Tertiary amines are also more volatile and have lower boiling points than primary and secondary amines (Albrecht and Stephenson, 1988). Although specific solubility data were not obtained for 1,1,4,7,7-pentamethyldiethylenetriamine, amine catalysts are considered to be very water soluble (Albrecht and Stephenson, 1988).

The identity and physicochemical properties of 1,1,4,7,7-pentamethyldiethylenetriamine are provided in Tables 1 and 2.

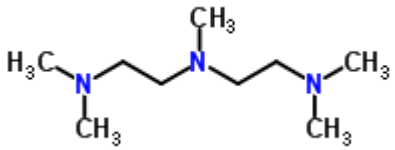
Table 1. Names, Structural Descriptors, and Molecular Formulas of 1,1,4,7,7-Pentamethyldiethylenetriamine (ACC, 2011; PubChem, 2005)	
CAS Number	3030-47-5
Chemical Name	1,1,4,7,7-Pentamethyldiethylenetriamine
Trade Name	POLYCAT 5; TOYOCAT DT; JEFFCAT PMDETA
Molecular Formula	C9H23N3
Structural Formula	
Molecular Weight	173.29902 g/mol
Synonyms	PMDT PMDTA N,N,N',N',N''-Pentamethyldiethylenetriamine N,N,N',N'',N''-Pentamethyldiethylenetriamine Pentamethyldiethylenetriamine
Purity/Impurities/Additives	No data

Table 2. Physicochemical Properties of 1,1,4,7,7-Pentamethyldiethylenetriamine	
Property	**Value**
Physical state	Colorless liquid (Chemical Book, 2008)
Melting point	<-20 ºC (BASF, 2011a)
Boiling point	199 ºC (BASF, 2011a)
Density	0.839 g/cm3 (20ºC; Chemical Book, 2008)
Vapor pressure	No data
Water solubility	No data
Partition coefficient n-octanol/water (log Kow)	No data
Henry's law constant	No data
Flash point (open cup)	53ºC (Chemical Book, 2008)

3. MANUFACTURE, SUPPLY, AND USE

Manufacture

Amine catalysts are produced from ammonia by replacing one or more hydrogen atoms with alkyl groups or nonacidic radicals containing hydrogen and carbon atoms (ACC, 2011). An Internet search was performed to identify companies that manufacture 1,1,4,7,7-pentamethyldiethylenetriamine. The Alibaba Group (2011) website listed four manufacturers of 1,1,4,7,7-pentamethyldiethylenetriamine in China. The names of the manufacturing companies

are Jiangdu Dajiang Chemical Industrial Co. Ltd., Jiangxi Dongxu Chemical Technology Co. Ltd., Shanghai Richem International Co. Ltd, and Shijiazhuang Sincere Chemicals Co. Ltd. The website also provided information on the manufacturing company ZX CHEMTECH, which produces 1,1,4,7,7-pentamethyldiethylenetriamine in the USA. Another search revealed that BASF (2011b) manufactures 1,1,4,7,7-pentamethyldiethylenetriamine in Germany and the USA under the brand name Lupragen® N301. However, information found on the Alibaba website suggests that Jiangdu Dajiang supplies amine catalysts to several chemical companies such as DOW, Huntsman, BASF and Momentive ECT. Therefore, it is unclear whether BASF actually manufactures 1,1,4,7,7-pentamethyldiethylenetriamine or if they purchase this amine catalyst from a manufacturing company like Jiangdu Dajiang Chemical.

Additional manufacturing data specific to 1,1,4,7,7-pentamethyldiethylenetriamine were not found.

Supply

Based on information found on the Alibaba website (2011), it appears that companies such as DOW, Huntsman, BASF and Momentive ECT may be suppliers of 1,1,4,7,7-pentamethyldiethylenetriamine. However, this information has not been confirmed.

Additional supply data specific to 1,1,4,7,7-pentamethyldiethylenetriamine were not found.

Use

Amine catalysts are primarily used in the production of polyurethane foam to promote the reaction between polyols and A-side chemicals. The American Chemistry Council (2010) reported that the reaction helps polyurethane foam cells develop sufficient strength to maintain their structure to resist collapsing or becoming deformed, and also helps with the completion of the reaction or "cure" in the finished foam. Amine catalysts are typically 0.1 to 5.0 percent of a polyurethane formulation (ACC, 2011). Although metal catalysts are also used in polyurethane foam, most catalysts used in SPF are amine based. 1,1,4,7,7-Pentamethyldiethylenetriamine can be used in flexible and rigid polyurethane foam applications (Dajiang Chemical, 2011).

4. TOXICOKINETICS

No toxicokinetic studies were located for 1,1,4,7,7-pentamethyldiethylenetriamine.

5. HAZARD INFORMATION

Exposure to the B-side chemicals can cause irritation of the respiratory tract, causing cough, sore throat, difficulty breathing, and runny nose (ACC, 2010). Inhalation of some amine catalyst vapors can temporarily cause vision to become foggy or blurry, and halos may appear around bright objects such as lights (ACC, 2010). Skin contact may cause moderate to severe irritation and burns, from redness and swelling to painful blistering, ulceration, and chemical burns (ACC, 2010). Amine catalysts can also irritate the eyes and may cause the following symptoms at low concentrations: corneal swelling without pain; blurred or "foggy" vision with a blue tint; and a halo phenomenon effect around lights. Higher vapor concentrations or direct contact with the liquid amines may result in severe irritation and tissue injury (ACC, 2011). If amines are ingested, this may result in severe irritation, ulceration, or burns of the mouth, throat, esophagus, and gastrointestinal tract. Other serious symptoms may include pain in the chest or abdomen, nausea, bleeding of the throat and gastrointestinal tract, diarrhea, dizziness, thirst, circulatory collapse, coma, and even death (ACC, 2011).

ACUTE DOSE TOXICITY

5.1. Acute Oral Toxicity

An oral median lethal dose (LD_{50}) of 1.63 mL/kg (confidence interval [CI]: 1.24–2.13 mL/kg) was reported based on an experiment in which groups of five male Carworth Wistar rats were administered a single oral dose of undiluted 1,1,4,7,7-pentamethyldiethylenetriamine via gavage and observed for 14 days (Smyth et al., 1969; methods described in Smyth et al., 1962). Dose groups were arranged in a logarithmic series differing by a factor of two (no further details of exposure levels reported), and LD_{50} estimates were calculated using the methods of Thompson (1947, as cited in Smyth et al., 1962) and Weil (1952, as cited in Smyth et al., 1962). Based on a density of 0.839 g/mL (Chemical Book, 2008), the LD_{50} is equivalent to 1,368 mg/kg (CI: 1,040–1,787 mg/kg). No other relevant studies were located.

5.2. Acute Dermal Toxicity

A dermal LD_{50} of 0.28 mL/kg (equivalent to 235 mg/kg) was reported by Smyth et al. (1969) based on an experiment in which groups of four male albino New Zealand rabbits had various concentrations of 1,1,4,7,7-pentamethyldiethylenetriamine applied to a clipped area of the trunk for 24 hours, according to the method of Draize et al. (1944, as cited in Smyth et al., 1962). The application site was covered and animals were immobilized during the 24-hour exposure period. After 14 days of observation for mortality, the LD_{50} was calculated as described above for acute oral toxicity. No other relevant studies were located.

5.3. Acute Inhalation Toxicity

Groups of six male or female albino rats were exposed to a flowing stream of air saturated with 1,1,4,7,7-pentamethyldiethylenetriamine vapor for various durations and observed for 14 days (Smyth et al., 1969; methods described in Smyth et al., 1962). Inhalation periods were arranged in a logarithmic series with a ratio of two extending from 15 minutes to 8 hours until the inhalation period killing about half the number of animals within the 14-day observation period was determined. No deaths from acute exposure to 1,1,4,7,7-pentamethyldiethylene-triamine were reported at durations of ≤8 hours.

5.4. Primary Skin Irritation

Smyth et al. (1969) reported that application of 1,1,4,7,7-pentamethyldiethylenetriamine to uncovered areas on the clipped belly of five albino rabbits for 24 hours resulted in Grade 7 (out of 10) skin irritation, indicating moderate irritant properties to skin (methods described in Smyth et al., 1949, 1962; see Appendix A). No other relevant studies were located.

5.5. Primary Eye Irritation

Smyth et al. (1969) reported that the instillation of 1,1,4,7,7-pentamethyldiethylenetriamine into the eye of rabbits (using the method of Carpenter and Smyth, 1946) resulted in severe corneal irritation (Grade 9 on a 10-point scale) (see Appendix A). No other relevant studies were located.

REPEAT DOSE TOXICITY

No repeat dose toxicity studies were located for 1,1,4,7,7-pentamethyldiethylenetriamine.

6. EXPOSURE

The American Chemistry Council (2010 and 2011) has reported that occupational exposure to amine catalysts may occur through inhalation, skin contact, eye contact, and ingestion. Although ingestion is unlikely in the workplace, the chemical may be inadvertently ingested if an individual eats, drinks, or smokes in areas where SPF chemicals are used.

In general, exposure limits are not yet established for the majority of the amine catalysts used in SPF systems. Only a few polyurethane amine catalysts have been assigned Occupational Exposure Limits (OELs) by regulatory and non-regulatory organizations (ACC, 2011) (Table 3). This includes the Ontario Ministry of Labour in Canada, which has established enforceable OELs. The U.S. Occupational Safety and Health Administration (OSHA) has also set enforceable permissible exposure limits (PELs) to protect workers. Other organizations that have established OELs include the American Conference of Government Industrial Hygienists (ACGIH), which has developed threshold limit values (TLVs). TLVs are generally provided as guidance and not legally enforceable. The OELs, PELs, and TLVs can be provided as a time-weighted average (TWA) or short-term exposure limits (STELs). A TWA is the average exposure over a certain period of time, which may be an 8-hour day. The STEL is the average exposure over a 15 minute period that should not be exceeded during a workday even if the 8-hour TWA is within the criteria (ACC, 2011).

Table 3. Permissible Exposure Levels and Threshold Limit Values of Some Polyurethane Amine Catalysts

Amine Catalyst	CASRN	Exposure Limit (Source)			
		PEL	STEL	TLV	TWA
Dimethylcyclohexylamine, N,N-	98-94-2	NR	5 ppm (Ontario)	NR	NR
N-ethylmorpholine	100-74-3	20 ppm Skin[2] (OSHA)	NR	NR	5 ppm Skin[1] (ACGIH)
Triethanolamine	102-71-6	NR	NR	NR	5 mg/m^3 (ACGIH)
Dimethylamino ethanol, 2-	108-01-0	NR	6 ppm (Ontario)	NR	3 ppm (Ontario)
N,N-Dimethylaminopropylamine	109-55-7	NR	NR	NR	0.5 ppm (ACGIH)
Diethanolamine	111-42-2	NR	NR	1 mg/m^3 (ACGIH)	3 ppm (ACGIH)
Triethylamine	121-44-8	25 ppm (OSHA)	3 ppm (ACGIH)	NR	NR
Triethylenediamine	280-57-9	NR	NR	NR	1 ppm Skin[1] (Ontario)
Bis (2-Dimethylaminoethyl) ether	3033-62-3	NR	0.15 ppm Skin[1] (ACGIH)	NR	0.05 ppm Skin[1] (ACGIH)

[1] Potential for significant contribution to overall exposure by skin.
[2] Substance which may be absorbed through the skin.

PEL = permissible exposure limit
STEL = short-term exposure limit
TLV = threshold limit value
TWA = time-weighted average
OSHA = Occupational Safety and Health Administration
ACGIH = American Conference of Government Industrial Hygienists
Ontario = Ontario Ministry of Labour in Canada
NR = Not reported

Reference: American Chemistry Council (2011)

7. DISCUSSION

Overall, very few toxicological and exposure studies on 1,1,4,7,7-pentamethyldiethylenetriamine were found during this assessment. The current literature is also limited on physicochemical, manufacture, supply, and use information.

Toxicity data associated with 1,1,4,7,7-pentamethyldiethylenetriamine are limited to a single range-finding study, which identified the compound as a skin and eye irritant, and reported LD_{50} values for oral and dermal exposures of 1,368 and 235 mg/kg, respectively. Absence of any repeat dose toxicity studies precludes the identification of no-observed-adverse-effect level

(NOAEL) or lowest-observed-adverse-effect level (LOAEL) values for reproductive, developmental, or repeated-dose systemic toxicity.

Only general occupational hazard and exposure data were found on amine catalysts. However, no exposure data associated with 1,1,4,7,7-pentamethyldiethylenetriamine were found for consumer or general populations.

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Appendix A. Skin and Eye Irritation Scoring Systems in Range Finding Studies of Smyth and Co-workers.

Table A.1. Skin Irritation Scoring System of Smyth et al. (1949, 1962)

Injury Grade	Definition
1	No reaction from undiluted chemical
2	Slight capillary injection from undiluted chemical
3	Strong capillary injection from undiluted chemical
4	Slight erythema from undiluted chemical
5	Strong erythema, edema or slight necrosis from undiluted chemical
6	Necrosis from undiluted chemical; no reaction greater than edema from 10% solution
7	Necrosis from undiluted chemical; no reaction greater than edema from 1% solution
8	Necrosis from undiluted chemical; no reaction greater than edema from 0.1% solution
9	Necrosis from undiluted chemical; no reaction greater than edema from 0.01% solution
10	Necrosis from undiluted chemical; necrosis from 0.01% solution

Table A.2. Eye Irritation Scoring System of Carpenter and Smyth (1946)

Injury Grade	Definition
1	0.5 mL undiluted gives mild injury
2	0.5 mL undiluted gives moderate injury
3	0.1 mL undiluted gives mild/moderate injury or 0.5 mL undiluted gives severe injury
4	0.02 mL undiluted gives mild/moderate injury or 0.1 mL undiluted gives severe injury
5	0.005 mL undiluted gives mild/moderate injury or 0.02 mL undiluted gives severe injury
6	Excess of 40% solution gives mild/moderate injury or 0.005 mL undiluted gives severe injury
7	Excess of 15% solution gives mild/moderate injury or excess of 40% solution gives severe injury
8	Excess of 5% solution gives mild/moderate injury or excess of 15% solution gives severe injury
9	Excess of 1% solution gives mild/moderate injury or excess of 5% solution gives severe injury
10	Excess of 1% solution gives severe injury

CASN 3033-62-3
bis(2-Dimethylaminoethyl)ether

DRAFT

TOXICITY REVIEW FOR BIS(2-DIMETHYLAMINOETHYL)ETHER (CASRN 3033-62-3)

Contract No. CPSC-D-06-0006
Task Order 015

Prepared by:

Versar Inc.
6850 Versar Center
Springfield, VA 22151

and

SRC, Inc.
7502 Round Pond Road
North Syracuse, NY 13212

Prepared for:

Melanie B. Biggs, Ph.D.
U.S. Consumer Product Safety Commission
4330 East West Highway
Bethesda, MD 20814

July 11, 2012

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APPENDICES

LIST OF ABBREVIATIONS AND ACRONYMS

ACC	American Chemistry Council
ACGIH	American Conference of Government Industrial Hygienists
ALK	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CAS	chemical abstracts service
CHO	Chinese hamster ovary
CI	confidence interval
CK	creatine kinase
CPSC	Consumer Product Safety Commission
GD	gestational day
GGT	γ-glutamyl transferase
HPLC	high-performance liquid chromatography
LD_{50}	median lethal dose
LDH	lactic dehydrogenase
LOAEL	lowest-observed-adverse-effect level
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDI	methylene diphenyl diisocyanate
NOAEL	no-observed-adverse-effect level
OEL	occupational exposure limit
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
PPM	Parts per million
SCE	sister chromatid exchange
SDH	sorbitol dehydrogenase
SPF	spray polyurethane foam
STEL	short-term exposure limit
TDI	toluene diisocyanate
TLV	threshold limit value
TWA	time-weighted average
UDS	unscheduled DNA synthesis

TOXICITY REVIEW FOR BIS(2-DIMETHYLAMINOETHYL)ETHER (CASRN 3033-62-3)

1. INTRODUCTION

This report summarizes available data on the identity, physicochemical properties, manufacture, supply, use, toxicity, and exposure information on bis(2-dimethylaminoethyl)ether. This assessment was prepared from several review articles (ACC, 2010; ACC, 2011; PubChem, 2005).

Bis(2-dimethylaminoethyl)ether is an amine catalyst primarily used in the production of spray polyurethane foam (SPF). SPF is an insulation or sealant product, which is formed via an exothermic chemical reaction between the A-side and B-side chemicals (ACC, 2010). The A-side consists of chemicals such as methylene diphenyl diisocyanate (MDI) or toluene diissocyante (TDI). Polyols are part of the B-side chemicals, which also include amine and/or metal catalysts, blowing agents, surfactants, and flame retardants. Amine and/or metal catalysts are used to promote the reaction between polyols and A-side chemicals, which help polyurethane foam cells develop sufficient strength to maintain their structure and resist collapsing (ACC, 2010). Recent concerns have emerged regarding potential health effects of amine catalysts in SPF due to their potential to cause respiratory-related problems, irritation to skin and eyes, temporary vision problems, and headaches (ACC, 2010).

2. IDENTITY and PHYSICOCHEMICAL CHARACTERISTICS

This section highlights the available identity and key physicochemical properties of bis(2-dimethylaminoethyl)ether. Amine catalysts are derivatives of ammonia and are primary, secondary, or tertiary depending on one or more of the three ammonia hydrogen atoms being replaced with hydrocarbon groups (ACC, 2011). Bis(2-dimethylaminoethyl)ether is classified as being tertiary and has basic and nucleophilic properties.

Tertiary amines are generally colorless liquids with very distinct and strong ammonia-like odors (ACC, 2011). Tertiary amines are also more volatile and have a lower boiling point than primary and secondary amines (Albrecht and Stephenson, 1988). Additionally, amine catalysts are considered to be very water soluble (Albrecht and Stephenson, 1988). This includes bis(2-dimethylaminoethyl)ether, which was reported as being completely soluble (BASF, 2009).

The identity and physicochemical properties of bis(2-dimethylaminoethyl)ether are provided in Tables 2.1 and 2.2.

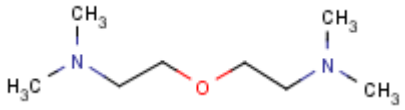
Table 2.1. Names, Structural Descriptors, and Molecular Formula of Bis(2-dimethylaminoethyl)ether (PubChem, 2005)	
CAS Number	3033-62-3
Chemical Name	Bis(2-dimethylaminoethyl)ether
Trade Name	NIAX A-99; DABCO BL-19; TOYOCAT ETS; JEFFCAT ZF-20; RC Catalyst 6433 (ACC, 2011)
Molecular Formula	C8H20N2O
Structural Formula	
Molecular Weight	160.2572 g/mol
Synonyms	Ethylamine, 2,2'-oxybis[N,N-dimethyl- N,N,N',N'-Tetramethyl-2,2'-oxybis(ethylamine) Bis-[2-(N,N-dimethylamino)ethyl] ether 2-[2-(dimethylamino)ethoxy]-N,N-dimethylethanamine
Purity/Impurities/Additives	No data

Table 2.2. Physicochemical Properties of Bis(2-dimethylaminoethyl)ether	
Property	**Value**
Physical state	Colorless to yellowish liquid with amine-like odor (BASF, 2009)
Melting point	No data
Boiling point	189ºC (760 mm Hg; Chemical Book, 2008); 188ºC (BASF, 2009)
Density	0.841 g/mL (25ºC; Chemical Book, 2008); 0.853g/cm3 (BASF, 2009)
Vapor pressure	0.28 mmHg (BASF, 2009)
Water solubility	Completely soluble (BASF, 2009)
Partition coefficient n-octanol/water (log Kow)	No data
Henry's law constant	No data
Flash point	66ºC (151 ºF; Chemical Book, 2008); 68ºC (BASF, 2009)

3. MANUFACTURE, SUPPLY, AND USE

Manufacture

Amine catalysts are produced from ammonia by replacing one or more hydrogen atoms with alkyl groups or nonacidic radicals containing hydrogen and carbon atoms (ACC, 2011). An Internet search was performed using the Chemical Abstracts Service (CAS) number and/or trade

names to identify companies that manufacture bis(2-dimethylaminoethyl)ether. The following five chemical companies were listed as manufacturers of bis(2-dimethylaminoethyl)ether: Air Products and Chemicals, Inc. (2011); BASF (2011); Huntsman Corporation (2005); Jiangdu Dajiang Chemical Industrial Co. Ltd (2006); and TOSOH Corporation (2011). The search also revealed that BASF (2011) manufactures bis(2-dimethylaminoethyl)ether in Germany and the USA under the brand name Lupragen® N205, and Jiangdu Dajiang Chemical Industrial manufactures bis(2-dimethylaminoethyl)ether in China. However, information found on the Alibaba Group website (2012) suggests that Jiangdu Dajiang supplies amine catalysts to several chemical companies, such as DOW, Huntsman, BASF and Momentive ECT. Therefore, it is unclear whether BASF and Huntsman actually manufacture bis(2-dimethylaminoethyl)ether or if they purchase this amine catalyst from a manufacturing company like Jiangdu Dajiang Chemical. The manufacturing locations of the other three companies (Air Products and Chemicals, Huntsman Corporation, and TOSOH Corporation) were not found.

Union Carbide was also listed as a manufacturer of bis(2-dimethylaminoethyl)ether in the USA under the brand name NIAX A-99, but has discontinued selling this product (NIOSH, 1978). No information was found regarding when Union Carbide discontinued the sale of bis(2-dimethylaminoethyl)ether.

Supply

Based on information found on the Alibaba website (2012), it appears that companies, such as BASF and Huntsman, may be suppliers of bis(2-dimethylaminoethyl)ether. However, this information has not been confirmed.

Additional supply data specific to bis(2-dimethylaminoethyl)ether were not found.

Use

Amine catalysts are primarily used in the production of polyurethane foam to promote the reaction between polyols and A-side chemicals. The American Chemistry Council (2010) reported that the reaction helps polyurethane foam cells develop sufficient strength to maintain their structure to resist collapsing or becoming deformed and also helps with the completion of the reaction or “cure” in the finished foam. Amine catalysts are typically 0.1 to 5.0 percent of a polyurethane formulation (ACC, 2011). Although metal catalysts are also used in polyurethane foam, most catalysts used in SPF are amine-based.

Bis(2-dimethylaminoethyl)ether is a highly efficient blowing catalyst that can be used in flexible and rigid polyurethane foam applications (Huntsman, 2005). Its strong catalytic effect on the blowing reaction can be balanced by adding a strong gelling catalyst (Jiangdu Dajiang Chemical, 2006). Jiangdu Dajiang Chemical Industrial (2006) reported that when used in a flexible slabstock formulation, bis(2-dimethylaminoethyl)ether can improve the processing of all grades of foam ranging from low to high density and from filled to high resiliency grades. Because of its unique characteristics, bis(2-dimethylaminoethyl)ether is effective for high resiliency molded foam.

4. TOXICOKINETICS

Available in vivo animal data indicate that bis(2-dimethylaminoethyl)ether is rapidly absorbed following inhalation or dermal exposure, widely distributed at low concentrations throughout the body, and eliminated slowly (relative to the rate of absorption) with excretion primarily as parent compound in the urine.

Jensen et al. (1997) performed a series of inhalation experiments in F344 rats. Three separate experiments were performed in which groups of 4 male rats were exposed to ^{14}C-labeled bis(2-dimethylaminoethyl)ether vapor head-only for 4 hours – an absorption study and two elimination studies. In the absorption study, blood was collected during the exposure period at 35 minutes, and at 1, 2, 3, and 4 hours. The measured exposure concentration in this study was 5.2 ppm. In the elimination studies, rats were exposed for 4 hours and then transferred to metabolism cages for collection of urine, feces, expired air and blood over the ensuing 48 hours, at which time the animals were sacrificed and their tissues collected. Measured exposure levels were 5.5 ppm in one elimination study and 5.6 ppm in the other. Rats from all exposure groups showed periocular encrustation and a progressive reduction in respiratory rate during exposure (13 to 30% lower than pre-exposure rates), suggestive of respiratory irritation. According to the researchers, this degree of respiratory irritation is below the level that would be expected to affect absorption or disrupt blood sampling results.

