Dimorpholinodiethyl ether
6425-39-4

OVERVIEW

Dimorpholinodiethyl ether came to the attention of the National Cancer Institute (NCI) Division of Cancer Biology as the result of a review of chemicals that do not meet the criteria for inclusion in the United States (U.S.) Environmental Protection Agency (EPA) HPV Challenge Program even though their production volume in 1998 exceeded 1 million pounds.

Dimorpholinoethyl ether is a blowing agent for the production of flexible, molded, and moisture-cured foams and coatings. Since this chemical is primarily an industrial intermediate, the main source of exposure would be anticipated to be workers.

No information on the toxicity of dimorpholinoethyl ether was found in the available literature. However there is concern that this compound could react with nitrites, such as those present in the mouth, to form a potent carcinogen, nitrosomorpholine. For this reason, the NCI requests specialized tests to determine if such a reaction does occur. It is not possible to determine if there are other testing needs for dimorpholinoethyl ether until this important consideration is resolved.

NCI's concern about the possible formation of nitrosomorpholine was presented to the Chemical Selection Working Group on December 15, 2005. This group concurred with NCI's evaluation.

INPUT FROM GOVERNMENT AGENCIES/INDUSTRY

In comments provided on January 25, 2006, Dr. John Walker supplied the following post-meeting information on Interagency Testing Committee (ITC) activities regarding 2',2'''-dithiobisbenzanilide. This chemical was added to Appendix B in the ITC's 56th Report (70 FR 61520, October 24, 2005) as one of 235 substances that were high production chemicals in the 1998 and 2002 Inventory Update Rules (IURs), but not in the 1990 or 1994 IURs. The ITC discussed a data-availability study of these 235 chemicals in its 56th Report and posted the results on its web site, http://www.epa.gov/opptintr/itc. Dimorpholinodiethyl ether is also in the

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American Chemistry Council (ACC), Soap and Detergent Association (SDA), and Synthetic Organic Chemical Manufacturers Association (SOCMA) Extended HPV (EHPV) Program. The goal of the EHPV Program is to collect and publish health and environmental information on chemicals that did not qualify as HPV chemicals under the EPA's HPV Challenge program but have since reached the 1 million pound per year threshold. As a result of these activities, there are ongoing efforts to obtain and make available health effects and environmental data for this compound.

Because of the ongoing EHPV and ITC activities, this information is also being forwarded to the ITC.

SUMMARY OF RELEVANT DATA FOR NOMINATION

CHEMICAL IDENTIFICATION

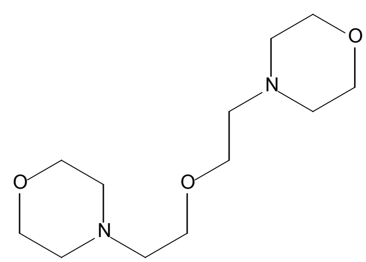
CAS Registry No.: 6425-39-4

CAS Name: Morpholine, 4,4'-(oxydi-2,1-ethanediyl)bis- (9CI)

Synonyms: Dimorpholinodiethyl ether; bis(morpholinoethyl)ether; bis(3-aminopropyl)ether diethylene glycol 2,2'-dimorpholinodiethyl ether; DMDEE; EINECS No. 229-194-7 (ChemID, 2005; ChemSources International, 2005)

Structural Class: Morpholine derivative

Structure, Molecular Formula, and Molecular Weight:



$C_{12}H_{24}N_2O_3$ Mol. wt. 244.3

Chemical and Physical Properties:

Description: Straw yellow viscous liquid (Jiangdu Dajiang Chemical Factory, 2003)

Melting point: -28 ºC (BASF, 2005)

Boiling point: 309 ºC (BASF, 2005; Sigma-Aldrich, 2004)

Density: 1.06 g/ml at 25 ºC (Sigma-Aldrich, 2004)

Flash point: >100 ºC (PMCC) (Jiangdu Dajiang Chemical Factory, 2003)

Stability: Avoid strong oxidizing agents and acids; hazardous polymerization will not occur (Sigma Aldrich, 2004)

log P: -0.67 (Accelrys, 2004)

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Technical Products and Impurities:

Dimorpholinodiethyl ether is available at 97 % purity in 100 and 500 ml glass bottles from the Aldrich Division of Sigma Aldrich (Sigma-Aldrich, 2005).

EXPOSURE INFORMATION

Production and Producers:

Dimorpholinodiethyl ether is available for the industrial market from Huntsman Corporation as part of the company's JEFFCAT® family of catalysts (Huntsman, 2004). This chemical is also available at ≥98% purity from BASF as Lupragen® N 106.