In the absorption study, levels of ^{14}C in the plasma increased linearly with time of exposure throughout the experiment; and a steady state level of ^{14}C in the plasma was not reached within the 4-hour exposure period (Jensen et al., 1997). At the conclusion of exposure, the concentration of ^{14}C in erythrocytes was increased relative to the plasma (1.0 vs. 0.6 µg equivalents/g plasma, $p<0.05$). Head wash from the animals found only 0.22% of total body burden of ^{14}C, indicating low potential for percutaneous absorption through the exposed head

region in this study. In the elimination experiments, the highest concentration of ^{14}C in the plasma was observed immediately after cessation of exposure at 4 hours, and plasma levels of ^{14}C decreased linearly with increasing post-exposure time throughout the 48-hour monitoring period, indicative of first-order elimination. Post-exposure half-times for elimination were 17.4 hours in elimination study 1 and 24.2 hours in elimination study 2. The concentration of ^{14}C in erythrocytes relative to the plasma was increased (non-significant in elimination study 1, $p<0.05$ in elimination study 2) at the end of exposure, but not at later time periods. Evaluations of the tissues, excreta, and carcass 48 hours post-exposure indicated that approximately 67 to 70% of the test substance had been eliminated by that time; while most of the rest of the test substance remained in the carcass (29 to 32% of the administered dose), with less than 1% detected in internal tissues. Low concentrations of radioactivity were found in all 11 tissues evaluated, but there was no indication of preferential accumulation in any specific tissue. The main route of excretion was via the urine (53 to 58%). Relatively low levels of ^{14}C were excreted in the feces (3 to 6%) or exhaled as $^{14}CO_2$ (2 to 3%) or as volatiles (trace). Another 5 to 7% of the administered radioactivity was recovered in the cage wash.

Cutaneous studies in F344 rats and New Zealand white rabbits found that the kinetic results were similar to those found by inhalation exposure and also showed that radioactivity recovered in the urine was primarily in the form of the parent compound (Jensen et al., 1998). Rats and rabbits (4 sex/group) were topically administered ^{14}C-labeled bis(2-dimethyl-aminoethyl)ether at target doses of 200 or 100 mg/kg (respectively) to the intact shaved dorsal trunk skin (4-6 cm^2 in rats, 50 cm^2 in rabbits) under occluded conditions for 48 hours (Jensen et al., 1998). No rationale was provided for choice of target dose levels. Actual doses were 184 mg/kg in male rats, 184-200 mg/kg in female rats, 92 mg/kg in male rabbits and 94 mg/kg in female rabbits. Doses of radioactivity were approximately 74 µCi/kg in male rats, 63-71 µCi/kg in female rats, 12 µCi/kg in male rabbits, and 11 µCi/kg in female rabbits.

Both species showed first-order kinetics with respect to absorption and elimination (Jensen et al., 1998). Absorption occurred rapidly, with absorption half-times averaging 26 minutes in male rats, 82 minutes in female rats, 22 minutes in male rabbits and 76 minutes in female rabbits. The maximum plasma level of ^{14}C was 12.9 µg/g at 117 minutes in male rats, 5.5 µg/g at 239 minutes in female rats, 3.2 µg/g at 79 minutes in male rabbits, and 2.4 µg/g at 101 minutes in female rabbits. The researchers noted the apparent sex-related differences in absorption parameters, but did not provide any discussion of this finding. Bioavailability, calculated by comparing the area under the plasma concentration-time curve for the dermal exposure to the same data for intravenous exposure (i.v. studies described below), was 78% for

male rats, 51% for female rats, 54% for male rabbits and 63% for female rabbits. Removal of ^{14}C from the plasma was slow, relative to the rate of absorption, and plasma elimination half-times were 29 hours in male rats, 31 hours in female rats, 41 hours in male rabbits, and 61 hours in female rabbits.

Total recovery of administered radioactivity in the tissues and excreta 48 hours after dosing was low in all groups (48% in male rats, 61% in female rats, 63% in male rabbits and 58% in female rabbits) (Jensen et al., 1998). There was little difference across species or sex in the recovery data. In each case, the largest proportion of the administered dose was detected in the urine (24% in rats of both sexes and 23-25% in both sexes of rabbits). High-performance liquid chromatography (HPLC) analyses of urine samples from male and female rats and rabbits indicated that the parent compound, bis(2-dimethylaminoethyl)ether, accounted for the majority of ^{14}C in the urine, and a small peak (possibly a metabolite) accounted for <1% ^{14}C. Recovery of ^{14}C from the feces was low (1-2% of administered dose in rats and 4% in rabbits). The internal tissues and carcass, respectively, accounted for approximately 7% and 2% in rats and 8% and 4% in rabbits. Percent of administered dose in occlusion devices and skin differed by species and sex (14% in male rats, 26% in female rats, 24% in male rabbits, and 17% in female rabbits), but this was almost entirely due to differences in recovery in the occlusive tape and jacket. Rats showed no preferential accumulation of ^{14}C in any internal tissue. In contrast, rabbits of both sexes showed significant accumulation of ^{14}C in the kidneys (3-4% of the administered dose), relative to other internal tissues.

Due to relatively low dose recovery in these studies, an additional epicutaneous experiment was conducted in rats employing "technique modifications" resulting in "enhanced occlusion conditions" (not further described) (Jensen et al., 1998). Although applied doses in this study were similar to the first rat study (198 mg/kg in males and 205 mg/kg in females), radioactivity doses were much higher: 170 μCi/kg in males and 318 μCi/kg in females. Because it is unclear what changes were made and because the findings in these groups were markedly different from the initial rat study in some respects, most dramatically the rate and extent of absorption and total recovery of radioactivity, the results of this study are reported separately. Absorption was markedly increased in the "enhanced occlusion" rat study relative to the initial rat study. Absorption half-times were 6.5 minutes in male rats and 8.4 minutes in female rats, with maximum plasma levels of 86.8 μg/g at 9.9 minutes in males and 175.7 μg/g at 13.2 minutes in females. Bioavailability for rats in the "enhanced occlusion" study was 83% for males and 94% for females. In the "enhanced occlusion" study, elimination half-times were 23 hours in male rats and 18 hours in female rats. Total recovery of administered dose was

increased relative to the initial rat study (79% in males and 76% in females). More of the administered dose was measured in the urine (52% in males and 47% in females) and carcass (11% in both sexes), similar amounts in the feces (0.5% in males and 2% in females), and less in the tissues (<1% in both sexes), skin and occlusion device (7% in males and 9% in females). As in the initial rat study, there was no evidence of accumulation of radioactivity in any internal tissue.

Exposure of rats and rabbits (4 males/group) to ^{14}C-labeled bis(2-dimethylaminoethyl)-ether via i.v. at 2 or 200 and 1 or 100 mg/kg (respectively) showed linearity of responses at the high and low doses (Jensen et al., 1998). Distribution of ^{14}C to the plasma occurred rapidly, and half-times were 0.67 to 0.82 minutes in rats and 1.42 to 1.95 minutes in rabbits. Removal of ^{14}C from the plasma occurred more slowly, with elimination half-times ranging from 14 to 18 hours in rats and 26 to 40 hours in rabbits. Total recovery of the administered dose (reflecting urine and feces only; ^{14}C was not measured in the tissues or carcass) in the 48 hours after dosing was 70 to 75% in rats and 39 to 49% in rabbits. The majority of the administered dose recovered was detected in the urine (60 to 65% for rats and 34 to 44% for rabbits), and <5% of administered ^{14}C was recovered from the feces (both species).

5. HAZARD INFORMATION

Exposure to the B-side chemicals can cause irritation of the respiratory tract, causing cough, sore throat, difficulty breathing, and runny nose (ACC, 2010). Inhalation of some amine catalyst vapors can temporarily cause vision to become foggy or blurry, and halos may appear around bright objects such as lights (ACC, 2010). Skin contact may cause moderate to severe irritation and burns, from redness and swelling to painful blistering, ulceration, and chemical burns (ACC, 2010). Amine catalysts can also irritate the eyes and may cause the following symptoms at low concentrations: corneal swelling without pain; blurred or “foggy” vision with a blue tint; and a halo phenomenon effect around lights. Higher vapor concentrations or direct contact with the liquid amines may result in severe irritation and tissue injury (ACC, 2011). If amines are ingested, this may result in severe irritation, ulceration, or burns of the mouth, throat, esophagus, and gastrointestinal tract. Other serious symptoms may include pain in the chest or abdomen, nausea, bleeding of the throat and gastrointestinal tract, diarrhea, dizziness, thirst, circulatory collapse, coma, and even death (ACC, 2011).

ACUTE DOSE TOXICITY

5.1. Acute Oral Toxicity

An oral median lethal dose (LD_{50}) of 1.23 mL/kg (confidence interval [CI]: 0.94–1.62 mL/kg) was reported for bis(2-dimethylaminoethyl)ether based on an experiment in which groups of five male Carworth-Wistar rats were administered a single oral dose of undiluted chemical via gavage and observed for 14 days (Smyth et al., 1969, 1962; Union Carbide Corp., 1987a). Dose groups were arranged in a logarithmic series differing by a factor of two (no further details of exposure levels reported), and LD_{50} estimates were calculated using the methods of Thompson (1947, as cited in Smyth et al., 1962) and Weil (1952, as cited in Smyth et al., 1962). Based on the density of 0.850 g/mL for bis(2-dimethylaminoethyl)ether (Texaco Chemical Corp., 1992), the LD_{50} is equivalent to 1,045 mg/kg (CI: 799–1,376 mg/kg). A similar study conducted using a 25% solution of bis(2-dimethylaminoethyl)ether in corn oil reported an oral LD_{50} of 1.07 mL/kg (CI: 0.77–1.50 mL/kg), equivalent to 909 mg/kg (CI: 654-1,274 mg/kg) (Union Carbide Corp., 1987a). In both studies, deaths occurred primarily within 4 hours of dosing and gross necropsy revealed congestion of the lungs and abdominal viscera and mottled livers (Union Carbide Corp., 1987a). Rats administered the undiluted material also had hemorrhage of the stomach. Other studies have reported LD_{50} values ranging from 571 mg/kg to 1,199 mg/kg (RTECS, 2011; Union Carbide Corp., 1987a).

5.2. Acute Dermal Toxicity

Ballantyne et al. (1986) conducted studies on the dermal toxicity of bis(2-dimethylaminoethyl)ether. Undiluted bis(2-dimethylaminoethyl)ether was applied to the intact, shaved dorsal skin (surface area not specified) of immobilized New Zealand White rabbits (5/sex/group) under occlusion at doses ranging from 0.25 to 1.00 mL/kg for 4 hours or 0.1 to 0.8 mL/kg for 24 hours. Animals were observed for 14 days following dosing (Ballantyne et al., 1986). Additional groups of rabbits (5/sex/dose) received 1.0 to 8.0 mL/kg of a 20% aqueous solution of the test substance under the same conditions for 24 hours. Mortality results are shown in Table 5.1. Although deaths were observed at doses as low as 0.10 mL/kg, most mortality occurred at ≥ 0.40 mL/kg (undiluted) or ≥ 2.0 mL/kg (20% dilution). Deaths occurred within 1 to 4 days after dosing. LD_{50} values were 350 (CI: 255-476) mg/kg for males and 536 (CI: 460-630) mg/kg for females after an undiluted 4-hour exposure, 315 mg/kg for both males and females (CI: 213-468 and 170-570, respectively) after an undiluted 24-hour exposure, and 364 (CI: 247-539) mg/kg for males and 481 (CI: 289-811) mg/kg for females after a 20%

solution was administered for 24 hours. Severe local erythema, edema, and necrosis at the application site were observed in animals that died, which also persisted throughout the observation period in survivors (all solutions and doses tested). Signs of systemic toxicity, including salivation, sluggishness, unsteady gait, and prostration, were observed in treated rats within a day of exposure, and survivors recovered within 2 days of exposure (doses at which these effects occurred were not specified). In a follow-up study by the same researchers performed under the same conditions, no deaths, signs of systemic toxicity, body weight changes or gross pathological lesions occurred in rabbits where 1.0 mL of 5, 10, or 20% bis(2-dimethylaminoethyl)ether in distilled water was applied for 24 hours.

Table 5.1. Mortality in New Zealand White rabbits administered bis(2-dimethylaminoethyl)ether percutaneously

Concentration	Contact Time	Sex	Dose (mL/kg)	Mortality Incidence[a]
Undiluted	4 hr	Male	1.00	5/5
			0.50	4/5
			0.25	0/5
		Female	1.00	5/5
			0.71	4/5
			0.30	0/5
Undiluted	24 hr	Male	0.80	5/5
			0.40	3/5
			0.20	0/5
		Female	0.80	5/5
			0.40	1/5
			0.20	2/5
			0.10	1/5
20% (v/v)	24 hr	Male	4.00	5/5
			2.00	2/5
			1.00	0/5
		Female	8.00	5/5
			4.00	3/5
			2.00	2/5
			1.00	0/5

[a]Number dead /number dosed

Reference: Ballantyne et al. (1986)

Other studies have reported dermal LD_{50} values of 0.250 to 0.40 mL/kg (approximately 213 to 340 mg/kg) for rabbits administered the undiluted test material under occluded conditions for 24 hours (Union Carbide Corp., 1987a; Smyth et al., 1969, 1962). Effects in exposed rabbits included mortality, body weight loss, gross internal lesions (congestion of the lungs, liver, spleen, and kidneys), and marked necrosis at the application site.

5.3. Acute Inhalation Toxicity

Inhalation studies of bis(2-dimethylaminoethyl)ether were reported by Union Carbide Corp. (1987b). No deaths occurred in Sprague-Dawley rats (5/sex/concentration) exposed whole-body to bis(2-dimethylaminoethyl)ether as a vapor at 24 ppm for 6 hours under static conditions and observed for 14 days following exposure. Clinical signs on the day of exposure were periocular and perinasal wetness and hypoactivity. In a follow-up study using higher exposure concentrations, rats (5/sex/group) were exposed to the test material as a vapor at 68, 200, or 248 ppm (generated by passing compressed air through a gas washing bottle or "bubbler" containing the test material) or 149 ppm (generated by passing the test material into a heated evaporator) for 6 hours under dynamic conditions and observed for up to 14 days post-exposure (Union Carbide Corp., 1987b). Although the evaporator method is preferred for generating vapor without aerosol while controlling humidity (which interfered with generation of the test atmosphere), the bubbler method was required to generate concentrations above 149 ppm. One male and one female died at 149 ppm, and all rats in the 200 and 248 ppm groups died within 2 days. Clinical signs of ocular and respiratory irritation were observed in all groups on the day of exposure. Additional effects seen in surviving animals on subsequent days included hypoactivity during the first week post-exposure at 149 ppm and ataxia and slow righting reflex on the first day post-exposure at 200 ppm (there were no survivors beyond the first post-exposure day at 200 ppm and none beyond the exposure day at 248 ppm). Rats that died showed periocular and perinasal encrustation and dark red discoloration of the lung tissue. The LC_{50} value for the combined sexes was 166 ppm (95% CI: 155-178) using the data from all of the dynamic exposure groups and 117 ppm (95% CI: 80-171) using data only from the exposures generated by the bubbler method (i.e., the 68, 200 and 248 ppm groups).

Earlier studies reported no mortality in female albino rats (n=6) exposed to bis(2-dimethylaminoethyl)ether as a saturated vapor under static or dynamic conditions for 8 hours and observed for 14 days (Union Carbide Corp., 1987a; Ballantyne et al., 1986; Smyth et al., 1969, 1962). Exposure levels in these studies were not further described except for one static study that estimated the concentration as 776 ppm based on weight loss of the chemical sample during vapor generation (Union Carbide Corp., 1987a).

5.4. Primary Skin Irritation

Several workers exposed occupationally to bis(2-dimethylaminoethyl)ether reported skin irritation with pain, swelling, severe redness, and blistering of the skin after handling of the

chemical (Texaco Chemical Corp., 1992). Irritation was severe enough to warrant medical attention for two of these employees. No further details are available. Patch-testing of 1% bis(2-dimethylaminoethyl)ether (vehicle not reported) was conducted in 223 Mayo Clinic patients suspected of allergy to plastics and glues between January, 2000 and December, 2007 using Finn Chambers on Scanpor tape (Shmidt et al., 2010). Patches were applied to the patient's upper back and removed after 48 hours. Reactions, evaluated initially at 48-72 and again at 96-168 hours, were categorized as negative, weak (e.g., non-vesicular erythema, infiltration), strong (edematous or vesicular), or extreme (ulcerative lesions). Reactions that diminished or disappeared between the initial and subsequent evaluations were generally considered irritant, while those that stayed the same or worsened were considered allergic. Approximately 3% of the subjects treated topically with 1% bis(2-dimethylaminoethyl)ether showed a transient skin reaction consistent with primary irritation, which is the highest irritation rate for any of the substances tested. No further details were reported regarding the nature of the irritation produced by 1% bis(2-dimethylaminoethyl)ether. The allergy results are presented in Section 5.6 below.

Studies by Ballantyne et al. (1986) in rabbits indicate that bis(2-dimethylaminoethyl)ether is severely irritating to the skin. New Zealand White rabbits (n = 6) that had 0.5 mL of undiluted bis(2-dimethylaminoethyl)ether applied to shaved dorsal skin under occluded conditions for 4 hours showed severe erythema, edema, ulceration, and/or necrosis at the application site 1 to 10 days after exposure. Moderate to severe erythema remained 14 days after exposure. Six rabbits exposed to the test material under the same exposure conditions for 3 minutes also exhibited severe erythema, edema, and necrosis at the application site. Severe irritation (including necrosis) persisted 3 days after exposure (Ballantyne et al., 1986). In additional studies conducted by Ballantyne et al. (1986), marked necrosis was observed 24 hours after a single unoccluded dermal application of 0.1 mL of undiluted chemical to the shaved dorsal skin of five male New Zealand White rabbits. Male rabbits (n = 5) exposed unoccluded to 0.1 mL of a 10% solution in distilled water showed moderate to marked erythema 24 hours after exposure.

Previous studies (Smyth et al., 1969, 1962; Union Carbide Corp., 1987a) reported that the application of 0.01 mL of undiluted bis(2-dimethylaminoethyl)ether to unoccluded areas on the clipped belly of five albino rabbits for 24 hours resulted in Grade 6 (out of 10) skin irritation, indicating moderate irritant properties of this chemical to skin (methods described in Smyth et al., 1949, 1962; see Appendix C).

5.5. Primary Eye Irritation

A property occupant exposed in the summer to bis(2-dimethylaminoethyl)ether in a detached home addition in Texas used as a photo studio (sheet metal walls and roof subject to intense, prolonged sunlight) complained of odor, watery eyes, hazy vision, and halo vision (Anonymous, 2010). Sampling performed 4 weeks after application of the SPF material indicated that levels of bis(2-dimethylaminoethyl)ether were "greater than the occupational exposure limit." This was not defined, but likely refers to the contemporaneous ACGIH (2001) TLV-TWA of 0.05 ppm or STEL of 0.15 ppm. No further details of this incident are available.

Animal studies indicate that bis(2-dimethylaminoethyl)ether is a severe ocular irritant. Smyth et al. (1969) reported that the instillation of bis(2-dimethylaminoethyl)ether into the eye of rabbits (using the method of Carpenter and Smyth, 1946) resulted in severe corneal irritation (Grade 9 on a 10-point scale) (see Appendix C). The same score was achieved in multiple tests performed over the years by the same methods (Union Carbide Corp., 1987a). Ballantyne et al. (1986) reported results suggesting slightly lower eye injury from bis(2-dimethylaminoethyl)ether, corresponding to a Grade of 8 on the 10-point scale described in Appendix C.

5.6. Sensitization

In the retrospective patch-testing study of 223 patients suspected of allergy to plastics and glues (Shmidt et al., 2010) described in Section 5.4, above, 16% of subjects tested with bis(2-dimethylaminoethyl)ether exhibited persistent reactions classified by the researchers as allergic responses. This was the highest allergy rate of the 56 substances tested. Of the patients that showed an allergic response, 77% had confirmed or possible prior contact with substances containing bis(2-dimethylaminoethyl)ether. Studies of the sensitizing potential of bis(2-dimethylaminoethyl)ether in laboratory animals were not located.

REPEAT DOSE TOXICITY

5.7. General Effects (Clinical Signs, Food/Water Consumption, Body Weight)

Data from short-term and subchronic inhalation and dermal studies indicate that bis(2-dimethylaminoethyl)ether elicits overt irritant effects in tissues with which it comes into immediate contact. It is lethal at higher exposure levels.

Inhalation: Bis(2-dimethylaminoethyl)ether shows a very steep dose-response curve for mortality in short-term inhalation studies in rats. In a pair of inhalation studies (6 hours/day, 5 days/week) conducted by Union Carbide Corp. (1989, 1988), all rats exposed to ≥40 ppm died or were sacrificed moribund before study day 11, while no deaths occurred at concentrations ≤20 ppm (Table 5.2). A subsequent subchronic inhalation study found no mortality in rats exposed to ≤5.8 ppm for 14 weeks (Union Carbide Corp., 1993a). The study authors did not identify any specific cause for the mortalities observed at higher concentrations in the short-term study. Rats exposed to bis(2-dimethylaminoethyl)ether showed clinical signs of toxicity, mostly indicative of ocular and respiratory irritation, in both the short-term and subchronic studies. Symptoms included swollen periocular tissue, blepharospasm, corneal cloudiness and opacity, periocular and perinasal encrustation, gasping, and skin discoloration (reddening of the ears and paws). In the short-term studies (exposure levels of 1 to 90 ppm), these effects were seen primarily at ≥20 ppm but also, to a limited extent, at 10 ppm. Ataxia was observed in some animals from the 40 and 90 ppm groups. In the subchronic study (exposure levels of 0.22 to 5.8 ppm), corneal cloudiness and periocular and perinasal encrustation were observed primarily at the high concentration of 5.8 ppm, but swelling of the periocular tissue was increased in all exposure groups during the study (≥0.22 ppm). Ophthalmologic examinations at the end of exposure revealed concentration-dependent increases in the incidence and severity of keratitis and blepharitis at ≥10 ppm in the short-term studies and at ≥1.25 ppm in the subchronic study.

Table 5.2. Mortality in Sprague-Dawley rats administered bis(2-dimethylaminoethyl)ether as a vapor 6 hours/day 5 days/week for 11 days (including 9 days of exposure)

	Exposure concentration (ppm)					
	0	**1**	**10**	**20**	**40**	**90**
	Union Carbide Corp. (1988)					
Males	0/25[a]	NE	NE	0/10	10/10[b]	25/25[b]
Females	0/10	NE	NE	0/10	10/10[b]	10/10[b]
	Union Carbide Corp. (1989)					
Males	0/10	0/10	0/10	0/10	NE	NE
Females	0/10	0/10	0/10	0/10	NE	NE

[a]Number affected/number examined (number of animals).
[b]Significantly different from controls at $p<0.05$ based on Fisher's exact test performed for this review.
NE = not evaluated

Reference: Union Carbide Corp. (1988, 1989)

In the short-term inhalation studies, rats exhibited significant reductions in food consumption and body weight at concentrations of ≥10 ppm. In the initial study (Union Carbide Corp, 1988), food consumption was reduced by as much as 28% at 20 ppm, and body weights were significantly ($p < 0.05$) decreased in rats from all exposure groups (Table 5.3). Final body

weights (measured on days 11, 8, and 4 for the 20, 40, and 90 ppm groups, respectively, due to early mortality) were reduced by 10% or more in all exposure groups compared to controls. In the follow-up study (Union Carbide Corp., 1989), food consumption was significantly decreased (by 30%) at 10 ppm (males only), and food and water consumption and body weight (decreased by >10% compared to controls) were all significantly decreased at 20 ppm (Table 5.4). In the subchronic study (Union Carbide Corp., 1993a), food consumption (measured only during week 14) was significantly decreased in females (but not males) at 5.8 ppm (18% lower than controls; see Appendix Table B.6). Although the mean body weight of males exposed to 5.8 ppm was significantly ($p < 0.05$) decreased relative to controls at this time point, mean body weights of rats from this and all other treatment groups were within 10% of their respective control groups throughout the study. Also, necropsy body weights of rats from this and other exposed groups were not significantly different from controls.

Table 5.3. Effects in Sprague-Dawley rats administered bis(2-dimethylaminoethyl)ether as a vapor 6 hours/day 5 days/week for 11 days (including 9 days of exposure)

Endpoint	Exposure concentration (ppm)			
	0	20	40	90
Food consumption (g/animal/d)				
Males	13.7 ± 3.7 (10)[a]	10.3 ± 3.0 (10)[b]	2.1 ± 3.2 (3)[c]	NE
Females	15.1 ± 2.1 (10)	10.9 ± 3.8 (10)[b]	NE	NE
Water consumption (mL/animal/d); males	18.5 ± 2.9 (10)	19.9 ± 6.4 (10)	5.7 ± 5.5 (3)[c]	NE
Body weight (g); males				
Day 4	267.0 ± 11.9 (25)	242.2 ± 13.2 (10)[b]	218.1 ± 12.0 (10)[b]	187.6 ± 0.3 (2)[c]
Day 8	278.0 ± 12.2 (25)	253.9 ± 12.1 (10)[b]	201.0 ± 20.1 (10)[b]	NE
Day 11	287.0 ± 13.8 (25)	233.2 ± 17.1 (10)[b]	NE	NE
Body weight (g); females				
Day 4	181.9 ± 14.0 (10)	163.9 ± 6.8 (10)[b]	140.6 ± 10.8 (10)[b]	156.9 ± 7.3 (10)[b]
Day 8	189.0 ± 13.7 (10)	175.5 ± 6.9 (10)[b]	142.0 ± 8.7 (7)[b]	NE
Day 11	193.8 ± 14.0 (10)	167.5 ± 11.0 (10)[b]	NE	NE

[a]Values represent means ± SDs
[b]Significantly different from controls at $p<0.05$ based on statistics performed by the study authors.
[c]Values not used in statistical tests by study authors (due to small group size).
NE = not evaluated

Reference: Union Carbide Corp. (1988)

Table 5.4. Effects in Sprague-Dawley rats administered bis(2-dimethylaminoethyl)ether as a vapor 6 hours/day 5 days/week for 11 days (including 9 days of exposure)				
Endpoint	**Exposure concentration (ppm)**			
	0	**1**	**10**	**20**
Food consumption (g/animal)				
Males	18.7 ± 2.6 (10)[a]	19.0 ± 2.9 (10)	13.1 ± 3.2 (10)[b]	9.6 ± 3.1 (10)[b]
Females	14.6 ± 1.9 (10)	14.0 ± 2.9 (10)	12.7 ± 2.1 (10)	10.0 ± 3.2 (10)[b]
Water consumption (mL/animal)				
Males	25.1 ± 2.9 (10)	24.9 ± 3.1 (10)	22.6 ± 10.3 (10)	10.9 ± 7.7 (10)[b]
Body weight- Day 12 (g)				
Males	301.6 ± 14.5 (20)	301.6 ± 20.9 (10)	301.5 ± 16.5 (10)	248.6 ± 26.9 (20)[c]
Females	208.3 ± 10.1 (20)	209.7 ± 11.0 (10)	208.5 ± 5.7 (10)	186.8 ± 13.8 (20)[b]
Final body weight (g)				
Males	304.4 ± 17.2 (10)	301.5 ± 20.9 (10)	301.5± 16.5 (10)	244.8 ± 31.8 (10)[b]
Females	210.3 ± 10.0 (10)	208.7 ± 11.0 (10)	206.5 ± 5.7 (10)	183.7 ± 16.2 (10)[b]

[a]Values represent means ± SDs
[b]Significantly different from controls at $p<0.05$ based on statistics performed by the study authors.
[c]Significantly different from controls at $p<0.05$ based on Student's t-test performed for this review, based on data presented in this table.

Reference: Union Carbide Corp. (1989)

Dermal: No treatment-related deaths were observed in rabbits exposed topically to bis(2-dimethylaminoethyl)ether under occluded conditions 6 hours/day 5 days/week at up to 10% (approximately 33 mg/kg-day) for 11 days or up to 2% (approximately 5 mg/kg-day) for 90 days (Ballantyne et al., 1986; Union Carbide Corp., 1984). Dermal irritation increased with dose and number of exposures, and was characterized by moderate to severe erythema and edema at the highest dose levels by the end of the short-term study and throughout most of the subchronic study. A dose-related increase in dermal irritation at the application site, in the absence of mortality or clinical signs, was also observed in a teratogenicity study with pregnant female New Zealand White rabbits (22/group) exposed to the test substance at up to 10% (approximately 24 mg/kg-day) under occluded conditions 6 hours/day on gestational days (GDs) 6 to 18 (Tyl et al., 1986; Union Carbide Corp., 1985).

In the short-term dermal toxicity study (Ballantyne et al., 1986; Union Carbide Corp., 1984), food consumption was significantly decreased in male rabbits at ≥5% (about 15 mg/kg-day) and non-significantly decreased in females at 10% (Table 5.5). All groups, including controls, lost weight during the course of the study in a dose-related manner. The amount of weight lost relative to controls was significantly increased in males exposed to 5 or 10% and in females exposed to 10%; body weight loss was >10% higher in all treatment groups compared to respective control groups. In the subchronic dermal toxicity study reported by Ballantyne et al. (1986) and Union Carbide Corp. (1984), rabbits exposed to bis(2-dimethylaminoethyl)ether at

lower doses (up to 2%, or approximately 5 mg/kg-day) for 90 days showed no significant effects on food consumption or body weights.

Table 5.5. Effects in New Zealand White rabbits (5/sex/group) topically exposed to bis(2-dimethylaminoethyl)ether 6 hours/day 5 days/week for 11 days (including 9 days of exposure)

Endpoint	Dose (%)			
	0	2.5	5.0	10
Males				
Food consumption (g/animal/day); Males				
Day 5	125.0 ± 46.9[a]	114.5 ± 36.2	93.3 ± 37.1	43.3 ± 28.6[b]
Day 8	157.2 ± 24.9	128.3 ± 36.9	96.4 ± 50.8[b]	65.5 ± 20.6[b]
Food consumption (g/animal/day); Females				
Day 5	120.6 ± 38.1	117.6 ± 32.9	114.6 ± 29.2	65.5 ± 30.0
Day 8	123.0 ± 32.0	126.3 ± 17.7	110.3 ± 44.4	83.5 ± 11.0
Body weight loss (g)				
Males	18.4 ± 58.2	41.0 ± 94.5	308.6 ± 144.4[b]	381.6 ± 132.9[b]
Females	76.0 ± 145.1	127.4 ± 65.8	197.0 ± 88.7	345.6 ± 115.8[b]

[a]Values represent means ± SDs.
[b]Significantly different from controls at $p<0.05$.

Reference: Union Carbide Corp. (1984)

Although the mean body weights of pregnant female rabbits exposed to bis(2-dimethylaminoethyl)ether on GDs 6-18 tended to decrease on GDs 12, 18, and 29 with increasing dose, body weights remained within 10% of control groups throughout the entire study (Tyl et al., 1986; Union Carbide Corp., 1985). Rabbits exposed at 10% (about 24 mg/kg-day) lost weight during GDs 12-18 and 6-18, and gained significantly less weight than controls during GDs 6-29 (Table 5.6). Untreated controls (maintained in the same room, but not treated in any way) gained almost twice as much weight during exposure (GDs 6-18) as treated controls exposed only to the water vehicle (165 g for untreated controls vs. 86 g for treated controls), suggesting that the treatment procedure contributed to decreased body weight gain in exposed rabbits. In support of these data, the mean body weights of exposed rabbits (uncorrected and corrected for gravid uterine weight) were not significantly different from controls by scheduled sacrifice on GD 29.

Table 5.6. Effects in New Zealand White rabbits (22/group) topically exposed to bis(2-dimethylaminoethyl)ether 6 hours/day on GDs 6-18.

Endpoint	Dose (%)				
	0 (treated control)	**0 (untreated control)**	**1.0**	**5.0**	**10**
Number of animals	22	22	22	22	22
Body weight gain (g)					
GDs 12-18	102.6±115.2[a]	96.4 ± 98.9	48.0 ± 99.2	24.6 ± 105.5	-123.8 ± 125.1[b]
GDs 6-18	85.9 ± 93.2	164.6 ± 156.9	54.6 ± 119.9	3.8 ± 166.1	-191.59 ± 152.6[b]
GDs 6-29	280.0 ± 146.9	265.1 ± 163.9	253.9 ± 165.7	197.52 ± 156.9	83.9 ± 174.6[b]
Body weight at sacrifice (g)	3,946 ± 455	3,910 ± 448	3,877 ± 334	3,843 ± 472	3,736 ± 389

[a]Values represent means ± SDs.
[b]Significantly different from controls at $p<0.05$.

Reference: Tyl et al. (1986); Union Carbide Corp. (1985)

5.8. Ocular, Respiratory, and Dermal Toxicities

As discussed in Section 5.7, bis(2 dimethylaminoethyl)ether induces ocular, dermal, and respiratory irritation in rats by repeated inhalation exposure and skin irritation at the application site in rabbits by repeated dermal exposure. Gross and histological pathology results reflect these effects and show that changes occurred at lower exposure levels than did overt symptoms.

In the short-term inhalation studies (Union Carbide Corp., 1989, 1988), gross pathology findings, including skin encrustation (especially of the head), eye opacity, periocular encrustation, and/or discoloration of the ears and lungs, were noted at 10 ppm and were significantly increased relative to controls at ≥20 ppm (see Appendix Tables B.2, B.3 and B.5). Histopathological examinations revealed increased incidences of respiratory tract lesions in exposed rats of all groups relative to controls. Vacuolar cytoplasmic swelling of cells from the nasal cavity was observed at ≥1 ppm; significant vacuolization of cells from other upper and lower respiratory tract tissues (nose, pharynx, larynx, trachea, and bronchi/bronchioles) and cell necrosis (of the eyelids or nasal cavity) were observed at ≥10 ppm.

In the 14-week inhalation study (Union Carbide Corp., 1993a), gross pathology findings, including an increased incidence of diffuse color changes to the eye in females (5/10 vs. 0/10 controls) and observations of swollen eye tissue in males ($p > 0.05$), were observed at 5.8 ppm. Histological examinations revealed a significantly increased incidence of cell vacuolization (epithelial and/or interstitial cells) within the nasal cavity at ≥0.22 ppm (Tables 5.7 and 5.8). The incidence of other ocular and respiratory effects (including dermatitis, rhinitis, vacuolization of cells from the eyes and the upper and lower respiratory tract, and alveolar histiocytosis) were

increased relative to controls at 1.25 and 5.8 ppm. Electron microscopic examinations of the nasal cavities of rats exposed to 5.8 ppm showed the presence of intracytoplasmic membrane-bound vacuoles in the mucosal epithelium (after 1 exposure) or mucosa and submucosa (after 3 to 5 exposures).

Table 5.7. Significant effects in male Sprague-Dawley rats administered bis(2-dimethylaminoethyl)ether as a vapor 6 hours/day 5 days/week for 14 weeks

	Exposure concentration (ppm)			
	0	**0.22**	**1.25**	**5.8**
Histopathology[a]				
Dermatitis				
Skin	0/10	0/10	0/10	6/10[b]
Nose	0/10	0/10	0/10	5/10[b]
Hyperkeratosis; nose	1/10	0/10	0/10	8/10[b]
Rhinitis	0/10	0/10	2/10	9/10[b]
Cell vacuolization				
Nose; epidermal	0/10	0/10	0/10	10/10[b]
Eyelids; epidermal	0/10	0/10	0/10	9/10[b]
Cornea; epithelial	0/10	0/10	2/10	7/10[b]
Nasal cavity; epithelial	0/10	10/10[b]	10/10[b]	10/10[b]
Nasal cavity; interstitial	0/10	4/10	10/10[b]	10/10[b]
Nasal cavity; submucosal gland	0/10	0/10	0/10	6/10[b]
Larynx; epithelial	0/10	0/10	0/10	8/10[b]
Trachea; epithelial	0/10	0/10	0/10	10/10[b]
Bronchi/bronchioles; epithelial	0/10	0/10	0/10	9/10[b]
Necrosis; olfactory epithelium	0/10	0/10	0/10	9/10[b]

[a]Number affected/number examined.
[b]Significantly different from controls at $p<0.05$ based on statistics performed by the study authors.

Reference: Union Carbide Corp. (1993a)

Table 5.8. Significant effects in female Sprague-Dawley rats administered bis(2-dimethylaminoethyl)ether as a vapor 6 hours/day 5 days/week for 14 weeks

	Exposure concentration (ppm)			
	0	**0.22**	**1.25**	**5.8**
Histopathology[a]				
Dermatitis				
Nose	0/10	0/10	0/10	7/10[b]
Epiderrnatitis; nose	0/10	0/10	0/10	7/10[b]
Hyperkeratosis; nose	0/10	0/10	0/10	8/10[b]
Rhinitis	0/10	0/10	0/10	10/10[b]
Submucosal mineralization				
Nasal cavity	3/10	5/10	7/10	9/10[b]
Cell vacuolization				
Nose; epidermal	0/10	0/10	0/10	10/10[b]
Eyelids; epidermal	0/10	0/10	0/10	10/10[b]
Cornea; epithelial	0/10	1/10	0/10	7/10[b]
Nasal cavity; epithelial	0/10	10/10[b]	10/10[b]	10/10[b]
Nasal cavity; interstitial	0/10	5/10[b]	10/10[b]	10/10[b]
Nasal cavity; submucosal gland	0/10	1/10	1/10	5/10[b]
Larynx; epithelial	0/10	0/10	0/10	7/10[b]
Trachea; epithelial	0/10	0/10	0/10	9/10[b]
Bronchi/bronchioles; epithelial	0/10	0/10	0/10	9/10[b]
Necrosis				
Nose	0/10	0/10	0/10	5/10[b]
Olfactory epithelium	0/10	0/10	8/10[b]	10/10[b]
Respiratory epithelium	0/10	3/10	2/10	5/10[b]
Squamous metaplasia				
Nasal cavity	0/10	0/10	0/10	5/10[b]
Histiocytosis; alveolar	0/10	1/10	0/10	5/10[b]

[a]Number affected/number examined.
[b]Significantly different from controls at $p<0.05$ based on statistics performed by the study authors.

Reference: Union Carbide Corp. (1993a)

Rabbits topically exposed to 2.5, 5, or 10% bis(2-dimethylaminoethyl)ether (about 8, 15, or 33 mg/kg-day) for 11 days showed signs of dermal irritation that increased with increasing dose and number of exposures (Ballantyne et al., 1986; Union Carbide Corp., 1984). By study termination on day 12, mean Draize scores were indicative of moderate to severe erythema and edema at doses ≥5% (see Appendix Table B.9). Other signs of dermal irritation noted by the study authors in the 5 and 10% groups were cracks and fissures, ulceration, desquamation, and cell necrosis at the application site. A treatment-related increase in vacuolar degeneration of epidermal cells at the application site was reported in rabbits from the 10% group (rabbits from low- and mid-dose groups not examined; incidence data not provided).

Rabbits exposed to lower concentrations (0.2, 0.7 or 2.0%, or about 0.5, 2, or 5 mg/kg-day) of the test material for 90 days showed dose-related increases in erythema and edema (Ballantyne et al., 1986; Union Carbide Corp., 1984). Mean Draize scores (presented

graphically) were indicative of well-defined erythema and very slight to slight edema at 2%; slight erythema and very slight edema occurred in lower dose groups. In addition to erythema and edema, desquamation, fissuring and cracking were observed in the 2% group. Gross examination at study termination did not show any treatment-related skin lesions, but histopathological examination found increased incidence of vacuolization of epidermal cells at the application site that was significantly increased relative to controls at ≥0.7% in females and at 2.0% in males (Table 5.9). Other histopathological signs of dermal irritation reported by the study authors in mid- and high-dose animals included acanthosis and dermatitis.

Table 5.9. Effects in New Zealand White rabbits (5 sex/group) topically exposed to bis(2-dimethylaminoethyl)ether 6 hours/day 5 days/week for 90 days

Endpoint	Dose (%)			
	0	0.2	0.7	2.0
Vacuolization of epidermal cells				
Males	0/10[a]	NR	2/10	10/10[b]
Females	0/10	NR	7/10[b]	10/10[b]

[a]Number affected/number examined.
[b]Significantly different from controls at $p<0.05$ based on Fisher's exact tests performed for this review.
NR = Not reported

Reference: Union Carbide Corp., 1985

A dose-related increase in dermal irritation at the application site was also seen in pregnant female rabbits applied 1.0, 5.0, or 10.0% of the test material during gestation (selected time points shown in Appendix Table B.11; Tyl et al., 1986; Union Carbide Corp., 1985). Animals in the 5.0% dose group and especially in the 10% dose group showed severe erythema to slight eschar formation and severe edema by GD 18; these lesions did not heal completely by study termination on GD 29. Other dermal lesions that occurred at the application site in groups exposed at ≥5% included rippled skin, open sores, scabs, pus-filled sacs, discoloration, and fissuring. The treated skin of exposed rabbits was not examined microscopically.

5.9. Hematological effects

There is limited evidence for an effect of bis(2-dimethylaminoethyl)ether on white blood cell count and differential from inhalation studies in rats. In short-term inhalation studies, male and female rats exposed to the test substance at 20 ppm showed significant increases in overall leukocyte counts (30 to 80% higher than controls) and neutrophil counts (3- to 5-fold higher than controls) (Table 5.10). Neutrophil counts were also significantly increased in males at 10 ppm (2-fold higher than controls). Other significant changes in these rats were increases in

lymphocyte and monocyte counts in females at 20 ppm (1.4- and 2.7-fold, respectively) and a decrease in platelet count in males at ≥10 ppm (17 to 18% lower than controls). Small changes in red cell parameters in the rats exposed to the higher levels were attributed by the study authors to the dehydrated and debilitated condition of the rats by study termination. In the subchronic inhalation study (Union Carbide Corp., 1993a), rats exposed to bis(2-dimethylaminoethyl)ether at 5.8 ppm showed significantly increased numbers of neutrophils in the blood at 6 weeks (62 and 145% higher in males and females, respectively, than controls) Neutrophils remained significantly higher in higher-exposure females (but not males) after 14 weeks of exposure (3.3-fold higher than controls) (Table 5.11). These changes occurred in the absence of any significant change in overall leukocyte count in this study. The subchronic dermal study in rabbits included hematological evaluations, but found no effects (Ballantyne et al., 1986; Union Carbide, 1984).

Table 5.10. Effects in Sprague-Dawley rats administered bis(2-dimethylaminoethyl)ether as a vapor 6 hours/day 5 days/week for 11 days (including 9 days of exposure)

Union Carbide Corp., 1988					
Endpoint		**Exposure concentration (ppm)**			
		0	**20**	**40**	**90**
Leukocytes (10^3/µl)					
	Males	9.4 ± 1.0 (10)[a]	15.0 ± 3.2 (10)[b]	NE	NE
	Females	9.1 ± 1.8 (10)	16.4 ± 3.1 (10)[b]	NE	NE
Segmented neutrophils					
	Males	1275 ± 725 (10)	5572 ± 2192 (10)[b]	NE	NE
	Females	988 ± 342 (10)	4839 ± 1391 (10)[b]	NE	NE
Lymphocytes	Females	7528 ± 1714 (10)	10,161 ± 2532 (10)[b]	NE	NE
Monocytes[c]	Females	480 ± 374 (10)	1319 ± 374 (10)[b]	NE	NE
Union Carbide Corp., 1989					
Endpoint		**Exposure concentration (ppm)**			
		0	**1**	**10**	**20**
Leukocytes (10^3/µl)					
	Males	12.6 ± 1.6 (10)[a]	12.0 ± 1.8 (10)	13.0 ± 3.1 (10)	14.3 ± 2.7 (10)
	Females	11.9 ± 1.6 (10)	13.5 ± 2.9 (10)	13.1 ± 2.7 (10)	15.2 ± 1.7 (9)[b]
Segmented neutrophils					
	Males	1372 ± 566 (10)	1601 ± 618 (9)	2484 ± 973 (10)[b]	3928 ± 532 (10)[b]
	Females	1046 ± 582 (10)	1190 ± 601 (10)	1252 ± 380 (10)	3526 ± 840 (9)[b]
Platelets (10^3/µl);	Males	852 ± 82 (10)	887 ± 75 (9)	701 ± 141 (10)[b]	705 ± 101 (10)[b]

[a]Values represent means ± SDs number of animals).
[b]Significantly different from controls at $p<0.05$.
[c]Values represent medians ± quartile deviations.
NE= Not evaluated

Reference: Union Carbide Corp. (1989, 1988)

Table 5.11. Effects in Sprague-Dawley rats administered bis(2-dimethylaminoethyl)ether as a vapor 6 hours/day 5 days/week for 14 weeks				
	Exposure concentration (ppm)			
	0	**0.22**	**1.25**	**5.8**
Males				
Segmented neutrophils (cells/µL); wk 6	918 ± 599 (13)[a]	NE	NE	1,478 ± 464 (15)[b]
Females				
Segmented neutrophils (cells/µL); wk 6	518 ± 262 (15)	NE	NE	1,268 ± 360 (15)[b]
Segmented neutrophils (cells/µL); wk 14	532 ± 255 (10)	NE	NE	1,737 ± 697 (10)[b]

aValues represent means ± SDs number of animals).
bSignificantly different from controls at $p<0.05$.
NE= Not evaluated

Reference: Union Carbide Corp. (1993a)

5.10. Renal Toxicity

Kidney effects (changes in urinalysis parameters, kidney weights, or kidney histopathology) were observed in short-term inhalation studies in rats and in short-term and teratogenicity studies in rabbits (dermal). The toxicological significance of these effects is uncertain because the dehydrated condition of the rats at study termination (indicated by decreased food and/or water consumption and decreased body weights) may have contributed to kidney effects in the short-term inhalation studies. Also, adverse effects were seen only after short-term (but not subchronic) inhalation or dermal exposure.

In the short-term inhalation studies (Union Carbide Corp., 1989, 1988), significant changes in urinalysis parameters were observed at 10 or 20 ppm (Table 5.12). Urine pH and total volume were decreased, while osmolality of the urine was concomitantly increased. Dehydration may have contributed to these effects. In the follow-up study, animals exposed to 10 or 20 ppm also showed significantly increased levels of potassium and creatinine in the urine, and a significantly decreased rate of creatinine clearance. However, these changes did not occur consistently in both sexes and/or were not concentration-related They were attributed by the study authors to the poor general condition of the animals. No treatment-related changes in kidney weights were observed. Rats exposed to bis(2-dimethylaminoethyl)ether at up to 5.8 ppm for 14 weeks showed decreased chloride (significant in females) but no significant changes in the pH, total volume, or osmolality of the urine (Union Carbide Corp., 1993a). Kidney weights were not affected by treatment, and high-concentration animals showed no evidence of histopathological kidney lesions.

Table 5.12. Changes in urinalysis parameters in Sprague-Dawley rats administered bis(2-dimethylaminoethyl)ether as a vapor 6 hours/day 5 days/week for 11 days (including 9 days of exposure)

Union Carbide Corp., 1988				
Endpoint	**Exposure concentration (ppm)**			
	0	**20**	**40**	**90**
pH				
Males	7.0 ± 0.5 (10)[a]	6.4 ± 0.5 (10)[b]	6.2 ± 0.5 (6)[b]	NE
Females	7.1 ± 0.3 (10)	6.2 ± 0.4 (10)[b]	NE	NE
Total volume (mL)				
Males	6.8 ± 1.5 (10)	3.9 ± 0.8 (10)[b]	1.8 ± 1.0 (6)[c]	NE
Females	6.8 ± 0.8 (10)	3.3 ± 0.9 (10)[b]	NE	NE
Osmolality				
Males	2,263 ± 412 (10)	3,151 ± 264 (10)[b]	3,588 ± 424 (6)[b]	NE
Females	2,043 ± 183 (10)	3,081 ± 424 (10)[b]	NE	NE
Union Carbide Corp., 1989				
Endpoint	**Exposure Concentration (ppm)**			
	0	**1**	**10**	**20**
pH				
Males	7.7 ± 0.5 (10)	7.5 ± 0.5 (10)	7.2 ± 0.4 (10)[b]	6.6 ± 0.5 (10)[b]
Females	7.5 ± 0.5 (10)	7.2 ± 0.4 (10)	8.0 ± 0 (10)[b]	7.0 ± 0 (10)[b]
Total volume (mL)				
Males	8.6 ± 2.0 (10)	9.0 ± 1.6 (10)	11.8 ± 10.8 (10)	4.0 ± 0.9 (10)[b]
Females	11.2 ± 3.1 (10)	7.7 ± 3.0 (10)[b]	20.1 ± 7.4 (10)[b]	4.5 ± 1.7 (10)[b]
Osmolality				
Males	2,070 ± 431 (10)[a]	1,996 ± 310 (10)	1,739 ± 619 (10)	2,781 ± 146 (10)[b]
Females	1,447 ± 264 (10)	1,845 ± 430 (10)[b]	716 ± 306 (10)[b]	2,639 ± 499 (10)[b]
Potassium (mmol/L)				
Males	326 ± 62 (10)	338 ± 59 (10)	272 ± 100 (10)	395 ± 62 (10)[b]
Females	221 ± 38 (10)	283 ± 65 (10)[b]	113 ± 45 (10)[b]	399 ± 69 (10)[b]
Creatinine (mg/dL)				
Males	97 ± 15 (10)	94 ± 15 (10)	91 ± 32 (10)	138 ± 12 (10)[b]
Females	52 ± 12 (10)	68 ± 15 (10)[b]	28 ± 9 (10)[b]	99 ± 21 (10)[b]
Creatinine clearance (mL/15 hr)				
Males	2,246 ± 452 (10)	NE	2,303 ± 263 (10)	1,617 ± 489 (10)[b]
Females	1,478 ± 352 (10)	NE	NE	1,277 ± 267 (10)

[a]Values represent means ± SDs number of animals).
[b]Significantly different from controls at $p<0.05$ based on statistics performed by the study authors.
[c]Significantly different from controls at $p<0.05$ based on Student's t-test performed for this review.
NE= Not evaluated

Reference: Union Carbide Corp. (1989, 1988)

Rabbits exposed to the test substance topically at 5 or 10% (about 15 or 33 mg/kg-day) 5 hours/day 6 days/week for 11 days showed significantly increased absolute and relative kidney weights (Table 5.13; Ballantyne et al., 1986; Union Carbide Corp., 1984). Treatment-related kidney lesions reportedly included hydropic degeneration (collecting ducts and cortex) and tubular dilation (cortex and medulla) in all dose groups, with increased severity in the 10% group (data not shown).

Pregnant female rabbits exposed topically to 10% during gestation showed increased relative kidney weight (+13%) and significantly increased incidence of vacuolar swelling of the collecting ducts in the kidneys compared to treated or untreated controls (Table 5.14; Tyl et al., 1986; Union Carbide Corp., 1985). This lesion was characterized by marked swelling of the cytoplasm in epithelial cells lining the outermost part of the inner medulla. No significant kidney effects were observed at ≤5.0% in this study. Rabbits exposed at up to 2% of the test substance (about 5 mg/kg-day) topically under occluded conditions for 90 days did not exhibit significant changes in urinalysis parameters, kidney weights, or kidney histopathology (Ballantyne et al., 1986; Union Carbide Corp., 1984).

Table 5.13. Kidney effects in New Zealand White rabbits (5/sex/group) topically exposed to bis(2-dimethylaminoethyl)ether 6 hours/day 5 days/week for 11 days (including 9 days of exposure)

	Dose (%)			
	0	**2.5**	**5.0**	**10**
Absolute kidney weight(g)				
Males	17.09 ± 1.18[a]	17.10 ± 0.79	18.07 ± 1.25[b]	24.03 ± 2.76[b]
Females	16.62 ± 1.56	16.78 ± 0.83	18.07 ± 1.25[b]	24.64 ± 4.92[b]
Relative kidney weight				
Males	0.62 ± 0.07	0.62 ± 0.02	0.72 ± 0.10[b]	1.08 ± 0.17[b]
Females	0.67 ± 0.07	0.67 ± 0.02	0.80 ± 0.13[b]	1.14 ± 0.18[b]

[a]Values represent means ± SDs.
[b]Significantly different from controls at $p<0.05$.

Reference: Union Carbide Corp. (1984)

Table 5.14. Maternal effects in New Zealand White rabbits (22/group) topically exposed to bis(2-dimethylaminoethyl)ether 6 hours/day on GDs 6-18.

Endpoint	**Dose (%)**				
	0 (treated control)	**0 (untreated control)**	**1.0**	**5.0**	**10**
Number of animals	22	22	22	22	22
Relative kidney weight	0.48 ± 0.06[a]	0.48 ± 0.06	0.49 ± 0.05	0.48 ± 0.05	0.54 ± 0.08[b]
Histopathology; kidney Vacuolar swelling; collecting ducts	0/22[c]	0/22	0/22	4/22	20/22[d]

[a]Values represent means ± SDs.
[b]Significantly different from controls at $p<0.05$ based on statistics performed by the study authors.
[c]Number affected/number examined.
[d]Significantly different from controls at $p<0.05$ based on Fisher's exact test performed for this review.

Reference: Tyl et al. (1986); Union Carbide Corp. (1985)

5.11. Prenatal, Perinatal, and Post-natal Toxicity

No treatment-related effects on the numbers of corpora lutea, total implantations, viable and nonviable implantations per litter, percentages of pre-implantational loss and live fetuses per litter, or sex ratio of the pups were observed in pregnant rabbits treated dermally with bis(2-dimethylaminoethyl)ether up to 10% (24 mg/kg-day) on GD 6-18 (Tyl et al., 1986; Union Carbide Corp., 1985). The mean body weights of fetuses (males and females combined) and female fetuses per litter were significantly decreased (by 12 and 13%, respectively) in the 10% dose group compared to controls (Table 5.15). There was no significant treatment-related effect on the incidence of fetuses or litters with external, visceral, skeletal, or total malformations in exposed rabbits compared to treated (vehicle-only) or untreated controls.

Table 5.15. Litter effects in New Zealand White rabbits (22/group) topically exposed to bis(2-dimethylaminoethyl)ether 6 hours/day on GDs 6-18.

Endpoint	Dose (%)				
	0 (treated control)	**0 (untreated control)**	**1.0**	**5.0**	**10**
Number of litters	21	19	19[e]	18	21
Fetal body weight per litter (g) Combined	45.36 ± 5.87[a]	42.42 ± 5.08	41.93 ± 4.00	42.36 ± 3.19	39.86 ± 5.13[b]
Males	44.24 ± 5.23[c]	42.50 ± 3.83[c]	42.82 ± 4.61	43.24± 4.56	40.37 ± 5.99
Females	45.29 ± 5.90[d]	41.95 ± 5.73	40.92 ± 4.47[b]	41.50 ± 2.83	39.32 ± 5.32[b,d]

[a]Values represent means ± SDs number of animals).
[b]Significantly different from controls at $p<0.05$.
[c]Data are for 19 and18 litters for treated and untreated controls; respectively; two litters (treated controls) or one litter (untreated controls) contained only female fetuses.
[d]Data are for 20 litters; one litter at 0 and 10% contained only male fetuses.
[e]The sex of one fetus in the 1.0% group was not recorded. Its weight (36.94 g) was included in the combined litter weight data, but not in fetal body weights by sex.

Reference: Tyl et al. (1986); Union Carbide Corp. (1985)

5.12. Carcinogenicity

Genotoxicity

Bis(2-dimethylaminoethyl)ether was negative in assays for reverse mutation in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 in the presence or absence of metabolic activation, a forward mutation at the HGPRT locus in Chinese hamster ovary (CHO) cells, and unscheduled DNA synthesis (UDS) in rat hepatocytes (Union Carbide Corp., 1987a). A weak but statistically significant increase in the frequency of sister chromatid exchange (SCE) in CHO cells treated with bis(2-dimethylaminoethyl)ether was reported with or

without metabolic activation, but the results were considered equivocal by the study authors. This is because a dose-response relationship was not observed, positive responses in treated cells were only 1.3 to 1.5 times higher than concurrent controls, the effect was not replicated in duplicate cultures, and statistical significance was achieved only when data for replicate samples were combined (Union Carbide Corp., 1987a). An in vivo assay for micronucleus formation in the peripheral blood of male and female Swiss Webster mice was negative when they were administered the test substance at 45, 90, or 145 mg/kg as a single dose via i.p. injection (Union Carbide Corp., 1993b).

Initiation and Promotion

No initiation or promotion studies were located for bis(2-dimethylaminoethyl)ether.

Carcinogenicity Studies

No carcinogenicity studies were located for bis(2-dimethylaminoethyl)ether.

6. EXPOSURE

The American Chemistry Council (2010 and 2011) has reported that occupational exposure to amine catalysts may occur through inhalation, skin contact, eye contact, and ingestion. Although ingestion is unlikely in the workplace, the chemical may be inadvertently ingested if an individual eats, drinks, or smokes in areas where SPF chemicals are used.

In general, exposure limits are not yet established for the majority of the amine catalysts used in SPF systems. Bis(2-dimethylaminoethyl)ether is one of the few polyurethane amine catalysts that has been assigned Occupational Exposure Limits (OELs) by regulatory and non-regulatory organizations (Table 6.1) (ACC, 2011). This includes the Ontario Ministry of Labour in Canada, which has established enforceable OELs. The U.S. Occupational Safety and Health Administration (OSHA) has also set enforceable permissible exposure limits (PELs) to protect workers. Other organizations that have established OELs include the American Conference of Government Industrial Hygienists (ACGIH), which has developed threshold limit values (TLVs). TLVs are generally provided as guidance and not legally enforceable. The OELs, PELs, and TLVs can be provided as a time-weighted average (TWA) or short-term exposure limits (STELs). A TWA is the average exposure over a certain period of time, which may be an 8-hour

day. The STEL is the average exposure over a 15 minute period that should not be exceeded during a workday, even if the 8-hour TWA is within the criteria (ACC, 2011).

The ACGIH has established a TWA of 0.05 ppm (Skin) and a STEL of 0.15 ppm (Skin) (ACC, 2011) for bis(2-dimethylaminoethyl)ether. These are based on the potential, significant contribution to the overall exposure by the cutaneous route including mucous membranes and the eyes by contact with vapors, liquids, and solids (ACGIH, 2005).

Table 6.1. Permissible Exposure Levels and Threshold Limit Values of Some Polyurethane Amine Catalysts

Amine Catalyst	CASRN	Exposure Limit (Source)			
		PEL	STEL	TLV	TWA
Dimethylcyclohexylamine, N,N-	98-94-2	NR	5 ppm (Ontario)	NR	NR
N-ethylmorpholine	100-74-3	20 ppm Skin[2] (OSHA)	NR	NR	5 ppm Skin[1] (ACGIH)
Triethanolamine	102-71-6	NR	NR	NR	5 mg/m^3 (ACGIH)
Dimethylamino ethanol, 2-	108-01-0	NR	6 ppm (Ontario)	NR	3 ppm (Ontario)
N,N-Dimethylaminopropylamine	109-55-7	NR	NR	NR	0.5 ppm (ACGIH)
Diethanolamine	111-42-2	NR	NR	1 mg/m^3 (ACGIH)	3 ppm (ACGIH)
Triethylamine	121-44-8	25 ppm (OSHA)	3 ppm (ACGIH)	NR	NR
Triethylenediamine	280-57-9	NR	NR	NR	1 ppm Skin[1] (Ontario)
Bis (2-Dimethylaminoethyl) ether	3033-62-3	NR	0.15 ppm Skin[1] (ACGIH)	NR	0.05 ppm Skin[1] (ACGIH)

[1] Potential for significant contribution to overall exposure by skin.
[2] Substance which may be absorbed through the skin.

PEL = permissible exposure limit
STEL = short-term exposure limit
TLV = threshold limit value
TWA = time-weighted average
OSHA = Occupational Safety and Health Administration
ACGIH = American Conference of Government Industrial Hygienists
Ontario = Ontario Ministry of Labour in Canada
NR = Not reported

Reference: American Chemistry Council (2011)

Exposure data specific to bis(2-dimethylaminoethyl)ether were not found for consumer or general populations.

7. DISCUSSION

While several toxicological studies on bis(2-dimethylaminoethyl)ether were found during this assessment, the current literature is limited on physicochemical, manufacture, supply, use, and exposure information.

Appendix A provides a summary of the no-observed-adverse-effect level (NOAEL) and lowest-observed-adverse-effect level (LOAEL) values for organ-specific endpoints for bis(2-dimethylaminoethyl)ether, which are derived from the repeat-dose inhalation toxicity studies of Union Carbide Corp. (1988, 1989, 1993a) in rats, the dermal toxicity studies of Ballantyne et al. (1986) and Union Carbide Corp. (1984) in rabbits, and the developmental toxicity study of Tyl et al. (1986) and Union Carbide Corp. (1985) in rabbits.

The most sensitive measures of effect in inhalation and dermal toxicity studies were observed in tissues that came in direct contact with bis(2-dimethylaminoethyl)ether, namely the ocular, dermal and respiratory tissues in inhalation studies and the skin in dermal studies. Short-term inhalation studies provided evidence for vacuolar cytoplasmic swelling in the nasal cavity of rats exposed at concentrations as low as 1 ppm for 6 hours/day, 5 days/week for 11 days (Union Carbide Corp., 1989, 1988). A subsequent subchronic-duration study (Union Carbide Corp., 1993a) was conducted over a period of 14 weeks and found vacuolar cytoplasmic swelling in the nasal cavity and swollen periocular tissue at concentrations as low as 0.22 ppm. Other histological changes to the eyes or the upper and lower respiratory tract tissues were observed at 1.25 and/or 5.8 ppm, respectively, after 14 weeks.

New Zealand White rabbits exposed for 90 days via the dermal route to bis(2-dimethylaminoethyl)ether at 0.7% in distilled water (approximately 2 mg/kg-day) showed effects on exposed skin including slight erythema and very slight edema and, in females, a significantly increased incidence of epidermal cell vacuolization at the application site. Similar but more severe effects were reported for rabbits exposed to the high-dose of bis(2-dimethylaminoethyl)ether (2% or approximately 5 mg/kg-day).

There is limited evidence for effects on white blood cells in the available studies. The short-term inhalation studies (Union Carbide Corp., 1989, 1988) showed significant increases in total leukocyte and neutrophil counts in rats exposed over 11 days at 20 ppm; neutrophil counts were also increased in males at 10 ppm. In the subchronic inhalation study, total leukocyte

counts were unchanged from controls, but neutrophil counts were increased at 6 weeks in males and females (and at 14 weeks in females) at 5.8 ppm.

Kidney effects (changes in urinalysis parameters, kidney weights, or histopathology) observed in some studies are of uncertain toxicological significance. In the short-term inhalation studies, although rats exposed at 10 or 20 ppm showed significant changes in some urinalysis parameters (decreased pH and total volume and increased osmolality of the urine), the dehydrated condition of exposed rats (indicated by decreased food and water consumption and decreased body weights) may have contributed to these effects. Other urinalysis changes did not occur consistently in both sexes and/or were not concentration related and were attributed by the study authors to the poor general condition of the animals. Rabbits topically administered 5% or 10% bis(2-dimethylaminoethyl)ether (about 15 or 33 mg/kg-day, respectively) over 11 days showed increased relative kidney weight and hydropic degeneration and tubular dilation of the kidneys. Increased relative kidney weight and vacuolar swelling of the collecting ducts of the kidneys were also found in pregnant rabbits administered 10% of the test material (about 24 mg/kg-day) on GDs 6 to 18 (Tyl et al., 1986; Union Carbide Corp., 1985). However, rats exposed via the inhalation route at up to 5.8 ppm for 14 weeks and rabbits exposed to up to 2% (about 5 mg/kg-day) dermally for 90 days did not show signs of kidney damage (Union Carbide Corp., 1993a; Ballantyne et al., 1986; Union Carbide Corp., 1984).

There was no effect on implantations or fetal loss following topical gestational exposure of pregnant rabbits to 2-dimethylaminoethyl)ether at 10% (about 24 mg/kg-day) on GD 6-18, but some fetotoxicity was indicated by significant decreases in fetal body weights (males and females combined and females alone) per litter compared to controls (Tyl et al., 1986; Union Carbide Corp., 1985). There was no significant effect on the incidence of malformations (external, visceral, skeletal, or total) in the offspring of exposed rabbits compared to untreated or treated controls**.**

No cancer bioassays or initiation/promotion studies were located. The available genotoxicity studies showed negative or equivocal results.

Bis(2-dimethylaminoethyl)ether is one of the few polyurethane amine catalysts that has been assigned OELs by ACGIH. Specifically, ACGIH has established a TWA of 0.05 ppm (Skin) and a STEL of 0.15 ppm (Skin) (ACC, 2011). However, no exposure data associated with bis(2-dimethylaminoethyl)ether were found for consumer or general populations.

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Appendix A. Summary of Endpoints by Organ System

Table A.1. Summary of NOAELs/LOAELs Identified for Bis(2-dimethylaminoethyl)ether by Organ System

Species (Gender)	Exposure Route	Dose (Number of Animals per Dose Group)	Dose Duration	Effect Category	Toxicological Endpoint	Toxicological Basis	Citation
Sprague-Dawley rats (M +F)	Inhalation	10/sex/group	0, 20, 40, or 90 ppm for 6 hrs/d 5 d/wk for 11 d (including 9 d of exposure)	General	NOAEL = None LOAEL = 20 ppm	Decreased food consumption (M); decreased body weights; swollen eyes	Union Carbide Corp., 1988
				Respiratory	NOAEL = None LOAEL = 20 ppm	histopathological lesions of the upper and lower respiratory tract (vacuolar cytoplasmic swelling)	
				Hematology	NOAEL = None LOAEL = 20 ppm	Increased leukocytes and neutrophils; increased lymphocytes and monocytes (F)	
Sprague-Dawley rats (M +F)	Inhalation	10/sex/group	0, 1, 10, or 20 ppm for 6 hrs/d 5 d/wk for 11 d (including 9 d of exposure)	General	NOAEL = 10 ppm LOAEL = 20 ppm	Decreased body weight (>10%); decreased food consumption	Union Carbide Corp., 1989
				Respiratory	NOAEL = None LOAEL = 1 ppm	Epithelial cell vacuolization of the nasal cavity	
				Hematology	NOAEL = 1 ppm LOAEL = 10 ppm	Increased neutrophils and decreased platelets (M)	
				Renal	NOAEL = 10 ppm LOAEL = 20 ppm	Increased osmolality and decreased total volume and pH; increased creatinine and potassium and decreased creatinine clearance (M)	

Table A.1. Summary of NOAELs/LOAELs Identified for Bis(2-dimethylaminoethyl)ether by Organ System							
Species (Gender)	**Exposure Route**	**Dose (Number of Animals per Dose Group)**	**Dose Duration**	**Effect Category**	**Toxicological Endpoint**	**Toxicological Basis**	**Citation**
Sprague-Dawley rats (M +F)	Inhalation	15/sex/group	0, 0.22, 1.25, or 5.8 ppm for 6 hrs/d 5 d/wk for 90 d	General	NOAEL = 1.25 ppm LOAEL = 5.8 ppm	Decreased body weight (M)	Union Carbide Corp., 1993a
				Respiratory	NOAEL = None LOAEL = 0.22 ppm	Epithelial cell vacuolization of the nasal cavity	
				Hematology	NOAEL = None LOAEL = 5.8 ppm	Increased neutrophils	
New Zealand White rabbit (M + F)	Dermal	5/sex/group	0, 2.5, 5, or 10% in water (~0, 8, 15, or 33 mg/kg-d) for 6 hrs/d 5 d/wk for 11 d (including 9 d of exposure)	General	NOAEL = 8 mg/kg-d LOAEL = 15 mg/kg-d	Decreased food consumption and body weight loss (M)	Ballantyne et al., 1986; Union Carbide Corp., 1984
				Dermal	NOAEL = 8 mg/kg-d LOAEL = 15 mg/kg-d	Erythema and edema	
				Renal	NOAEL = 8 mg/kg-d LOAEL = 15 mg/kg-d	Increased absolute and relative kidney weights	
New Zealand White rabbit (M + F)	Dermal	10/sex/group	0, 0.2, 0.7, or 2% in water (~0, 0.5, 2, or 5 mg/kg-d) for 6 hrs/d 5 d/wk for 90 d	General	NOAEL = 5 mg/kg-d LOAEL = None	No effects on food consumption or body weights.	Ballantyne et al., 1986; Union Carbide Corp., 1984
				Dermal	NOAEL = None LOAEL = 2 mg/kg-d	Epidermal cell vacuolization	
New Zealand White rabbit (F)	Dermal	22/group	0, 1, 5, or 10% in water (~0, 2, 12, or 24 mg/kg-d) for 6 hrs/d on GDs 6 to 18	General	NOAEL = 12 mg/kg-d LOAEL = 24 mg/kg-d	Decreased body weight gain on GDs 6-29	Tyl et al., 1986; Union Carbide Corp., 1985
				Dermal	NOAEL = 2 mg/kg-d LOAEL = 12 mg/kg-d	Erythema and edema	
				Renal	NOAEL = 12 mg/kg-d LOAEL = 24 mg/kg-d	Increased relative kidney weight accompanied by increased vacuolar cytoplasmic swelling in the collecting ducts	
				Development	NOAEL = 12 mg/kg-d LOAEL = 24 mg/kg-d	Decreased fetal body weights (F and M+F)	

GD = gestation day

Appendix B. Critical Study Reviews

Union Carbide Corp. (1988) examined the short-term inhalation toxicity of bis(2-dimethylaminoethyl)ether. Sprague-Dawley rats (10/sex/group) were whole-body exposed to bis(2-dimethylaminoethyl)ether (96% pure) as a vapor at nominal concentrations of 0 (air-exposed control), 20, 40, or 90 ppm 6 hours/day for 5 days. After two days without exposure, exposures were continued for another 4 days. Measured concentrations (mean ± SD) for the low-, mid-, and high-exposure groups were 22 ± 2, 47 ± 5, and 90 ± 5 ppm, respectively. The first day of exposure was designated as study day 0. Additional groups of 15 male rats exposed to bis(2-dimethylaminoethyl)ether at 0 or 90 ppm were designated for perfusion fixation of the kidneys or to serve as a 4-week recovery group. Mortality and clinical signs of toxicity were monitored daily. Ophthalmologic examinations (including indirect ophthalmoscopy and slit lamp bioscopy) were conducted in all rats prior to study initiation, before and after the sixth exposure, and before the final exposure on study day 11. Body weights were recorded prior to the start of the study and on study days 1, 4, 7, 8, and 11 (prior to sacrifice). Food and water consumption were measured for 15 hours after the eighth (males) or final (females) exposure.

Hematological endpoints were evaluated at sacrifice (Union Carbide Corp., 1988). These included erythyrocyte, platelet, reticulocyte, leukocyte, and differential leukocyte counts; hemoglobin concentration, hematocrit, and mean corpuscular volume [MCV]; hemoglobin [MCH] and hemoglobin concentration [MCHC]); and clinical chemistry (concentrations of serum calcium, phosphorus, sodium, potassium, chloride, glucose, urea nitrogen, creatinine, total protein, albumin, globulin, and total, direct and indirect bilirubin and the activities of aspartate aminotransferase [AST], alanine aminotransferase [ALT], creatine kinase [CK], lactic dehydrogenase [LDH], γ-glutamyl transferase [GGT], sorbitol dehydrogenase [SDH], and alkaline phosphatase [ALK]). Urinalysis endpoints evaluated at study termination included assessments of volume, pH, color, turbidity, and osmolality; semi-quantitative measurements of blood, protein, glucose, ketone, bilirubin, urobilinogen, and microscopic constituents; creatinine, sodium, potassium, and chloride levels; and an estimate of creatinine clearance. At scheduled sacrifice on study day 11, organ weights (brain, liver, kidneys, lungs, heart, adrenal glands, and testes) were recorded, and complete gross pathology evaluations (including examinations of about 58 tissues and all gross lesions) were performed on all rats. Selected tissues were examined histologically in 10 rats/sex/exposure concentration including the eye, lungs, heart, adrenal gland, spleen, testes, kidney, brain, nasal turbinates, larynx, liver, thymic region, and trachea.

All rats in the 40 and 90 ppm groups died or were sacrificed moribund (Table B.1) (Union Carbide Corp., 1988). This includes the supplemental male rats in the 90 ppm group designated for renal perfusion and recovery studies. Deaths occurred on study days 6 to 11 at 40 ppm and study days 3 to 4 at 90 ppm. The study authors did not identify any specific cause for the observed mortalities. No deaths occurred in the 20 ppm or control groups. Rats from all groups exposed to bis(2-dimethylaminoethyl)ether showed clinical signs of toxicity mostly indicative of ocular and respiratory irritations. Symptoms included swollen periocular tissue, blepharospasm, corneal cloudiness and opacity, periocular and perinasal encrustation, gasping, and skin discoloration (reddening of the ears and paws), all of which were increased in incidence compared with controls. Ataxia was observed in some animals from the higher-exposure groups. Ophthalmologic examinations revealed concentration-dependent increases in the incidence and severity of keratitis and blepharitis in rats exposed to 20 and 40 ppm. Although ophthalmic exams were not formally conducted in the 90 ppm rats (due to early mortality), the study authors noted corneal opacities and cloudiness in these animals during the first week of the study.

Table B.1. Effects in Sprague-Dawley rats administered bis(2-dimethylaminoethyl)ether as a vapor 6 hours/day 5 days/week for 11 days (including 9 days of exposure)

Endpoint	Exposure concentration (ppm)			
	0	20	40	90
Males				
Mortality	0/25[a]	0/10	10/10[b]	25/25[b]
Food consumption (g/animal/d)	13.7 ± 3.7 (10)[c]	10.3 ± 3.0 (10)[d]	2.1 ± 3.2 (3)[e]	NE
Water consumption (mL/animal/d)	18.5 ± 2.9 (10)	19.9 ± 6.4 (10)	5.7 ± 5.5 (3)[e]	NE
Body weight (g)				
Day 1	257.8 ± 10.9 (25)	252.9 ± 12.0 (10)	255.9 ± 8.6 (10)	238.1 ± 14.3 (25)[d]
Day 4	267.0 ± 11.9 (25)	242.2 ± 13.2 (10)[d]	218.1 ± 12.0 (10)[d]	187.6 ± 0.3 (2)[d]
Day 8	278.0 ± 12.2 (25)	253.9 ± 12.1 (10)[d]	201.0 ± 20.1 (10)[d]	NE
Day 11	287.0 ± 13.8 (25)	233.2 ± 17.1 (10)[d]	NE	NE
Hematology				
Leukocytes (10^3/µl)	9.4 ± 1.0 (10)	15.0 ± 3.2 (10)[d]	NE	NE
Segmented neutrophils	1,275 ± 725 (10)	5,572 ± 2192 (10)[d]	NE	NE
Clinical chemistry				
Total protein (g/L)	60 ± 2 (10)	56 ± 2 (10)[d]	NE	NE
Albumin (g/L)	32 ± 1 (10)	28 ± 1 (10)[d]	NE	NE
ALK (U/L)	188 ± 41 (10)	141 ± 22 (10)[d]	NE	NE
Urinalysis				
pH	7.0 ± 0.5 (10)	6.4 ± 0.5 (10)[d]	6.2 ± 0.5 (6)[d]	NE
Total volume (mL)	6.8 ± 1.5 (10)	3.9 ± 0.8 (10)[d]	1.8 ± 1.0 (6)[b]	NE
Osmolality	2,263 ± 412 (10)	3,151 ± 264 (10)[d]	3,588 ± 424 (6)[d]	NE

Table B.1. Effects in Sprague-Dawley rats administered bis(2-dimethylaminoethyl)ether as a vapor 6 hours/day 5 days/week for 11 days (including 9 days of exposure)				
Endpoint	**Exposure concentration (ppm)**			
	0	**20**	**40**	**90**
Females				
Mortality	0/10	0/10	10/10[b]	10/10[b]
Food consumption (g/animal)	15.1 ± 2.1 (10)	10.9 ± 3.8 (10)[d]	NE	NE
Body weight (g)				
Day 1	170.3 ± 13.4 (10)	167.1 ± 8.0 (10)	162.9 ± 7.7 (10)	156.9 ± 7.3 (10)[d]
Day 4	181.9 ± 14.0 (10)	163.9 ± 6.8 (10)[d]	140.6 ± 10.8 (10)[d]	156.9 ± 7.3 (10)[d]
Day 8	189.0 ± 13.7 (10)	175.5 ± 6.9 (10)[d]	142.0 ± 8.7 (7)[d]	NE
Day 11	193.8 ± 14.0 (10)	167.5 ± 11.0 (10)[d]	NE	NE
Hematology				
Leukocytes (10^3/µl)	9.1 ± 1.8 (10)	16.4 ± 3.1 (10)[d]	NE	NE
Segmented neutrophils	988 ± 342 (10)	4839 ± 1391 (10)[d]	NE	NE
Lymphocytes	7,528 ± 1714 (10)	10,161 ± 2532 (10)[d]	NE	NE
Monocytes[f]	480 ± 374 (10)	1,319 ± 374 (10)[d]	NE	NE
Clinical chemistry				
Total protein (g/L)	58 ± 3 (10)	54 ± 2 (10)[d]	NE	NE
Albumin (g/L)	32 ± 1 (10)	28 ± 1 (10)[d]	NE	NE
CK (U/L)	117 ± 28 (10)	180 ± 56 (10)[d]	NE	NE
LDH (U/L)	182 ± 57 (10)	243 ± 62 (10)[d]	NE	NE
Urinalysis				
pH	7.1 ± 0.3 (10)	6.2 ± 0.4 (10)[d]	NE	NE
Total volume (mL)	6.8 ± 0.8 (10)	3.3 ± 0.9 (10)[d]	NE	NE
Osmolality	2,043 ± 183 (10)	3,081 ± 424 (10)[d]	NE	NE

[a]Number affected/number examined.
[b]Significantly different from controls at $p<0.05$ based on Fisher's exact tests (categorical data) or Student's t-test (continuous data) performed for this review.
[c]Values represent means ± SDs (number of animals).
[d]Significantly different from controls at $p<0.05$ based on statistics performed by the study authors.
[e]The study authors reported that this value not used in statistical tests (due to small sample size).
[f]Values represent medians ± quartile deviation as presented in the study report.
NE = Not evaluated.

Reference: Union Carbide Corp. (1988)

Due to the early mortality in the two higher exposure groups, few toxicological endpoints were assessed in these groups. Table B.1 shows the effects observed in the study and denotes endpoints that were not evaluated in the 40 and/or 90 ppm groups. Food and water intake and body weight were all reduced in treated rats. Food consumption was decreased 25 to 28% in 20 ppm males and females and 85% in 40 ppm males relative to respective controls; water consumption was also 69% lower than controls in males exposed at 40 ppm (Union Carbide Corp., 1988). Mean body weights of males and females were statistically significantly lower than controls in 20 and 40 ppm rats from study day 4 and in 90 ppm rats from study day 1; body weights in all exposure groups were reduced by more than 10% relative to controls by the final time point in which body weights were measured (study days 11, 8 and 4 for the 20, 40, and 90 ppm groups, respectively).

Male and female rats showed statistically significant increases in mean leukocyte (60 and 80% higher than controls) and neutrophil counts (4- to 5-fold higher than controls) at 20 ppm. Mean lymphocyte and median monocyte counts were also increased significantly in the 20 ppm females (1.4- and 2.7-fold, respectively), and these values tended to be increased (albeit not significantly) in males as well. Other small but statistically significant changes in hematological endpoints at 20 ppm (increased erythrocytes, hemoglobin, and hematocrit and decreased reticulocytes in males and females, and decreased MCV and MCH in males) were attributed by the study authors to the debilitated and dehydrated condition of the animals by study termination.

Decreased serum albumin (7% lower than controls) and total protein (13% lower than controls) were observed in rats of both sexes exposed to bis(2-dimethylaminoethyl)ether at 20 ppm (Table B.1) (Union Carbide Corp., 1988). Although the activities of CK and LDH were significantly increased in females (by 54 and 34%, respectively), they remained within 2-fold of control values. A statistically significant decrease in ALK activity in 20 ppm males (25% lower than controls) was noted but is of uncertain toxicological significance because typically an increase in ALK would be considered indicative of an adverse effect. Other changes in clinical chemistry parameters (significantly increased serum urea nitrogen, potassium, and sodium and decreased glucose and creatinine in males and increased phosphorus in females) occurred in only one sex and were attributed by the study authors to the debilitated and dehydrated condition of animals by study termination.

Urinalysis showed that rats exposed to bis(2-dimethylaminoethyl)ether at 20 or 40 ppm had significantly decreased total volume and pH and increased osmolality of the urine, and dehydration may have contributed to these effects. Other changes in urinalysis endpoints (decreased sodium and chloride in 40 ppm males, increased potassium and creatinine and decreased creatinine clearance in 20 ppm females, and changes in protein levels in both sexes) did not occur consistently in both sexes and/or were not concentration-related. Therefore, they were attributed by the study authors to the poor general condition of the surviving animals.

At scheduled sacrifice, the body weights of rats from all exposed groups were reduced 10% or more relative to controls (Union Carbide Corp., 1988; Table B.2 and B.3). Rats that were sacrificed on schedule or died spontaneously showed skin encrustation (especially of the head), eye opacity with periocular encrustation, and/or discoloration of the ears and lungs in all exposed groups. Mean absolute weights of the liver, heart and testes (males), and the kidneys (both sexes) were significantly lower in 20 ppm animals than respective controls. However, these effects were considered by the study authors to be a by-product of body weight loss, since

mean relative organ weights (normalized to body weight) were significantly higher in 20 ppm males and females than in respective control groups.

Table B.2. Effects in male Sprague-Dawley rats administered bis(2-dimethylaminoethyl)ether as a vapor 6 hours/day 5 days/week for 11 days (including 9 days of exposure)

	Exposure concentration (ppm)			
	0	**20**	**40**	**90**
Final body weight (g)	286.0 ± 14.9 (10)[a]	233.2 ± 17.1(10)[b]	201.0 ± 20.1 (10)[b,c]	187.6 ± 0.3 (2)[b,c]
Gross pathology[d]				
Head encrustation	0/10	9/10[e]	9/10[e]	25/25[e]
Eyes				
Diffuse color changes	0/10	0/10	7/10[e]	25/25[e]
Increased thickness	0/10	0/10	9/10[e]	25/25[e]
Opacity	0/10	1/10	4/10	16/25[e]
Swollen	0/10	7/10[e]	10/10[e]	22/25[e]
Histopathology[d]				
Cell vacuolization				
Heart; arterial	0/10	0/10	10/10[b]	10/10[b]
Liver; hepatocellular	0/10	2/10	10/10[b]	10/10[b]
Spleen	0/10	0/10	10/10[b]	9/10[b]
Eye; corneal epithelium	0/10	0/10	4/10	5/10[b]
Eyelids; epidermal	0/10	10/10[b]	7/10[b]	10/10[b]
Nose; epithelial	0/10	10/10[b]	10/10[b]	10/10[b]
Larynx; epithelial	0/10	8/10[b]	10/10[b]	10/10[b]
Trachea; epithelial	0/10	9/10[b]	10/10[b]	10/10[b]
Bronchi/bronchioles; epithelial	0/10	10/10[b]	10/10[b]	10/10[b]
Cell necrosis				
Eyelids, epidermal	0/10	10/10[b]	9/10[b]	8/10[b]
Nose; epithelial	0/10	2/10	9/10[b]	8/10[b]
Lymphoid degeneration; thymus	0/9	0/8	9/9[b]	10/10[b]

[a]Values represent means ± SDs (number of animals).
[b]Significantly different from controls at $p<0.05$ based on statistics performed by the study authors.
[c]Final body weights for 40 and 90 ppm males were measured on study days 8 and 4 (respectively).
[d]Number affected/number examined.
[e]Significantly different from controls at $p<0.05$ based on Fisher's exact tests performed for this review.
NE = Not evaluated

Reference: Union Carbide Corp. (1988)

Table B.3. Effects in female Sprague-Dawley rats administered bis(2-dimethylaminoethyl)ether as a vapor 6 hours/day 5 days/week for 11 days (including 9 days of exposure)

	Exposure concentration (ppm)			
	0	**20**	**40**	**90**
Final body weight (g)	193.8 ± 14.0 (10)[a]	167.5 ± 11.0(10)[b]	142.0 ± 8.7 (7)[b,c]	156.9 ± 7.3 (10)[b,c]
Gross pathology[d]				
Head encrustation	0/10	7/10[e]	8/10[e]	9/10[e]
Eyes				
Diffuse color changes	0/10	0/10	8/10[e]	10/10[e]
Increased thickness	0/10	0/10	6/10[e]	9/10[e]
Swollen	0/10	7/10[e]	7/10[e]	8/10[e]
Histopathology[d]				
Cell vacuolization				
Heart; arterial	0/10	4/10	10/10[b]	10/10[b]
Esophagus; epithelial	0/10	0/8	NE	3/4[b]
Liver; hepatocellular	0/10	0/10	0/10	6/10[e]
Spleen	0/10	4/10	10/10[b]	10/10[b]
Eyelids; epidermal	0/10	10/10[b]	7/10[b]	10/10[b]
Nose; epithelial	0/10	10/10[b]	10/10[b]	10/10[b]
Larynx; epithelial	0/10	10/10[b]	10/10[b]	10/10[b]
Trachea; epithelial	0/10	10/10[b]	9/9[b]	9/9[b]
Bronchi/bronchioles; epithelial	0/10	10/10[b]	10/10[b]	10/10[b]
Cell necrosis				
Eyelids, epidermal	0/10	5/10[b]	7/10[b]	10/10[b]
Laryngitis	0/10	10/10[b]	10/10[b]	10/10[b]
Lymphoid degeneration; thymus	0/9	0/7	1/8	9/10[b]
Lungs; alveolar histiocytosis	0/10	0/10	0/10	7/10[b]

[a]Values represent means ± SDs (number of animals).
[b]Significantly different from controls at $p<0.05$ based on statistics performed by the study authors.
[c]Final body weights for 40 and 90 ppm females were measured on study days 8 and 1 (respectively).
[d]Number affected/number examined.
[e]Significantly different from controls at $p<0.05$ based on Fisher's exact tests performed for this review.
NE = Not evaluated

Reference: Union Carbide Corp. (1988)

Histopathological analyses of animals from all exposure groups revealed lesions primarily to the skin, eyes and respiratory tract but also to some tissues not in direct contact with bis(2-dimethylaminoethyl)ether vapor (Union Carbide Corp., 1988). Vacuolar cytoplasmic swelling of cells of the eyes and eyelids and from the upper and lower respiratory tract (nose, pharynx, larynx, trachea, and bronchi/bronchioles) was increased at ≥20 ppm. Cell necrosis was increased in epidermal cells of the eyelids at ≥20 ppm (both sexes) and epithelial cells lining the nasal cavity in males exposed to 40 or 90 ppm (Tables B.2 and B.3). Vacuolar cytoplasmic swelling was increased in internal non-respiratory organs at ≥40 ppm in rats of both sexes.

Based on these data, the low concentration of 20 ppm is identified as a LOAEL for significantly reduced food consumption and body weight, clinical signs of ocular and respiratory irritation, and increased incidences of gross and histopathological lesions (including vacuolization and/or necrosis of cells in ocular and respiratory tissues). A NOAEL was not identified.

Union Carbide Corp. (1989) conducted a follow-up study in which Sprague-Dawley rats (10/sex/group) were whole-body exposed to bis(2-dimethylaminoethyl)ether (98% pure) as a vapor at nominal concentrations of 0 (air-exposed control), 1, 10, or 20 ppm 6 hours/day 5 days/week for 11 days (including 9 days of exposure) and sacrificed on study day 12. Additional groups of rats exposed to bis(2-dimethylaminoethyl)ether at 0 or 20 ppm were designated for perfusion fixation (5/sex/group) or served as a 3-week recovery group (5/sex/group). Mean measured concentrations of bis(2-dimethylaminoethyl)ether for the 1, 10, and 20 ppm groups were 1.0, 7.8, and 17 ppm, respectively. The same endpoints evaluated in the previous inhalation exposure study (Union Carbide Corp, 1988) were evaluated in this study with the following exceptions or inclusions: ophthalmologic examinations were conducted prior to study initiation and after the final exposure on day 11; ophthalmologic examinations were also conducted in control, mid-, and high-exposure rats on day 12; body weights were recorded prior to the start of the study and on study days 2, 3 (control animals only), 5, 8, 9, and 12 (prior to sacrifice); recovery animals were weighed weekly during the 3-week recovery period (on study days 19, 26, and 33); food and water consumption were measured for 15 hours after the third (males) or final (females) exposure; and the spleen was included in the list of organs weighed (on day 12 for main study or day 33 for recovery animals). The lungs, trachea, larynx, nasal turbinates, and skin (dorsum of head and ear) were examined microscopically in rats from all exposure groups. Additional tissues examined in control and 20 ppm rats included the kidneys, lymph nodes, heart, thymus, liver, spleen, and eye.

No mortality occurred at any exposure level (Union Carbide Corp., 1989). Clinical signs of toxicity observed in bis(2-dimethylaminoethyl)ether-treated animals (primarily at 20 ppm but also to a limited extent at 10 ppm) were similar to those observed in the earlier study (symptoms of ocular or respiratory irritation, including swollen periocular tissue, blepharospasm, corneal cloudiness and opacity, periocular and perinasal encrustation, and/or audible respiration). Ophthalmologic examinations revealed concentration-dependent increases in the incidence and severity of keratitis and blepharitis at ≥10 ppm on days 11 and 12. Other than swollen periocular tissue, no significant clinical signs were observed 2 weeks post-exposure in the recovery group. Food consumption was significantly decreased in males at 10 and 20 ppm (30 and 49% lower

than controls, respectively) and in females at 20 ppm (32% lower than controls); water consumption was also decreased significantly (by 57%) in high-exposed males (Table B.4). Rats exposed to the high concentration of 20 ppm of bis(2-dimethylaminoethyl)ether lost weight during the course of the study, and body weights for this group were reduced more than 10% relative to controls on day 12 (Table B.4). The body weights of 20 ppm recovery animals were similar to or higher than non-exposed controls in the three weeks following exposure.

Table B.4. Effects in Sprague-Dawley rats administered bis(2-dimethylaminoethyl)ether as a vapor 6 hours/day 5 days/week for 11 days (including 9 days of exposure)

	Exposure concentration (ppm)			
	0	**1**	**10**	**20**
Males				
Food consumption (g/animal)	18.7 ± 2.6 (10)[a]	19.0 ± 2.9 (10)	13.1 ± 3.2 (10)[b]	9.6 ± 3.1 (10)[b]
Water consumption (mL/animal)	25.1 ± 2.9 (10)	24.9 ± 3.1 (10)	22.6 ± 10.3 (10)	10.9 ± 7.7 (10)[b]
Body weight-				
Day 1 (g)	278.9 ± 10.4 (20)	275.7 ± 15.3 (10)	278.7 ± 13.6 (10)	283.9 ± 12.8 (20)
Day 12 (g)	301.6 ± 14.5 (20)	301.6 ± 20.9 (10)	301.5 ± 16.5 (10)	248.6 ± 26.9 (20)[c]
Hematology				
Leukocytes (10^3/ul)	12.6 ± 1.6 (10)	12.0 ± 1.8 (10)	13.0 ± 3.1 (10)	14.3 ± 2.7 (10)
Segmented neutrophils	1,372 ± 566 (10)	1,601 ± 618 (9)	2,484 ± 973 (10)[b]	3,928 ± 532 (10)[b]
Platelets (10^3/µl)	852 ± 82 (10)	887 ± 75 (9)	701 ± 141 (10)[b]	705 ± 101 (10)[b]
Clinical chemistry				
Urea nitrogen (mg/L)	209 ± 32 (10)	207 ± 24 (9)	209 ± 24 (10)	230 ± 23 (10)
Albumin (g/L)	32 ± 2 (10)	32 ± 1 (10)	31 ± 1 (10)	29 ± 2 (10)[b]
Phosphorus (mg/L)	77 ± 4 (9)	74 ± 3 (10)	72 ± 4 (10)[b]	66 ± 5 (10)[b]
Chloride (mmol/L)	106 ± 1 (10)	106 ± 1 (9)	105 ± 1 (10)[b]	105 ± 1 (10)[b]
ALT (U/L)	33 ± 4 (10)	34 ± 5 (10)	38 ± 7 (10)[b]	40 ± 6 (10)[b]
Urinalysis				
Osmolality	2,070 ± 431 (10)	1,996 ± 310 (10)	1,739 ± 619 (10)	2,781 ± 146 (10)[b]
pH	7.7 ± 0.5 (10)	7.5 ± 0.5 (10)	7.2 ± 0.4 (10)[b]	6.6 ± 0.5 (10)[b]
Total volume (mL)	8.6 ± 2.0 (10)	9.0 ± 1.6 (10)	11.8 ± 10.8 (10)	4.0 ± 0.9 (10)[b]
Creatinine (mg/dL)	97 ± 15 (10)	94 ± 15 (10)	91 ± 32 (10)	138 ± 12 (10)[b]
Potassium (mmol/L)	326 ± 62 (10)	338 ± 59 (10)	272 ± 100 (10)	395 ± 62 (10)[b]
Creatinine clearance (mL/15 hrs)	2,246 ± 452 (10)	NE	2,303 ± 263 (10)	1,617 ± 489 (10)[b]
Females				
Food consumption (g/animal)	14.6 ± 1.9 (10)	14.0 ± 2.9 (10)	12.7 ± 2.1 (10)	10.0 ± 3.2 (10)[b]
Body weight-				
Day 1 (g)	189.2 ± 8.9 (20)	188.4 ± 10.6 (10)	190.8 ± 7.8 (10)	188.9 ± 10.9 (20)
Day 12 (g)	208.3 ± 10.1 (20)	209.7 ± 11.0 (10)	208.5 ± 5.7 (10)	186.8 ± 13.8 (20)[b]
Hematology				
Leukocytes (10^3/µl)	11.9 ± 1.6 (10)	13.5 ± 2.9 (10)	13.1 ± 2.7 (10)	15.2 ± 1.7 (9)[b]
Segmented neutrophils	1,046 ± 582 (10)	1,190 ± 601 (10)	1,252 ± 380 (10)	3,526 ± 840 (9)[b]
Clinical chemistry				
Urea nitrogen (mg/L)	176 ± 24 (10)	190 ± 35 (10)	167 ± 18 (10)	227 ± 42 (10)[b]
Albumin (g/L)	34 ± 1 (9)	33 ± 1 (10)	33 ± 1 (10)	31 ± 2 (10)[b]
Phosphorus (mg/L)	88 ±6 (9)	88 ± 4 (10)	88 ± 4 (10)	81 ± 4 (10)[b]
Chloride (mmol/L)	108 ± 1 (10)	107 ± 2 (10)	106 ± 2 (10)	106 ± 1 (10)[b]
ALT (U/L)	28 ± 4 (10)	29 ± 4 (10)	33 ± 6 (10)[b]	33 ± 4 (10)[b]
AST (U/L)	65 ± 12 (10)	61 ± 10 (10)	68 ± 11 (10)	77 ± 13 (10)[b]

Table B.4. Effects in Sprague-Dawley rats administered bis(2-dimethylaminoethyl)ether as a vapor 6 hours/day 5 days/week for 11 days (including 9 days of exposure)				
	Exposure concentration (ppm)			
	0	1	10	20
Urinalysis				
Osmolality	1,447 ± 264 (10)	1,845 ± 430 (10)[b]	716 ± 306 (10)[b]	2,639 ± 499 (10)[b]
pH	7.5 ± 0.5 (10)	7.2 ± 0.4 (10)	8.0 ± 0 (10)[b]	7.0 ± 0 (10)[b]
Total volume (mL)	11.2 ± 3.1 (10)	7.7 ± 3.0 (10)[b]	20.1 ± 7.4 (10)[b]	4.5 ± 1.7 (10)[b]
Creatinine (mg/dL)	52 ± 12 (10)	68 ± 15 (10)[b]	28 ± 9 (10)[b]	99 ± 21 (10)[b]
Potassium (mmol/L)	221 ± 38 (10)	283 ± 65 (10)[b]	113 ± 45 (10)[b]	399 ± 69 (10)[b]
Creatinine clearance (mL/15 hrs)	1,478 ± 352 (10)	NE	NE	1,277 ± 267 (10)

[a]Values are means ± SD (number of animals).
[b]Significantly different from controls at $p < 0.05$ based on statistics performed by the study authors.
[c]Significantly different from controls at $p < 0.05$ based on student's t-test performed for this review.

Reference: Union Carbide Corp. (1989)

Leukocyte and neutrophil counts were increased in male and female rats at 20 ppm (Union Carbide Corp., 1989). In males, mean leukocyte count was non-significantly increased by 13% at 20 ppm, while females showed a statistically significant 28% increase in leukocytes at this exposure level (Table B.4). Both male and female rats showed significant increases in mean neutrophil counts (2.9- to 3.4-fold higher than controls) at 20 ppm; males also showed a significant increase (1.8-fold) at 10 ppm. Mean platelet counts were significantly decreased in males exposed at 10 and 20 ppm (17 to 18% lower than controls). Other statistically significant changes in hematological endpoints (increased erythrocytes, hemoglobin, and hematocrit and decreased reticulocytes in males) were not concentration-related and/or were attributed by the study authors to dehydration of the animals at 20 ppm.

Rats exposed to bis(2-dimethylaminoethyl)ether showed small but statistically significant changes in clinical chemistry parameters (Table B.4). These changes included decreased serum albumin at 20 ppm (9% lower than controls in both sexes without a concomitant change in total protein), decreased serum phosphorus and chloride (6 to 14% and 1 to 2% lower than controls, respectively) at ≥10 ppm in males and at 20 ppm in females, and increased urea nitrogen at 20 ppm (29%) in females. There was also a non-significant 10% increase in urea nitrogen in males. The activities of ALT (in both sexes) and AST (in females only) were statistically significantly increased (by 15 to 21% and 18%, respectively) at 10 and/or 20 ppm, although these changes were < 2-fold different than respective controls. The toxicological significance of all of these changes is uncertain due to small magnitudes and inconsistencies as previously noted.

Urinalysis showed increased urine osmolality (34 to 82% higher than controls), accompanied by decreased total volume (53 to 60% lower than controls) and pH (7 to 14% lower than controls) in both males and females exposed at 20 ppm; creatinine and potassium levels were likewise increased in both sexes at this concentration (by 21 to 42% in males and 81 to 90% in females) (Union Carbide Corp., 1989). The estimated rate of creatinine clearance was significantly decreased in 20 ppm males (28% lower than control males) and tended to be decreased in 20 ppm females (14% lower than control females; not statistically significant). Sporadic changes in some of these parameters were also observed at lower exposure concentrations, but were not consistent with the findings in the high-exposure group. Some other statistically significant changes in urinalysis parameters (including median ketone concentration in males and females and mean total protein and chloride levels in females) were not considered treatment-related by the study authors.

At sacrifice, the body weights of males and females exposed at 20 ppm were reduced more than 10% relative to controls (Table B.5). The mean body weights of rats in other exposure groups were not significantly different from controls (Union Carbide Corp., 1989). Swollen and encrusted eyelids, corneal opacities and cloudiness, and perinasal encrustation were noted at gross necropsy at 10 ppm and were significantly increased at 20 ppm. Although significant decreases in absolute organ weights were observed at 20 ppm (liver, lung, and kidney weights in males and spleen weights in both sexes), the organ-to-body weight ratios were generally unchanged from controls suggesting the decreases in absolute weights reflected the decrease in body weight at this concentration. Organ weights were not significantly changed relative to controls in 20 ppm recovery animals sacrificed at day 33. Histological examinations revealed epithelial cell vacuolization in the nasal cavity of all rats of both sexes at $\geq$1 ppm. At higher exposure concentrations (10 and/or 20 ppm), significant and concentration-related changes were observed (Table B.5) These changes involved the incidence (and reportedly the severity, although the data were not shown) of dermal, ocular and respiratory tract lesions, namely vacuolar cytoplasmic swelling in epidermal cells of the skin (head, ears, and eyelids) and epithelial cells of the nasal cavity, larynx (males only), trachea, and bronchi/bronchioles; cell necrosis of the eyelids (males) or the nasal cavity (females); dermatitis (males) and rhinitis and cell necrosis within the nasal cavity (females). Recovery animals (males and females) sacrificed at day 33 showed increased incidences of epithelial cell vacuolization and olfactory mucosa atrophy within the nasal cavity, and all other tissues appeared similar to controls. Based on these data, a LOAEL of 1 ppm is identified for an increased incidence of cell vacuolization in the nasal cavity, and no NOAEL was identified.

Table B.5. Effects in Sprague-Dawley rats administered bis(2-dimethylaminoethyl)ether as a vapor 6 hours/day 5 days/week for 11 days (including 9 days of exposure)				
	Exposure concentration (ppm)			
	0	**1**	**10**	**20**
Males				
Final body weight (g)	304.4 ± 17.2 (10)[a]	301.5 ± 20.9 (10)	301.5± 16.5 (10)	244.8 ± 31.8 (10)[b]
Gross pathology[c]				
Skin; encrustation	1/15	1/10	3/10	15/15[b]
Nose/nares; encrustation	0/15	1/10	2/10	15/15[b]
Eye				
Opacity	0/15	1/10	0/10	8/15[b]
Color change; diffuse	0/15	1/10	2/10	5/15[b]
Histopathology[c]				
Cell necrosis; eyelids	0/10	0/10	2/10	8/10[d]
Cell vacuolization				
Head; epidermal	0/10	0/10	3/10	10/10[d]
Ears; epidermal	0/10	0/10	0/10	10/10[d]
Eyelids; epidermal	0/10	0/10	7/10[d]	10/10[d]
Nasal cavity; epithelial	0/9	10/10[d]	10/10[d]	10/10[d]
Larynx; epithelial	0/10	0/10	1/10	8/10[d]
Trachea; epithelial	0/10	0/10	0/10	9/10[d]
Bronchi/bronchioles; epithelial	0/10	0/10	3/10	10/10[d]
Females				
Final body weight (g)	210.3 ± 10.0 (10)	208.7 ± 11.0 (10)	206.5 ± 5.7 (10)	183.7 ± 16.2 (10)[d]
Organ weights				
Spleen (g)	0.62 ± 0.06 (10)	0.64 ± 0.08 (10)	0.59 ± 0.05 (10)	0.48 ± 0.09 (10)[d]
Relative spleen (% body weight)	0.29 ± 0.02 (10)	0.31 ± 0.05 (10)	0.29 ± 0.02 (10)	0.26 ± 0.03 (10)[d]
Gross pathology[c]				
Skin; encrustation	0/15	1/10	1/10	12/15[b]
Nose/nares; encrustation	0/15	0/10	1/10	15/15[b]
Histopathology[c]				
Dermatitis	0/10	0/10	0/10	10/10[d]
Rhinitis	0/10	0/10	0/10	6/10[d]
Atrophy; olfactory epithelium	0/10	0/10	6/10[d]	5/10[d]
Cell vacuolization				
Head; epidermal	0/10	0/10	1/10	7/10[d]
Ears; epidermal	0/10	0/10	5/10[d]	9/10[d]
Eyelids; epidermal	0/10	0/10	5/10[d]	10/10[d]
Nasal cavity; epithelial	0/10	10/10[d]	10/10[d]	10/10[d]
Trachea; epithelial	0/10	0/10	0/10	8/10[d]
Bronchi/bronchioles; epithelial	0/10	0/10	3/10	10/10[d]
Recovery males				
Histopathology[d]				
Atrophy; olfactory epithelium	0/5	NE	NE	5/5[d]
Cell vacuolization				
Nasal cavity; epithelial	0/5	NE	NE	5/5[d]
Recovery females				
Histopathology[d]				
Atrophy; olfactory epithelium	0/5	NE	NE	5/5[d]
Cell vacuolization				
Nasal cavity; epithelial	0/5	NE	NE	4/5[d]

[a]Values are means ± SD (number of animals).
[b]Significantly different from controls at $p < 0.05$ based on Fisher's exact tests (categorical data) or Student's t-test (continuous data) performed for this review.
[c]Number affected/number examined.
[d]Significantly different from controls at $p < 0.05$ based on statistics performed by the study authors.
NE = Not evaluated.

Reference: Union Carbide Corp. (1989)

Building on the data from the short-term studies, Union Carbide Corp. (1993a) examined the subchronic inhalation toxicity of bis(2-dimethylaminoethyl)ether. Sprague-Dawley rats (15/sex/group) were whole-body exposed to bis(2-dimethylaminoethyl)ether (≥97% pure) as a vapor at nominal concentrations of 0 (air-exposed control), 0.22, 1.25, or 5.8 ppm 6 hours/day 5 days/week for 14 weeks. They were sacrificed immediately after exposure (10 sex/group) or after a 6-week recovery period (5/sex/group). Additional groups of rats exposed to 0 or 5.8 ppm (4 sex/group) were sacrificed on study days 1, 3, or 5 for examination of the nasal cavity using electron microscopy. Mean measured concentrations of bis(2-dimethylaminoethyl)ether for the 0.22, 1.25, and 5.8 ppm groups were 0.23, 1.25, and 5.80 ppm, respectively. Mortality and clinical signs of toxicity were monitored daily. Ophthalmologic examinations (including indirect ophthalmoscopy and slit lamp bioscopy) were conducted in all rats prior to study initiation and at week 13. Food and water consumption were measured over approximately 15 hours during week 14 and/or 20 (for recovery animals). Body weights were recorded prior to the first exposure, weekly during the 14 weeks of exposure (and 6 weeks of recovery, if applicable), and immediately prior to sacrifice.

Hematology and clinical chemistry parameters were evaluated in all rats at 4 weeks (after 27 and 28 exposures for males and females, respectively) in 10 rats/sex/group at the end of exposure (14 weeks) and in recovery animals at 20 weeks. Urinalysis endpoints were assessed at 14 and 20 weeks. The same hematology, clinical chemistry, and urinalysis endpoints evaluated in the initial short-term inhalation study (Union Carbide Corp., 1988) were evaluated in this study with the following exceptions or inclusions: differential leukocyte smears were evaluated for rats of the control and high-exposure groups, prothrombin time was measured at 14 and 20 week time points, and the rate of creatinine clearance was not estimated. At scheduled sacrifice at 14 weeks (main study) or 20 weeks (recovery animals), organ weights (brain, liver, kidneys, lungs, spleen, heart, adrenal glands, and testes) were recorded and complete gross pathology evaluations (including examinations of about 38 tissues and all gross lesions) were performed on all rats. Tissues examined histologically in control and high exposure animals at 14 and 20 weeks included the adrenals, bone marrow (sternal), brain (brain stem, cerebellum, cerebrum),

ears, esophagus, eyes, heart, kidneys, larynx, liver, lungs, nasal turbinates, ovaries, pancreas, parathyroids, pituitary muscle, sciatic nerve, skin (dorsum of head, ears, and eyelids), spleen, stomach, submandibular lymph nodes, testes, thymus, thyroids, trachea/bronchi, urinary bladder, and gross lesions.

No mortality occurred; however, clinical signs of toxicity (symptoms of ocular or respiratory irritation) were observed in bis(2-dimethylaminoethyl)ether-treated animals (Union Carbide Corp., 1993a). All exposure groups showed swelling of the periocular tissue, and rats exposed to the high concentration of bis(2-dimethylaminoethyl)ether also showed increased incidences of corneal cloudiness and perinasal encrustation during the study compared with controls. Periocular encrustation was observed in 1.25 and 5.8 ppm males and 5.8 ppm females. Based on the ophthalomologic examinations conducted at week 13, all rats exposed to 5.8 ppm exhibited mild keratitis, and minimal keratitis was also observed in 6 of the 15 females in the 1.25 ppm group. No ophthalmologic abnormalities were apparent in recovery animals at 20 weeks. Food consumption in week 14 was significantly decreased in females (but not males) exposed to 5.8 ppm (18% lower than controls; Table B.6). Although the mean body weight of 5.8 ppm males was significantly decreased relative to control males at week 14, mean body weights of all exposed rats stayed within 10% of their respective control groups during the exposure and recovery (for high-exposure rats) periods.

Table B.6. Effects in Sprague-Dawley rats administered bis(2-dimethylaminoethyl)ether as a vapor 6 hours/day 5 days/week for 14 weeks

	Exposure concentration (ppm)			
	0	**0.22**	**1.25**	**5.8**
Males				
Body weight; week 14 (g)	400.4 ± 26.5 (15)[a]	399.1 ± 33.9 (15)	402.9 ± 31.5 (15)	374.2 ± 25.7 (15)[b]
Hematology				
Segmented neutrophils (cells/µL); wk 6	918 ± 599 (13)	NE	NE	1478 ± 464 (15)[b]
Clinical chemistry				
Total protein (g/L); wk 6	59 ± 1.9 (15)	58 ± 2 (15)	57 ± 1.7 (15)[b]	56 ± 2.1 (15)[b]
Phosphorus (mg/L); wk 6	71 ± 4 (15)	65 ± 4.6 (15)[b]	63 ± 2.7 (15)[b]	60 ± 3.9 (15)[b]
Phosphorus (mg/L); wk 14	46 ± 3.2 (10)	51 ± 6.1 (10)	50 ± 7.2 (10)	56 ± 5.9 (10)[b]
Creatinine (mg/L); wk 14	6 ± 0.8 (10)	5 ± 0.6 (10)[c]	5 ± 0.6 (10)[b]	5 ± 0.7 (10)[b]
Urinalysis				
Chloride (mmol/L); wk 14	166 ± 47.8 (10)	147 ± 45.3 (10)	152 ± 61.8 (10)	125 ± 55.9 (8)
Females				
Body weight; week 14 (g)	259.2 ± 10.6 (15)	255.9 ± 25.6 (15)	254.3 ± 14.6 (15)	248.7 ± 11.8 (15)
Food consumption (g/animal)	12.4 ± 0.9 (10)	11.8 ± 1.7 (10)	11.6 ± 2.5 (10)	10.2 ± 1.3 (10)[b]
Hematology				
Segmented neutrophils; wk 6 (cells/µL)	518 ± 262 (15)	NE	NE	1268 ± 360 (15)[b]
Segmented neutrophils; wk 14 (cells/µL)	532 ± 255 (10)	NE	NE	1737 ± 697 (10)[b]

Table B.6. Effects in Sprague-Dawley rats administered bis(2-dimethylaminoethyl)ether as a vapor 6 hours/day 5 days/week for 14 weeks				
	Exposure concentration (ppm)			
	0	**0.22**	**1.25**	**5.8**
Clinical chemistry				
Total protein (g/L); wk 6	60 ± 1.8 (15)	55 ± 3.4 (15)[b]	56 ± 2.2 (15)[b]	58 ± 1.6 (15)[b]
Phosphorus (mg/L); wk 6	63 ± 5.3 (15)	52 ± 4.8 (15)[b]	49 ± 5.2 (15)[b]	51 ± 4.0 (15)[b]
Phosphorus (mg/L); wk 14	45 ± 5.9 (10)	42 ± 5.5 (10)	43 ± 4.8 (10)	51 ± 6.8 (10)[b]
Creatinine (mg/L); wk 14	5 ± 0.7 (10)	5 ± 0.8 (10)	5 ± 0.7 (10)	4 ± 1.4 (10)[b]
Urinalysis				
Chloride (mmol/L); wk 14	140 ± 16.9 (9)	143 ± 39.9 (10)	145 ± 52.4 (9)	97 ± 30.5 (10)[b]

[a]Values represent means ± SD (number of animals).
[b]Significantly different from controls at $p<0.05$.
[c]Significantly different from controls at $p<0.05$ based on Student's t-test (continuous data) performed for this review.
NE = Not evaluated.

Reference: Union Carbide Corp. (1993a)

Rats exposed to bis(2-dimethylaminoethyl)ether at 5.8 ppm showed significantly increased numbers of neutrophils in the blood at 6 weeks without a concomitant increase in leukocyte count (62 and 145% higher in males and females, respectively, than controls) (Table B.6). Neutrophils remained significantly higher in high exposure females (but not males) after 14 weeks exposure (226% higher than controls) (Union Carbide Corp., 1993a). In general, effects on clinical chemistry parameters (including decreased serum creatinine and total protein and changes in serum phosphorus levels) did not show a dose-related response, occurred in only one sex, and/or the direction of the response was not consistent at different time points. By 14 weeks, the level of chloride in the urine of females exposed to 5.8 ppm was significantly decreased (by 31%) relative to controls and tended to be decreased (albeit not significantly) in males (25% lower than controls). No exposure-related changes in hematology, clinical chemistry, or urine parameters were observed in recovery animals 6 weeks following exposure.

Significant effects observed in exposed rats at sacrifice are shown in Tables B.7 (males) and B.8 (females) (Union Carbide Corp., 1993a). Upon sacrifice at 14 weeks, the body weights of rats exposed to bis(2-dimethylaminoethyl)ether were not significantly different from control animals. Female rats exposed to 5.8 ppm showed a significantly ($p<0.05$) increased incidence of diffuse color changes to the eye (5/10 vs. 0/10 controls), and high-exposed males tended to have swollen eye tissue ($p>0.05$). Although not statistically significant, swollen periocular tissue was noted in recovery animals mainly in the 1.25 and 5.8 ppm groups at 20 weeks. Males exposed at 5.8 ppm showed increased relative adrenal gland and testes weights (relative to body weight) compared with controls (17 and 14% higher than controls, respectively; see Table B.7), and females showed no significant and concentration-related changes in relative organ weights at 14-

week sacrifice. Increased relative lung weight in 5.8 ppm recovery females (14% higher than controls) at 20 weeks was considered spurious by the study authors because a similar increase was not observed in rats of either sex immediately following 14 weeks of exposure or in the 5.8 ppm recovery males.

Cell vacuolization within the nasal cavity (epithelial and/or interstitial cells) was significantly increased in males and females exposed at 0.22 ppm and higher after 14 weeks of exposure (Tables B.7 and B.8; Union Carbide Corp., 1993a). Significant and concentration-related increases in the incidences of other lesions in tissues directly exposed to bis(2-dimethylaminoethyl)ether were observed at 1.25 and/or 5.8 ppm**.** These findings included dermatitis (skin and nose); hyperkeratosis (nose); rhinitis; vacuolar cytoplasmic swelling of cells of the skin (nose, ears, and eyelids), nasal cavity (epithelial cells, interstitial cells and submucosal gland), larynx, trachea, and bronchi/bronchioles; necrosis of cells lining the nasal cavity (females), olfactory epithelium, or respiratory epithelium (females); and histiocytosis (alveolar and submandibular lymph nodes, in females only). Recovery animals sacrificed 6 weeks after termination of exposure continued to show significant cell vacuolization of epithelial and interstitial cells within the nasal cavity (Tables B.7 and B.8). The incidence of submucosal mineralization was increased in males, and hyperplasia/dysplasia of the olfactory epithelium was observed in both sexes. All other tissues appeared normal in the recovery animals at 20 weeks. In animals designated for electron microscopic examinations of the nasal cavity, the presence of intracytoplasmic membrane-bound vacuoles in the mucosal epithelium (after 1 day of exposure) or in the mucosa and submucosa (after 3 and 5 exposures) were reported. The severity of this effect reportedly increased with duration of exposure (data for the incidence and severity of these lesions were not shown). These data identify a LOAEL of 0.22 ppm (and no NOAEL) based on a significantly increased incidence of cell vacuolization in the nasal cavity of male and female rats exposed for 14 weeks.

Table B.7. Significant effects in male Sprague-Dawley rats administered bis(2-dimethylaminoethyl)ether as a vapor 6 hours/day 5 days/week for 14 weeks				
	Exposure concentration (ppm)			
	0	**0.22**	**1.25**	**5.8**
Final body weight (g)	392.5 ± 25.0 (10)[a]	392.8 ± 28.7 (10)	401.2± 33.4 (10)	372.4 ± 30.7 (10)
Organ weights				
Relative adrenal gland	0.012 ± 0.002 (10)	0.013 ± 0.001 (10)	NL[b]	0.014 ± 0.002 (10)[c]
Relative testes	0.85 ± 0.10 (10)	0.91 ± 0.09 (10)	0.88 ± 0.09 (10)	0.97 ± 0.09 (10)[c]
Histopathology[d]				
Dermatitis				
Skin	0/10	0/10	0/10	6/10[c]
Nose	0/10	0/10	0/10	5/10[c]
Hyperkeratosis; nose	1/10	0/10	0/10	8/10[c]
Rhinitis	0/10	0/10	2/10	9/10[c]
Cell vacuolization				
Nose; epidermal	0/10	0/10	0/10	10/10[c]
Ears; epidermal	0/10	0/10	0/10	9/10[c]
Eyelids; epidermal	0/10	0/10	0/10	9/10[c]
Cornea; epithelial	0/10	0/10	2/10	7/10[c]
Nasal cavity; epithelial	0/10	10/10[c]	10/10[c]	10/10[c]
Nasal cavity; interstitial	0/10	4/10	10/10[c]	10/10[c]
Nasal cavity; submucosal gland	0/10	0/10	0/10	6/10[c]
Larynx; epithelial	0/10	0/10	0/10	8/10[c]
Trachea; epithelial	0/10	0/10	0/10	10/10[c]
Bronchi/bronchioles; epithelial	0/10	0/10	0/10	9/10[c]
Necrosis; olfactory epithelium	0/10	0/10	0/10	9/10[c]
Recovery males				
Histopathology[d]				
Submucosal mineralization	0/5	1/5	0/5	4/5[c]
Cell vacuolization				
Nasal cavity; epithelial	0/5	5/5[c]	5/5[c]	5/5[c]
Nasal cavity; interstitial	0/5	0/5	4/5[c]	5/5[c]
Hyperplasia/dysplasia				
Olfactory epithelium	0/5	0/5	5/5[c]	4/5[c]

[a]Values represent means ± SDs (number of animals).
[b]Data are not clearly legible in the study report.
[c]Significantly different from controls at $p<0.05$.
[d]Number affected/number examined.

Reference: Union Carbide Corp. (1993a)

Table B.8. Significant effects in female Sprague-Dawley rats administered bis(2-dimethylaminoethyl)ether as a vapor 6 hours/day 5 days/week for 14 weeks

	Exposure concentration (ppm)			
	0	**0.22**	**1.25**	**5.8**
Final body weight (g)	262.0 ± 15.8 (10)	254.8 ± 18.2 (10)	249.2 ± 12.5 (10)	245.9 ± 12.5 (10)
Histopathology[d]				
Dermatitis				
Skin	0/10	0/10	0/10	6/10[c]
Nose	0/10	0/10	0/10	7/10[c]
Epiderrnatitis; nose	0/10	0/10	0/10	7/10[c]
Hyperkeratosis; nose	0/10	0/10	0/10	8/10[c]
Rhinitis	0/10	0/10	0/10	10/10[c]
Submucosal mineralization				
Nasal cavity	3/10	5/10	7/10	9/10[c]
Cell vacuolization				
Nose; epidermal	0/10	0/10	0/10	10/10[c]
Ears; epidermal	0/10	0/10	0/10	10/10[c]
Eyelids; epidermal	0/10	0/10	0/10	10/10[c]
Cornea; epithelial	0/10	1/10	0/10	7/10[c]
Nasal cavity; epithelial	0/10	10/10[c]	10/10[c]	10/10[c]
Nasal cavity; interstitial	0/10	5/10[c]	10/10[c]	10/10[c]
Nasal cavity; submucosal gland	0/10	1/10	1/10	5/10[c]
Larynx; epithelial	0/10	0/10	0/10	7/10[c]
Trachea; epithelial	0/10	0/10	0/10	9/10[c]
Bronchi/bronchioles; epithelial	0/10	0/10	0/10	9/10[c]
Necrosis				
Nose	0/10	0/10	0/10	5/10[c]
Olfactory epithelium	0/10	0/10	8/10[c]	10/10[c]
Respiratory epithelium	0/10	3/10	2/10	5/10[c]
Squamous metaplasia				
Nasal cavity	0/10	0/10	0/10	5/10[c]
Histiocytosis				
Aleveolar	0/10	1/10	0/10	5/10[c]
Submandibular lymph node; sinus	0/10	NE	NE	5/10[c]
Recovery females				
Histopathology[d]				
Cell vacuolization				
Nasal cavity; epithelial	0/5	5/5[c]	5/5[c]	5/5[c]
Nasal cavity; interstitial	0/5	0/5	5/5[c]	5/5[c]
Hyperplasia/dysplasia				
Olfactory epithelium	0/5	0/5	5/5[c]	4/5[c]

[a]Values represent means ± SDs (number of animals).
[b]Data are not clearly legible in the study report.
[c]Significantly different from controls at $p<0.05$.
[d]Number affected/number examined.

Reference: Union Carbide Corp. (1993a)

A short-term dermal study of bis(2-dimethylaminoethyl)ether was reported by Union Carbide Corp. (1984) and Ballantyne et al. (1986). New Zealand White rabbits (5/sex/group) were topically exposed to 1.0 mL bis(2-dimethylaminoethyl)ether (purity not reported) to the intact, shaved skin of the trunk under occluded conditions at 0 (vehicle-only control), 2.5, 5, or

10% in water 6 hours/day 5 days/week for 11 days (including 9 days of exposure). They were sacrificed on study day 12. Based on the mean initial body weights of the males and females, doses of 8, 15, or 33 mg/kg-day were estimated for this review. Mortality and clinical signs of toxicity were evaluated on each exposure day. Dermal irritation (scored according to the Draize method) was assessed in all animals immediately prior to their next exposure. Body weights were recorded prior to the first exposure, twice weekly during exposure, and immediately prior to sacrifice. Food consumption was measured twice weekly during exposure. At sacrifice on study day 12, organ weights (liver, kidneys, and heart) were recorded, and complete gross pathology evaluations (including examinations of >30 tissues and all gross lesions) were performed on all rats. Tissues examined histopathologically in control and high-dose animals included the liver, kidneys, and heart.

No mortality occurred, and no signs of clinical toxicity other than dermal irritation were observed in exposed rabbits (Ballantyne et al., 1986; Union Carbide Corp., 1984). Signs of dermal irritation generally increased with increasing dose and number of exposures. By study termination, mean Draize scores were indicative of moderate to severe erythema and edema in the 5 and 10% dose groups (Table B.9). Other signs of dermal irritation noted by the study authors in the 5 and 10% groups were cracks and fissures, ulceration, desquamation, and cell necrosis at the application site (incidence data not shown). Food consumption was significantly decreased in males exposed to bis(2-dimthylaminoethyl)ether at 10% on day 5 (2.9-fold lower than controls) and at 5 and 10% on study day 8 (1.6- and 2.4-fold lower than controls; respectively). Food consumption also tended to be decreased in females exposed at 10% (p>0.05; Table B.9). All groups, including controls, lost weight during the course of the study. The amount of weight lost relative to controls was significantly increased in males exposed at 5 or 10% and in females exposed at 10%. Body weight loss was >10% in all treatment groups compared to respective vehicle-only control groups.

Table B.9. Effects in New Zealand White rabbits (5/sex/group) topically exposed to bis(2-dimethylaminoethyl)ether 6 hours/day 5 days/week for 11 days (including 9 days of exposure)

	Dose (%)			
	0	**2.5**	**5.0**	**10**
Males				
Dermal irritation				
Erythema and eschar[a]				
After 4 exposures	0.0	2.2	0.8	2.0
After 8 exposures	0.6	0.8	3.8	4.0
Edema[b]				
After 4 exposures	0.0	1.4	0.0	1.6
After 8 exposures	0.4	0.4	3.0	4.0

Table B.9. Effects in New Zealand White rabbits (5/sex/group) topically exposed to bis(2-dimethylaminoethyl)ether 6 hours/day 5 days/week for 11 days (including 9 days of exposure)				
	Dose (%)			
	0	2.5	5.0	10
Food consumption (g/animal/day)				
Day 5	125.0 ± 46.9[c]	114.5 ± 36.2	93.3 ± 37.1	43.3 ± 28.6[d]
Day 8	157.2 ± 24.9	128.3 ± 36.9	96.4 ± 50.8[d]	65.5 ± 20.6[d]
Body weight loss (g)	18.4 ± 58.2	41.0 ± 94.5	308.6 ± 144.4[d]	381.6 ± 132.9[d]
Organ weight				
Kidney (g)	17.09 ± 1.18	17.10 ± 0.79	18.07 ± 1.25	24.03 ± 2.76[d]
Relative kidney	0.62 ± 0.07	0.62 ± 0.02	0.72 ± 0.10	1.08 ± 0.17[d]
Females				
Dermal irritation				
Erythema and eschar[a]				
After 4 exposures	0.4	0.2	1.2	2.0
After 8 exposures	0.4	2.2	4.0	4.0
Edema[b]				
After 4 exposures	0.2	0.0	0.6	1.4
After 8 exposures	0.2	1.2	4.0	4.0
Food consumption (g/animal/day)				
Day 5	120.6 ± 38.1	117.6 ± 32.9	114.6 ± 29.2	65.5 ± 30.0
Day 8	123.0 ± 32.0	126.3 ± 17.7	110.3 ± 44.4	83.5 ± 11.0
Body weight loss (g)	76.0 ± 145.1	127.4 ± 65.8	197.0 ± 88.7	345.6 ± 115.8[d]
Organ weight				
Kidney (g)	16.62 ± 1.56	16.78 ± 0.83	18.07 ± 1.25[d]	24.64 ± 4.92[d]
Relative kidney	0.67 ± 0.07	0.67 ± 0.02	0.80 ± 0.13[d]	1.14 ± 0.18[d]

[a]Values represent mean Draize scores, where 0 = no erythema, 1 = very slight erythema, 2 = well-defined erythema, 3= moderate to severe erythema, and 4 = severe erythema to slight eschar formation.
[b]Values represent mean Draize scores, where 0 = no edema, 1 = very slight edema, 2 = slight edema, 3= moderate edema, and 4 = severe edema.
[c]Values represent means ± SD.
[d]Significantly different from controls at $p<0.05$.

Reference: Union Carbide Corp. (1984).

Upon sacrifice, gross pallor of the kidneys was noted in rabbits of the 10% dose group (data not shown; Union Carbide Corp., 1984). Absolute and relative kidney weights were significantly increased in males exposed in the 10% dose group (40 and 74% higher than controls, respectively) and in females in the 5% (9 and 19% higher than controls) and 10% dose groups (48 and 70% higher than controls; Table B.9). Histopathological incidence data were not provided in the study report. Reportedly, treatment-related findings were limited to the skin and kidneys and included vacuolar degeneration of the epidermal cells and hydropic degeneration (collecting ducts and cortex) and tubular dilation (cortex and medulla) of the kidneys. Effects on the kidney were observed in all treated groups and were more severe in the 10% group. Other histological lesions of the skin in exposed rabbits, including dermatitis (occasionally ulcerative), folliculitis, and hyperplasia of epidermal cells, reportedly occurred in unexposed controls and were not clearly associated with treatment. Based on these data, NOAEL and LOAEL values of

2.5 and 5% (8 and 15 mg/kg-day, respectively) were identified for significant signs of dermal irritation (erythema and edema), decreased body weight (males), and increased absolute and relative kidney weights.

A subchronic, dermal study was reported by Union Carbide Corp. (1984) and Ballantyne et al. (1986). Bis(2-dimethylaminoethyl)ether (99.6% pure) was applied to a patch of intact and shaved dorsal skin (4 in^2 area) of New Zealand White rabbits (10/sex/group) at nominal concentrations of 0 (vehicle-only control), 0.2, 0.7, or 2% in water (1.0 mL total volume) under occluded conditions 6 hours/day 5 days/week for 90 days. They were sacrificed on day 92. Additional groups of rats exposed to bis(2-dimethylaminoethyl)ether at 0 or 2% (10/sex/group) served as a 4-week recovery group and were sacrificed on day 121. Based on monthly analyses of dosage dilutions, the average doses actually received in the 0.2, 0.7, and 2% groups were 2.5, 7.5, and 20 mg/animal, respectively. Using the mean body weights for animals in the main study of each exposure group during treatment, doses of 0, 0.5, 2, and 5 mg/kg-day for males and females were calculated for this review. Mortality was monitored daily, and clinical signs of toxicity were evaluated on weekdays only. Dermal irritation (scored according to the Draize method) was assessed in all animals immediately prior to each exposure (weekdays only). Body weights were recorded prior to the start of the study, weekly during exposure, and immediately prior to sacrifice. Recovery animals were weighed prior to recovery sacrifice but not during the recovery period. Food consumption was measured weekly for males and twice weekly for females after week 1, and food consumption was not measured in recovery animals during the recovery period.

Hematological (erythyrocyte, platelet, reticulocyte, leukocyte, and differential leukocyte counts; hemoglobin, hematocrit, and MCV, MCH, MCHC) and clinical chemistry endpoints (concentrations of serum calcium, phosphorus, sodium, potassium, chloride, glucose, total carbon dioxide, creatinine, total protein, albumin, globulin, and total bilirubin; and the activities of AST, ALT, CK, GGT, and ALK) were evaluated prior to study initiation, at sacrifice (main study), and prior to recovery sacrifice (recovery males only) (Ballantyne et al., 1986; Union Carbide, 1984). Urinalysis endpoints (16-hour volume, specific gravity, blood, total protein, glucose, ketones, bilirubin, urobilinogen, and sediment) were evaluated in control and high-dose rabbits (2/group) during weeks 6, 10, and 13 (males), or 5, 9, and 13 (females). Urine from recovery animals (both sexes) was evaluated on week 12 only. Complete gross necropsies were performed on all animals that died spontaneously and those sacrificed at study termination. Organ weights (brain, liver, kidneys, adrenal glands, and testes) were recorded for animals in the main study but not for the recovery animals. All tissues (not individually specified) were

examined histologically in control and high-dose rabbits, and treated skin was examined microscopically in the other dose groups.

One high-dose female was sacrificed moribund on day 12 and one low-dose female was found dead on day 2; no mortality occurred in the other dose groups (Ballantyne et al., 1986; Union Carbide, 1984). No signs of clinical toxicity other than dermal irritation were observed in exposed rabbits. Signs of dermal irritation (edema, desquamation, fissuring and cracking) increased in a dose-related manner. Mean Draize scores (presented graphically in the study report) are indicative of well-defined erythema and very slight to slight edema throughout the study for males and females of the 2% dose group; very slight or barely perceptible signs of erythema or edema occurred in the other dose groups. Animals in the 2% recovery groups showed marked improvement of these effects, and signs of dermal irritation were not apparent in most animals by the end of the recovery period (incidence data not shown). No treatment-related effect on food consumption was observed, and the body weights of exposed rabbits remained within 10% of controls throughout the study. There were no changes in hematology, clinical chemistry, or urinalysis endpoints or organ weights attributed to bis(2-dimethylaminoethyl)ether exposure (data not shown). Gross pathology showed no treatment-related effects. Microscopic effects were limited to the treated skin. Vacuolization of epidermal cells was reported in 10 animals/sex at the high-dose and in 2/10 males and 7/10 females in the 0.7% dose group compared to 0% of control animals (Table B.10; data for the 0.2% group were not provided). Acanthosis was reportedly more prevalent and/or more pronounced in high-dose males and mid- and high-dose females compared to controls. The incidence of dermatitis was also increased in exposed females but not males (data not shown). These data identify a LOAEL value of 0.7% (2 mg/kg-day) based on a significantly increased incidence of epidermal cell vacuolization in females. The 0.2% dose cannot be classified as a NOAEL (or LOAEL) due to missing histology data for the critical endpoint at this dose. There was no evidence in this study of the renal effects observed in the short-term dermal study.

Table B.10. Significant effects in New Zealand White rabbits (10/sex/group) topically exposed to bis(2-dimethylaminoethyl)ether 6 hours/day 5 days/week for 90 days				
	Dose (%)			
	0	0.2	0.7	2.0
Males				
Histopathology[a]				
Vacuolization of epidermal cells	0/10	NR	2/10	10/10[b]
Females				
Histopathology[a]				
Vacuolization of epidermal cells	0/10	NR	7/10[b]	10/10[b]

[a]Number affected/number examined
[d]Significantly different from controls at $p<0.05$ based on Fisher's exact test performed for this review.
NR = Not reported

Reference: Union Carbide Corp. (1984).

A report by Union Carbide Corp. (1985) and published as Tyl et al. (1986) investigated the teratogenicity of bis(2-dimethylaminoethyl)ether by dermal exposure in rabbits. Groups of 22 timed-pregnant New Zealand White rabbits were administered 1.0 mL bis(2-dimethylaminoethyl)ether (98.7% pure) on a 9 cm^2 area of shaved intact dorsal skin at 0 (treated control), 1.0, 5.0, or 10.0% in water under occluded conditions for 6 hours/day. They were administered these doses on gestational days (GD) 6 to 18 and sacrificed on GD 29. An untreated control group of 22 females was also used. Based on the mean body weights during the exposure period (GD 6-18), doses of 2, 12, or 24 mg/kg-day were estimated for this review. Mortality and clinical signs of toxicity, and dermal irritation (eschar formation, erythema and edema; presumably scored according to the Draize method) were monitored daily during treatment. Maternal body weights were recorded on GDs 0, 6, 12 and 18, and 29 prior to sacrifice. At sacrifice, the gravid uterus, ovaries, cervix, vagina, and peritoneal and thoracic cavities were examined grossly. Also, selected organ weights (liver, kidneys, and uterus [with attached ovaries and oviducts]) were recorded. The uteri of sacrificed does were examined to determine numbers of implantation sites, resorptions, and dead and live fetuses. The number of corpora lutea in the ovaries was recorded. Histopathological evaluations were limited to the kidneys and treated skin. Fetuses were weighed, sexed, and examined for external anomalies (including cleft palate). Half of the fetuses from each litter were examined for thoracic and peritoneal visceral abnormalities, and the other half was subjected to skeletal examinations. The litter was considered the unit for statistical analyses.

Significant effects in bis(2-dimethylaminoethyl)ether-treated rabbits are summarized in Table B.11 (Union Carbide Corp., 1985; Tyl et al., 1986). No mortality occurred; however, a

dose-related increase in dermal irritation at the application site was observed. In general, erythema and edema was very slight or barely perceptible in the 1.0% dose group, and recovery from these effects occurred by GD 20. Animals in the 5.0% and 10% dose groups showed severe erythema to slight eschar formation and severe edema by GD 18; these lesions did not heal completely by study termination. More severe dermal lesions (including rippled skin, open sores, scabs, pus-filled sacs, discoloration, and fissuring) also occurred at the application site in rabbits from the 5 and/or 10% dose groups. Other clinical signs of (systemic) toxicity did not exhibit dose-related trends and were not attributed to treatment. Although mean body weights of treated animals tended to decrease with increasing dose on GDs 12, 18, and 29, body weights remained within 10% of control groups throughout the entire study. However, in contrast to other dose groups, rabbits exposed at 10% lost weight during GDs 12-18 and 6-18 and gained significantly less weight than controls during GDs 6-29 (Table B.11). Untreated controls gained almost twice as much weight during exposure (GDs 6-18) than treated controls (165 g for untreated controls vs. 86 g for treated controls), suggesting that the treatment procedure also contributed to decreased body weight gains in exposed rabbits.

Table B.11. Effects in New Zealand White rabbits (22/group) topically exposed to bis(2-dimethylaminoethyl)ether 6 hours/day on GDs 6-18.

Endpoint	Dose (%)				
	0 (treated control)	**0 (untreated control)**	**1.0**	**5.0**	**10**
Maternal effects					
Number of animals	22	22	21	21	22
Dermal irritation					
Erythema and eschar[a]					
GD 12	0.1 ± 0.4	NE	0.4 ± 0.5[b]	2.2 ± 0.4[b]	2.8 ± 0.5[b]
GD 18	0.5 ± 0.5	NE	0.8 ± 0.6	3.9 ± 0.3[b]	4.0 ± 0.0[b]
GD 29	0.0 ± 0.0	NE	0.0 ± 0.0	2.0 ± 0.6[b]	2.9 ± 0.6[b]
Edema[c]					
GD 12	0.0 ± 0.0	NE	0.0 ± 0.0	1.6 ± 0.8[b]	2.5 ± 0.9[b]
GD 18	0.0 ± 0.0	NE	0.2 ± 0.5	3.9 ± 0.3[b]	4.0 ± 0.0[b]
GD 29	0.0 ± 0.0	NE	0.0 ± 0.0	0.2 ± 0.4[b]	0.8 ± 0.9[b]
Body weight gain (g)					
GDs 12-18	102.6±115.2[d]	96.4 ± 98.9	48.0 ± 99.2	24.6 ± 105.5	-123.8 ± 125.1[e]
GDs 6-18	85.9 ± 93.2	164.6 ± 156.9	54.6 ± 119.9	3.8 ± 166.1	-191.59 ± 152.6[e]
GDs 6-29	280.0 ± 146.9	265.1 ± 163.9	253.9 ± 165.7	197.52 ± 156.9	83.9 ± 174.6[e]
Body weight at sacrifice (g)	3,946 ± 455	3,910 ± 448	3,877 ± 334	3,843 ± 472	3,736 ± 389
Organ weight					
Relative kidney	0.48 ± 0.06	0.48 ± 0.06	0.49 ± 0.05	0.48 ± 0.05	0.54 ± 0.08[e]
Histopathology; kidney[f]					
Vacuolar swelling; collecting ducts	0/22	0/22	0/22	4/22	20/22[b]
Litter effects					
Number of litters	21	19	19[g]	18	21

Table B.11. Effects in New Zealand White rabbits (22/group) topically exposed to bis(2-dimethylaminoethyl)ether 6 hours/day on GDs 6-18.

Endpoint		Dose (%)				
		0 (treated control)	0 (untreated control)	1.0	5.0	10
Fetal body weight per litter (g)	Combined	45.36 ± 5.87	42.42 ± 5.08	41.93 ± 4.00	42.36 ± 3.19	39.86 ± 5.13[e]
	Males	44.24 ± 5.23[h]	42.50 ± 3.83[h]	42.82 ± 4.61	43.24± 4.56	40.37 ± 5.99
	Females	45.29 ± 5.90[i]	41.95 ± 5.73	40.92 ± 4.47[e]	41.50 ± 2.83	39.32 ± 5.32[e,i]

[a]Values represent mean Draize scores ± SD, where 0 = no erythema, 1 = very slight erythema, 2 = well-defined erythema, 3= moderate to severe erythema, and 4 = severe erythema to slight eschar formation. Evaluations were made in the morning prior to exposure.
[b]Significantly different from controls at $p<0.05$ based on Fisher's exact tests (categorical data) or Student's t-test (continuous data) performed for this review performed for this review.
[c]Values represent mean Draize scores ± SD, where 0 = no edema, 1 = very slight edema, 2 = slight edema, 3= moderate edema, and 4 = severe edema. Evaluations were made in the morning prior to exposure.
[d]Values represent means ± SDs.
[e]Significantly different from controls at $p<0.05$ based on statistics performed by the study authors.
[f]Number affected/number examined.
[g]The sex of one fetus in the 1.0% group was not recorded. Its weight (36.94 g) was included in the combined litter weight data, but not in fetal body weights by sex.
[h]Data are for 19 and 18 litters for treated and untreated controls, respectively; two litters (treated controls) or one litter (untreated controls) contained only female fetuses.
[i]Data are for 20 litters; one litter at 0 and 10% contained only male fetuses.
NE = Not evaluated.

Reference: Union Carbide Corp. (1985)

At scheduled sacrifice on GD 29, the mean body weights of exposed rabbits (uncorrected and corrected for gravid uterine weight) were not significantly different from controls (Table B.11; Tyl et al., 1986; Union Carbide Corp., 1985). Relative (but not absolute) kidney weight was increased in the 10% group (by 13%) compared to treated or untreated controls. Although a tendency for a dose-related increase in relative liver weight was noted by the study authors, this effect was not statistically significant, and relative liver weights of exposed animals were within ~10% of untreated and treated controls even in the 10% dose group. The treated skin of exposed rabbits was not examined microscopically. Animals exposed at 10% showed a significantly increased incidence of vacuolar swelling of the collecting ducts in the kidneys compared to control groups. This lesion was characterized by marked swelling of the cytoplasm in epithelial cells lining the outermost part of the inner medulla.

No treatment-related effects were observed relating to the numbers of corpora lutea, total implantations, and viable and nonviable implantations per litter, percentages of pre-implantational loss and live fetuses per litter, or sex ratio of the pups (Union Carbide Corp., 1985; Tyl et al., 1986). The mean body weights of fetuses (males and females combined) and female fetuses per litter were significantly decreased (by 12 and 13%, respectively) in the 10%

dose group compared to controls (Table B.11). There was no significant treatment-related effect on the incidence of fetuses or litters with external, visceral, skeletal, or total malformations in exposed rabbits compared to treated (vehicle-only) or untreated controls. Based on these data, maternal NOAEL and LOAEL values of 1 and 5% (2 and 12 mg/kg-day, respectively) were identified for significantly increased incidences of dermal irritation (erythema and edema). Developmental NOAEL and LOAEL values of 5 and 10% (12 and 24 mg/kg-day, respectively) were identified based on decreased mean fetal body weights (of females and males and females combined).

Appendix C. Skin and Eye Irritation Scoring Systems in Range Finding Studies of Smyth and Co-workers.

Table C.1. Skin Irritation Scoring System of Smyth et al. (1949, 1962)	
Injury Grade	**Definition**
1	No reaction from undiluted chemical
2	Slight capillary injection from undiluted chemical
3	Strong capillary injection from undiluted chemical
4	Slight erythema from undiluted chemical
5	Strong erythema, edema or slight necrosis from undiluted chemical
6	Necrosis from undiluted chemical; no reaction greater than edema from 10% solution
7	Necrosis from undiluted chemical; no reaction greater than edema from 1% solution
8	Necrosis from undiluted chemical; no reaction greater than edema from 0.1% solution
9	Necrosis from undiluted chemical; no reaction greater than edema from 0.01% solution
10	Necrosis from undiluted chemical; necrosis from 0.01% solution

Table C.2. Eye Irritation Scoring System of Carpenter and Smyth (1946)	
Injury Grade	**Definition**
1	0.5 mL undiluted gives mild injury
2	0.5 mL undiluted gives moderate injury
3	0.1 mL undiluted gives mild/moderate injury or 0.5 mL undiluted gives severe injury
4	0.02 mL undiluted gives mild/moderate injury or 0.1 mL undiluted gives severe injury
5	0.005 mL undiluted gives mild/moderate injury or 0.02 mL undiluted gives severe injury
6	Excess of 40% solution gives mild/moderate injury or 0.005 mL undiluted gives severe injury
7	Excess of 15% solution gives mild/moderate injury or excess of 40% solution gives severe injury
8	Excess of 5% solution gives mild/moderate injury or excess of 15% solution gives severe injury
9	Excess of 1% solution gives mild/moderate injury or excess of 5% solution gives severe injury
10	Excess of 1% solution gives severe injury

CASN 3855-32-1
N-[3-(dimethylamino)propyl]-N,N’,N’-trimethyl-1,3-propanediamine

REVISED DRAFT

TOXICITY REVIEW FOR N-[3-(DIMETHYLAMINO)PROPYL]-N,N',N'-TRIMETHYL PROPANEDIAMINE (CASRN 3855-32-1)

Contract No. CPSC-D-06-0006
Task Order 015

Prepared by:

Versar Inc.
6850 Versar Center
Springfield, VA 22151

and

SRC, Inc.
7502 Round Pond Road
North Syracuse, NY 13212

Prepared for:

Melanie B. Biggs, Ph.D.
U.S. Consumer Product Safety Commission
4330 East West Highway
Bethesda, MD 20814

June 15, 2012

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LIST OF ABBREVIATIONS AND ACRONYMS

ACC	American Chemistry Council
ACGIH	American Conference of Government Industrial Hygienists
CPSC	Consumer Product Safety Commission
LOAEL	lowest-observed-adverse-effect level
MDI	methylene diphenyl diisocyanate
NOAEL	no-observed-adverse-effect level
OEL	occupational exposure limit
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
SPF	spray polyurethane foam
STEL	short-term exposure limit
TDI	toluene diisocyanate
TLV	threshold limit value
TWA	time-weighted average

TOXICITY REVIEW FOR
N-[3-(DIMETHYLAMINO)PROPYL]-N,N',N'-TRIMETHYL PROPANEDIAMINE
(CASRN 3855-32-1)

1. INTRODUCTION

This report summarizes available data on the identity, physicochemical properties, manufacture, supply, use, toxicity, and exposure information on n-[3-(dimethylamino)propyl]-n,n',n'-trimethyl propanediamine. This assessment was prepared from several review articles (ACC, 2010; ACC, 2011; PubChem, 2005).

N-[3-(dimethylamino)propyl]-n,n',n'-trimethyl propanediamine is an amine catalyst primarily used in the production of spray polyurethane foam (SPF). SPF is an insulation or sealant product, which is formed via an exothermic chemical reaction between the A-side and B-side chemicals (ACC, 2010). The A-side consists of chemicals such as methylene diphenyl diisocyanate (MDI) or toluene diissocyante (TDI). Polyols are part of the B-side chemicals, which also include amine and/or metal catalysts, blowing agents, surfactants, and flame retardants. Amine and/or metal catalysts are used to promote the reaction between polyols and A-side chemicals, which help polyurethane foam cells develop sufficient strength to maintain their structure and resist collapsing (ACC, 2010). Recent concerns have emerged regarding potential health effects of amine catalysts in SPF due to their potential to cause respiratory-related problems, irritation to skin and eyes, temporary vision problems, and headaches (ACC, 2010).

2. IDENTITY and PHYSICOCHEMICAL CHARACTERISTICS

This section highlights the available identity and key physicochemical properties of n-[3-(dimethylamino)propyl]-n,n',n'-trimethyl propanediamine. Amine catalysts are a derivative of ammonia and are primary, secondary, or tertiary amines depending if one or more of the three hydrogen atoms of ammonia are replaced with hydrocarbon groups. N-[3-(dimethylamino)propyl]-n,n',n'-trimethyl propanediamine is classified as being tertiary and has basic and nucleophilic properties.

Tertiary amines are generally colorless liquids with a very distinct and strong ammonia-like odor (ACC, 2011). Tertiary amines are also more volatile and have a lower boiling point than primary and secondary amines (Albrecht and Stephenson, 1988). Although specific solubility data were not found for n-[3-(dimethylamino)propyl]-n,n',n'-trimethyl

propanediamine, amine catalysts are considered to be very water soluble (Albrecht and Stephenson, 1988).

The identity and physicochemical properties of n-[3-(dimethylamino)propyl]-n,n',n'-trimethyl propanediamine are provided in Tables 1 and 2.

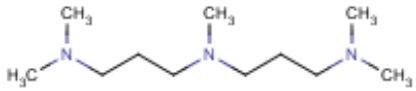
Table 1. Names, Structural Descriptors, and Molecular Formulas of N-[3-(dimethylamino)propyl]-n,n',n'-trimethyl propanediamine (ACC, 2011; PubChem, 2005)	
CAS Number	3855-32-1
Chemical Name	N-[3-(dimethylamino)propyl]-n,n',n'-trimethyl propanediamine
Trade Name	POLYCAT 77; JEFFCAT ZR40
Molecular Formula	C11H27N3
Structural Formula	
Molecular Weight	201.35218 g/mol
Synonyms	N,N,N'-Trimethyl-N'-(3-(dimethylamino)propyl)-1,3 propanediamine N-[3-(Dimethylamino)propyl]-N,N',N'-trimethylpropane-1,3-diamine
Purity/Impurities/Additives	No data

Table 2. Physicochemical Properties of N-[3-(dimethylamino)propyl]-n,n',n'-trimethyl propanediamine	
Property	**Value**
Physical state	Colorless to light yellow liquid with ammonia-like odor (Dajiang Chemical, 2011; ExpoMix, 2011)
Melting point	No data
Boiling point	227 ºC (ExpoMix, 2011)
Density	No data
Vapor pressure	4.10 mmHg @ 21 ºC (ExpoMix, 2011)
Water solubility	No data
Partition coefficient n-octanol/water (log Kow)	No data
Henry's law constant	No data
Flash point (open cup)	92 ºC (Dajiang Chemical, 2011; ExpoMix, 2011)

3. MANUFACTURE, SUPPLY, AND USE

Manufacture

Amine catalysts are produced from ammonia by replacing one or more hydrogen atoms with alkyl groups or nonacidic radicals containing hydrogen and carbon atoms (ACC, 2011). An Internet search was performed to identify companies that manufacture n-[3-(dimethylamino)propyl]-n,n',n'-trimethyl propanediamine. The Alibaba Group website (2011) listed one manufacturer of n-[3-(dimethylamino)propyl]-n,n',n'-trimethyl propanediamine in China. The name of the manufacturing company is Jiangdu Dajiang Chemical Industrial Co. Ltd. No other manufacturers were listed.

Additional manufacturing data specific to n-[3-(dimethylamino)propyl]-n,n',n'-trimethyl propanediamine were not found.

Supply

Supply data specific to n-[3-(dimethylamino)propyl]-n,n',n'-trimethyl propanediamine were not found.

Use

Amine catalysts are primarily used in the production of polyurethane foam to promote the reaction between polyols and A-side chemicals. The American Chemistry Council (2010) reported that the reaction helps polyurethane foam cells develop sufficient strength to maintain their structure to resist collapsing or becoming deformed, and also helps with the completion of the reaction or "cure" in the finished foam. Amine catalysts are typically 0.1 to 5.0 percent of a polyurethane formulation (ACC, 2011). Although metal catalysts are also used in polyurethane foam, most catalysts used in SPF are amine based. N-[3-(dimethylamino)propyl]-n,n',n'-trimethyl propanediamine can be used in all types of polyurethane foam (Dajiang Chemical, 2011). Several advantages to using this amine catalyst includes: balanced gelation and blowing; provides more open-celled foam; produces softer foam when used in high-water formulations; and enhances the performance of cell opening surfactants (Dajiang Chemical, 2011). Cell opening surfactants are used in polyurethane foam to stabilize the cell-walls and prevent the foam from shrinking or collapsing (Dow Polyurethanes, 2011). Silicon-based surfactants are used for this specific reason in many types of polyurethane foam.

4. TOXICOKINETICS

No toxicokinetic studies were located for n-[3-(dimethylamino)propyl]-n,n',n'-trimethyl propanediamine.

5. HAZARD INFORMATION

Exposure to the B-side chemicals can cause irritation of the respiratory tract, causing cough, sore throat, difficulty breathing, and runny nose (ACC, 2010). Inhalation of some amine catalyst vapors can temporarily cause vision to become foggy or blurry, and halos may appear around bright objects such as lights (ACC, 2010). Skin contact may cause moderate to severe irritation and burns, from redness and swelling to painful blistering, ulceration, and chemical burns (ACC, 2010). Amine catalysts can also irritate the eyes and may cause the following symptoms at low concentrations: corneal swelling without pain; blurred or "foggy" vision with a blue tint; and a halo phenomenon effect around lights. Higher vapor concentrations or direct contact with the liquid amines may result in severe irritation and tissue injury (ACC, 2011). If amines are ingested, this may result in severe irritation, ulceration, or burns of the mouth, throat, esophagus, and gastrointestinal tract. Other serious symptoms may include pain in the chest or abdomen, nausea, bleeding of the throat and gastrointestinal tract, diarrhea, dizziness, thirst, circulatory collapse, coma, and even death (ACC, 2011).

No acute or repeat dose toxicity studies were located for n-[3-(dimethylamino)propyl]-n,n',n'-trimethyl propanediamine.

6. EXPOSURE

The American Chemistry Council (2010 and 2011) has reported that occupational exposure to amine catalysts may occur through inhalation, skin contact, eye contact, and ingestion. Although ingestion is unlikely in the workplace, the chemical may be inadvertently ingested if an individual eats, drinks, or smokes in areas where SPF chemicals are used.

In general, exposure limits are not yet established for the majority of the amine catalysts used in SPF systems. Only a few polyurethane amine catalysts have been assigned Occupational Exposure Limits (OELs) by regulatory and non-regulatory organizations (ACC, 2011) (Table 3). This includes the Ontario Ministry of Labour in Canada, which has established enforceable OELs. The U.S. Occupational Safety and Health Administration (OSHA) has also set

enforceable permissible exposure limits (PELs) to protect workers. Other organizations that have established OELs include the American Conference of Government Industrial Hygienists (ACGIH), which has developed threshold limit values (TLVs). TLVs are generally provided as guidance and are not legally enforceable. The OELs, PELs, and TLVs can be provided as a time-weighted average (TWA) or short-term exposure limits (STELs). A TWA is the average exposure over a certain period of time, which may be an 8-hour day. The STEL is the average exposure over a 15 minute period that should not be exceeded during a workday even if the 8-hour TWA is within the criteria (ACC, 2011).

Table 3. Permissible Exposure Levels and Threshold Limit Values of Some Polyurethane Amine Catalysts

Amine Catalyst	CASRN	Exposure Limit (Source)			
		PEL	STEL	TLV	TWA
Dimethylcyclohexylamine, N,N-	98-94-2	NR	5 ppm (Ontario)	NR	NR
N-ethylmorpholine	100-74-3	20 ppm Skin[2] (OSHA)	NR	NR	5 ppm Skin[1] (ACGIH)
Triethanolamine	102-71-6	NR	NR	NR	5 mg/m^3 (ACGIH)
Dimethylamino ethanol, 2-	108-01-0	NR	6 ppm (Ontario)	NR	3 ppm (Ontario)
N,N-Dimethylaminopropylamine	109-55-7	NR	NR	NR	0.5 ppm (ACGIH)
Diethanolamine	111-42-2	NR	NR	1 mg/m^3 (ACGIH)	3 ppm (ACGIH)
Triethylamine	121-44-8	25 ppm (OSHA)	3 ppm (ACGIH)	NR	NR
Triethylenediamine	280-57-9	NR	NR	NR	1 ppm Skin[1] (Ontario)
Bis (2-Dimethylaminoethyl) ether	3033-62-3	NR	0.15 ppm Skin[1] (ACGIH)	NR	0.05 ppm Skin[1] (ACGIH)

[1] Potential for significant contribution to overall exposure by skin.
[2] Substance which may be absorbed through the skin.

PEL = permissible exposure limit
STEL = short-term exposure limit
TLV = threshold limit value
TWA = time-weighted average
OSHA = Occupational Safety and Health Administration
ACGIH = American Conference of Government Industrial Hygienists
Ontario = Ontario Ministry of Labour in Canada
NR = Not reported

Reference: American Chemistry Council (2011)

Exposure data specific to n-[3-(dimethylamino)propyl]-n,n',n'-trimethyl propanediamine were not found for consumer or general populations.

7. DISCUSSION

Overall, very few toxicological and exposure studies on n-[3-(dimethylamino)propyl]-n,n',n'-trimethyl propanediamine were found during this assessment. The current literature is also limited on physicochemical, manufacture, supply, and use information.

No toxicity data associated with n-[3-(dimethylamino)propyl]-n,n',n'-trimethyl propanediamine exposure were located. This precludes the identification of no-observed-adverse-effect level (NOAEL) or lowest-observed-adverse-effect level (LOAEL) values for reproductive, developmental, or repeated-dose systemic toxicity.

Only general occupational hazard and exposure data were found on amine catalysts. However, no exposure data associated with n-[3-(dimethylamino)propyl]-n,n',n'-trimethyl propanediamine were found for consumer or general populations.

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CASN 6711-48-4
Tetramethylimino-bis(propylamine)

DRAFT

TOXICITY REVIEW FOR TETRAMETHYLDIPROPYLENETRIAMINE (TMPT, CASRN 6711-48-4)

Contract No. CPSC-D-06-0006
Task Order 015

Prepared by:

Versar Inc.
6850 Versar Center
Springfield, VA 22151

and

SRC, Inc.
7502 Round Pond Road
North Syracuse, NY 13212

Prepared for:

Melanie B. Biggs, Ph.D.
U.S. Consumer Product Safety Commission
4330 East West Highway
Bethesda, MD 20814

July 3, 2012

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APPENDICES

LIST OF ABBREVIATIONS AND ACRONYMS

ACC	American Chemistry Council
ACGIH	American Conference of Government Industrial Hygienists
CAS	chemical abstracts service
CI	confidence interval
CPSC	Consumer Product Safety Commission
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
MDI	methylene diphenyl diisocyanate
NOAEL	no-observed-adverse-effect level
OEL	occupational exposure limit
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
RTECS	Registry for Toxic Effects on Chemical Substances®
SPF	spray polyurethane foam
STEL	short-term exposure limit
TDI	toluene diisocyanate
TLV	threshold limit value
TMPT	tetramethyldipropylenetriamine
TWA	time-weighted average

TOXICITY REVIEW FOR TETRAMETHYLDIPROPYLENETRIAMINE (TMPT, CASRN 6711-48-4)

1. INTRODUCTION

This report summarizes available data on the identity, physicochemical properties, manufacture, supply, use, toxicity, and exposure information on tetramethyldipropylenetriamine (TMPT). This assessment was prepared from several review articles (ACC, 2010; ACC, 2011; PubChem, 2005).

TMPT is an amine catalyst primarily used in the production of spray polyurethane foam (SPF). SPF is an insulation or sealant product, which is formed via an exothermic chemical reaction between the A-side and B-side chemicals (ACC, 2010). The A-side consists of chemicals such as methylene diphenyl diisocyanate (MDI) or toluene diissocyanate (TDI). Polyols are part of the B-side chemicals, which also include amine and/or metal catalysts, blowing agents, surfactants, and flame retardants. Amine and/or metal catalysts are used to promote the reaction between polyols and A-side chemicals, which help polyurethane foam cells develop sufficient strength to maintain their structure and resist collapsing (ACC, 2010). Recent concerns have emerged regarding potential health effects of amine catalysts in SPF due to their potential to cause respiratory-related problems, irritation to skin and eyes, temporary vision problems, and headaches (ACC, 2010).

2. IDENTITY and PHYSICOCHEMICAL CHARACTERISTICS

This section highlights the available identity and key physicochemical properties of TMPT. Amine catalysts are a derivative of ammonia and are primary, secondary, or tertiary amines depending if one or more of the three hydrogen atoms of ammonia are replaced with hydrocarbon groups (ACC, 2011). TMPT is classified as being tertiary and has basic and nucleophilic properties.

Tertiary amines are generally colorless liquids with very distinct and strong ammonia-like odors (ACC, 2011). Tertiary amines are also more volatile and have a lower boiling point than primary and secondary amines (Albrecht and Stephenson, 1988). Although specific solubility data were not obtained for TMPT, amine catalysts are considered to be very water soluble (Albrecht and Stephenson, 1988).

The identity and physicochemical properties of TMPT are provided in Tables 1 and 2.

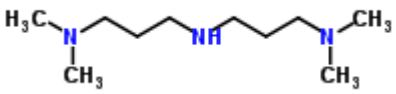
Table 1. Names, Structural Descriptors, and Molecular Formulas of TMPT (PubChem, 2005)	
CAS Number	6711-48-4
Chemical Name	Tetramethyldipropylenetriamine (TMPT)
Trade Name	POLYCAT 15; JEFFCAT ZR-50B (ACC, 2011) JEFFCAT Z-130 (Huntsman 2005)
Molecular Formula	C10H25N3
Structural Formula	
Molecular Weight	187.3256 g/mol
Synonyms	Bis(3-dimethylamino-1-propyl)amine Bis-(dimethylaminopropyl)amine Dipropylamine, 3,3'-bis(dimethylamino)- N,N,N',N'-Tetramethyldipropylenetriamine N,N,N',N'-Tetramethyliminobis(propylamine) 2,6,10-Triazaundecane, 2,10-dimethyl-
Purity/Impurities/Additives	No data

Table 2. Physicochemical Properties of TMPT	
Property	**Value**
Physical state	Colorless liquid with amine-like odor (ITWC, 2005; Dajiang Chemical, 2006)
Melting point	-78ºC (Chemical Book, 2008)
Boiling point	128-131ºC (20mm Hg ; Chemical Book, 2008); 220ºC (ITWC, 2005)
Density	0.841 g/mL (25ºC; Chemical Book, 2008)
Vapor pressure	2.74 mm Hg
Water solubility	No data
Partition coefficient n-octanol/water (log Kow)	No data
Henry's law constant	No data
Flash point	98.33ºC (Chemical Book, 2008); 88.33ºC (ITWC, 2005)

3. MANUFACTURE, SUPPLY, AND USE

Manufacture

Amine catalysts are produced from ammonia by replacing one or more hydrogen atoms with alkyl groups or nonacidic radicals containing hydrogen and carbon atoms (ACC, 2011). An Internet search was performed using the Chemical Abstracts Service (CAS) number and/or trade names to identify companies that manufacture TMPT. The following three chemical companies were listed as being manufacturers of TMPT: Air Products and Chemicals, Inc. (2011);

Huntsman Corporation (2005); and Jiangdu Dajiang Chemical Industrial Co. Ltd (2006). Jiangdu Dajiang Chemical Industrial manufactures TMPT in China. The manufacturing locations of the other two companies were not found.

Additional manufacturing data specific to TMPT were not found.

Supply

Supply data specific to TMPT were not found.

Use

Amine catalysts are primarily used in the production of polyurethane foam to promote the reaction between polyols and A-side chemicals. The American Chemistry Council (2010) reported that the reaction helps polyurethane foam cells develop sufficient strength to maintain their structure to resist collapsing or becoming deformed, and also helps with the completion of the reaction or "cure" in the finished foam. Amine catalysts are typically 0.1 to 5.0 percent of a polyurethane formulation (ACC, 2011). Although metal catalysts are also used in polyurethane foam, most catalysts used in SPF are amine based. TMPT can be used in flexible, semi-flexible, and rigid polyurethane foam applications (Dajiang Chemical, 2006).

4. TOXICOKINETICS

No toxicokinetic studies were located for TMPT.

5. HAZARD INFORMATION

Exposure to the B-side chemicals can cause irritation of the respiratory tract, causing cough, sore throat, difficulty breathing, and runny nose (ACC, 2010). Inhalation of some amine catalyst vapors can temporarily cause vision to become foggy or blurry, and halos may appear around bright objects such as lights (ACC, 2010). Skin contact may cause moderate to severe irritation and burns, from redness and swelling to painful blistering, ulceration, and chemical burns (ACC, 2010). Amine catalysts can also irritate the eyes and may cause the following symptoms at low concentrations: corneal swelling without pain; blurred or "foggy" vision with a blue tint; and a halo phenomenon effect around lights. Higher vapor concentrations or direct contact with the liquid amines may result in severe irritation and tissue injury (ACC, 2011). If

amines are ingested, this may result in severe irritation, ulceration, or burns of the mouth, throat, esophagus, and gastrointestinal tract. Other serious symptoms may include pain in the chest or abdomen, nausea, bleeding of the throat and gastrointestinal tract, diarrhea, dizziness, thirst, circulatory collapse, coma, and even death (ACC, 2011).

ACUTE DOSE TOXICITY

5.1. Acute Oral Toxicity

An oral median lethal dose (LD_{50}) of 1.62 mL/kg (confidence interval [CI]: 1.02–2.60 mL/kg) was reported for TMPT based on an experiment in which groups of five male Carworth-Wistar rats were administered a single oral dose of undiluted TMPT via gavage and observed for 14 days (Smyth et al., 1962). Dose groups were arranged in a logarithmic series differing by a factor of two (no further details of exposure levels reported), and LD_{50} estimates were calculated using the methods of Thompson (1947, as cited in Smyth et al., 1962) and Weil (1952, as cited in Smyth et al., 1962). Based on the density of 0.841 g/mL for TMPT (Chemical Book, 2008), the LD_{50} is equivalent to 1,362 mg/kg (CI: 856–2,184 mg/kg).

The oral lethality of TMPT was also evaluated in a study from the Russian literature (Sidorin et al., 1984). Study details are presented here as reported in the tables and English abstract of the report and as reported in the Registry of Toxic Effects on Chemical Substances® (RTECS, 2011). Test animals (species not reported) were administered single oral doses of TMPT via gavage. The oral LD_{50} was 1,095 mg/kg (CI: 869–1,379 mg/kg). RTECS (2011) lists somnolence (general depressed activity) and excitement as behavioral effects at this dose. No additional details were located in the available English language sources for this study.

5.2. Acute Dermal Toxicity

Smyth et al. (1962) identified a dermal LD_{50} of 0.31 mL/kg (CI: 0.06–1.50 mL/kg) based on an experiment in which groups of four male albino New Zealand rabbits had various concentrations of TMPT applied to a clipped area of the trunk for 24 hours, according to the method of Draize et al. (1944, as cited in Smyth et al., 1962). The application site was covered, and animals were immobilized during the 24-hour exposure period. After 14 days of observation for mortality, the LD_{50} was calculated as described above for acute oral toxicity. The LD_{50} is equivalent to 261 mg/kg (CI: 50–1,260 mg/kg). No other relevant studies were located.

5.3. Acute Inhalation Toxicity

In a study designed to assess lethality, groups of six male or female albino rats were exposed to a flowing stream of air saturated with TMPT vapor for various durations and observed for 14 days (Smyth et al., 1962). Inhalation periods were arranged in a logarithmic series with a ratio of two extending from 15 minutes to 8 hours until the inhalation period killing about half the number of animals within the 14-day observation period was determined. No deaths from acute exposure to TMPT were reported at durations of ≤8 hours.

Sidorin et al. (1984) included evaluation of sublethal effects in animals exposed to TMPT via inhalation for 4 hours (further details on exposures not available). Results are presented here as reported in the English abstract of the Russian language report. A "ceiling concentration" of 180 mg/m^3 for inhalation exposure of TMPT was identified based on unspecified changes in "central nervous system indices." No additional details were presented in the English abstract for this study.

5.4. Acute Parental Toxicity

In the Russian study described above (Sidorin et al., 1984), animals (species not reported) were administered single intraperitoneal injections of TMPT or repeated injections over 3 days. Results are presented here as reported in the tables and English abstract of the report and as reported in RTECS (2011). Sidorin et al. (1984) identified an acute single-dose intraperitoneal LD_{50} for TMPT of 74 mg/kg (CI: 62–89 mg/kg). RTECS (2011) lists somnolence and excitement as behavioral effects at this dose. Animals administered injections of TMPT at a dose of one-third of the LD_{50} once daily for 3 days were reported to show unspecified "enzyme activity impairments which influenced processes of detoxification and energy biotransformation" after the third dose. No further information is available in the English language sources for this study, and no other relevant studies were located.

5.5. Primary Skin Irritation

Smyth et al. (1962) reported that the application of TMPT to uncovered areas on the clipped belly of five albino rabbits for 24 hours resulted in Grade 6 (out of 10) skin irritation, indicating moderate irritant properties of this chemical to skin (methods described in Smyth et al., 1949, 1962; see Appendix A). No other relevant studies were located.

5.6. Primary Eye Irritation

Smyth et al. (1962) reported that the instillation of TMPT into the eye of rabbits (using the method of Carpenter and Smyth, 1946) resulted in severe corneal irritation (Grade 9 on a 10-point scale) (see Appendix A). No other relevant studies were located.

5.7. Sensitization

In the Russian study described above (Sidorin et al., 1984), TMPT reportedly tested negative for sensitization. No additional details were presented in the English abstract for this study, so the reliability of this result is uncertain. No other relevant studies were located.

REPEAT DOSE TOXICITY

No repeat dose toxicity studies were located for TMPT.

6. EXPOSURE

The American Chemistry Council (2010 and 2011) has reported that occupational exposure to amine catalysts may occur through inhalation, skin contact, eye contact, and ingestion. Although ingestion is unlikely in the workplace, the chemical may be inadvertently ingested if an individual eats, drinks, or smokes in areas where SPF chemicals are used.

In general, exposure limits are not yet established for the majority of the amine catalysts used in SPF systems. Only a few polyurethane amine catalysts have been assigned Occupational Exposure Limits (OELs) by regulatory and non-regulatory organizations (ACC, 2011) (Table 3). This includes the Ontario Ministry of Labour in Canada, which has established enforceable OELs. The U.S. Occupational Safety and Health Administration (OSHA) has also set enforceable permissible exposure limits (PELs) to protect workers. Other organizations that have established OELs include the American Conference of Government Industrial Hygienists (ACGIH), which has developed threshold limit values (TLVs). TLVs are generally provided as guidance and not legally enforceable. The OELs, PELs, and TLVs can be provided as a time-weighted average (TWA) or short-term exposure limits (STELs). A TWA is the average exposure over a certain period of time, which may be an 8-hour day. The STEL is the average exposure over a 15 minute period that should not be exceeded during a workday even if the 8-hour TWA is within the criteria (ACC, 2011).

Table 3. Permissible Exposure Levels and Threshold Limit Values of Some Polyurethane Amine Catalysts

Amine Catalyst	CASRN	Exposure Limit (Source)			
		PEL	STEL	TLV	TWA
Dimethylcyclohexylamine, N,N-	98-94-2	NR	5 ppm (Ontario)	NR	NR
N-ethylmorpholine	100-74-3	20 ppm Skin[2] (OSHA)	NR	NR	5 ppm Skin[1] (ACGIH)
Triethanolamine	102-71-6	NR	NR	NR	5 mg/m^3 (ACGIH)
Dimethylamino ethanol, 2-	108-01-0	NR	6 ppm (Ontario)	NR	3 ppm (Ontario)
N,N-Dimethylaminopropylamine	109-55-7	NR	NR	NR	0.5 ppm (ACGIH)
Diethanolamine	111-42-2	NR	NR	1 mg/m^3 (ACGIH)	3 ppm (ACGIH)
Triethylamine	121-44-8	25 ppm (OSHA)	3 ppm (ACGIH)	NR	NR
Triethylenediamine	280-57-9	NR	NR	NR	1 ppm Skin[1] (Ontario)
Bis (2-Dimethylaminoethyl) ether	3033-62-3	NR	0.15 ppm Skin[1] (ACGIH)	NR	0.05 ppm Skin[1] (ACGIH)

[1] Potential for significant contribution to overall exposure by skin.

[2] Substance which may be absorbed through the skin.

PEL = permissible exposure limit
STEL = short-term exposure limit
TLV = threshold limit value
TWA = time-weighted average
OSHA = Occupational Safety and Health Administration
ACGIH = American Conference of Government Industrial Hygienists
Ontario = Ontario Ministry of Labour in Canada
NR = Not reported

Reference: American Chemistry Council (2011)

Exposure data specific to TMPT were not found for consumer or general populations.

7. DISCUSSION

Overall, very few toxicological and exposure studies on TMPT were found during this assessment. The current literature is also limited on physicochemical, manufacture, supply, and use information.

Toxicity data associated with TMPT are also limited. A range-finding study reported that TMPT is a skin and eye irritant and reported LD_{50} values for oral and dermal exposures of 1,362 and 261 mg/kg, respectively. A study from the Russian literature reported a similar oral LD_{50} (1,095 mg/kg), as well as an intraperitoneal LD_{50} of 74 mg/kg. This study suggested that acute exposure to TMPT may have adverse effects in the central nervous system and the liver, but further details and specifics are not available in English language sources for this study (study and tables are reported in Russian). Absence of any subchronic or chronic repeat dose toxicity studies precludes the identification of no-observed-adverse-effect level (NOAEL) or lowest-observed-adverse-effect level (LOAEL) values for reproductive, developmental, or repeated-dose systemic toxicity.

Only general occupational hazard and exposure data were found on amine catalysts. However, no exposure data associated with TMPT were found for consumer or general populations.

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Appendix A. Skin and Eye Irritation Scoring Systems in Range Finding Studies of Smyth and Co-workers.

Table A.1. Skin Irritation Scoring System of Smyth et al. (1949, 1962)

Injury Grade	Definition
1	No reaction from undiluted chemical
2	Slight capillary injection from undiluted chemical
3	Strong capillary injection from undiluted chemical
4	Slight erythema from undiluted chemical
5	Strong erythema, edema or slight necrosis from undiluted chemical
6	Necrosis from undiluted chemical; no reaction greater than edema from 10% solution
7	Necrosis from undiluted chemical; no reaction greater than edema from 1% solution
8	Necrosis from undiluted chemical; no reaction greater than edema from 0.1% solution
9	Necrosis from undiluted chemical; no reaction greater than edema from 0.01% solution
10	Necrosis from undiluted chemical; necrosis from 0.01% solution

Table A.2. Eye Irritation Scoring System of Carpenter and Smyth (1946)

Injury Grade	Definition
1	0.5 mL undiluted gives mild injury
2	0.5 mL undiluted gives moderate injury
3	0.1 mL undiluted gives mild/moderate injury or 0.5 mL undiluted gives severe injury
4	0.02 mL undiluted gives mild/moderate injury or 0.1 mL undiluted gives severe injury
5	0.005 mL undiluted gives mild/moderate injury or 0.02 mL undiluted gives severe injury
6	Excess of 40% solution gives mild/moderate injury or 0.005 mL undiluted gives severe injury
7	Excess of 15% solution gives mild/moderate injury or excess of 40% solution gives severe injury
8	Excess of 5% solution gives mild/moderate injury or excess of 15% solution gives severe injury
9	Excess of 1% solution gives mild/moderate injury or excess of 5% solution gives severe injury
10	Excess of 1% solution gives severe injury