Dimorpholinodiethyl ether is produced by reacting diethylene glycol with ammonia under pressure at an elevated temperature in the presence of hydrogen (Riechers *et al.*, 2000).

Bis-(morpholino-N-alkyl) ethers have been produced by many other methods. In one method for dimorpholinodiethyl ether synthesis, N-(2-chloroethyl)morpholine is reacted with N-(2-hydroxyethyl)morpholine and sodium. Another method involves the reaction of triethanolamine in the presence of hydrochloric acid. Still another method involves the reaction of morpholine with bis-(2-chloroethyl)ether. These processes have been criticized as involving caustic neutralization or requiring the use of excess reagents to react with liberated chlorine compounds. In addition, these methods are said to involve the use of chemical intermediates difficult to obtain or to produce the desired product in low yield (Brennan *et al.*, 1978).

Another method involves the vapor phase reaction of N-(2-hydroxyethyl)morpholine in the presence of an activated alumina catalyst to form dimorpholinodiethyl ether. This method is said to suffer the attendant problems of vapor phase synthesis with low yields and extensive by-product formation (Brennan *et al.*, 1978).

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It has been found that bis-(morpholino-N-alkyl) ethers can be selectively produced directly from the corresponding N-(hydroxyalkyl)morpholine in liquid phase without the attendant deficiencies of previously known processes. Under rigorous reaction conditions, *i.e.* temperatures in the 200 to 300 ºC range, the process is selective to the desired product (Brennan *et al.*, 1978).

Production/Import Level:

The EPA's Inventory Update Rule reports nonconfidential production ranges of chemicals every four years. The production levels of dimorpholinodiethyl ether during the years 1986-2002 are listed in Table 1.

Table 1. Production Levels of Dimorpholinodiethyl ether

Year	Production Range (lbs.)
1986	10,000 - 500,000
1990	10,000 - 500,000
1994	10,000 - 500,000
1998	> 1,000,000 - 10,000,000
2002	> 1,000,000 - 10,000,000

Source: EPA (2005)

Dimorpholinodiethyl ether is listed as an LPV chemical in the European Union, meaning that annual production was 10 - 1,000 metric tons and the chemical was produced or imported between 1990 and 1994. The European producer is BASF in Germany (European Chemicals Bureau, 2005).

Use Pattern:

Dimorpholinodiethyl ether is a specialty amine catalyst used to produce slabstock flexible foam and high-resilient (HR) molded foam; it is also used in coatings and adhesives

(Huntsman, 2004). This amine blowing catalyst is also particularly suitable for one- and two-component rigid foam sealant systems (Jiangdu Dajiang Chemical Factory, 2003). It has also been patented as a catalyst for preparation of products such as orthopedic casts with controlled flexibility (Morris & Alvarez, 2004), rigid polyurethane foams (Sieker & Gabrieli, 2002), and prepolymer compositions for polyurethane insulating foams released from pressurized cans (Pauls & Schumacher, 2000).

Dimorpholinodiethyl ether is also an ingredient of reactive hot melt urethane adhesives. Hot melt urethane systems are solid at room temperature, melt to a viscous liquid when heated to moderate temperatures, and are applied in a molten state to an appropriate substrate. On the substrate, the adhesive cools to a solid state to provide an initial bond strength ("green strength") and eventually the adhesive achieves its ultimate bond strength in a curing reaction with ambient moisture (Tangen & Waid, 2004).

A total of 113 patents citing dimorpholinodiethyl ether, 20 patents citing DMDEE and not dimorpholinodiethyl ether, and 14 patents citing 4,4-(oxydi-2,1-ethanediyl)bis-morpholine were on file with the U.S. Patent and Trademark Office since 1976 as of October 2005. Titles cited inventions for hot melt polyurethane adhesive compositions, moisture cure catalystst and adhesives, insulating foams, reagents for heat activated polymer crosslinking, and polyurethane foams. Warm melt polyurethanes for bookbinding applications, orthopedic splints, expansible sealants and other similar applications were mentioned (USPTO, 2005).

Human Exposure:

The primary exposure to dimorpholinodiethyl ether would be expected to occur in the workplace during the manufacture of slabstock flexible foam, HR molded foam, hot melt adhesives, and possibly other products.

Blowing catalysts used for the production of polyester slabstock foam are typically based on morpholine structures. During the foaming process the liquid chemicals are laid down through a variety of techniques onto a moving conveyor contained within a channel. As the foam ingredients react, the exothermic reaction results in the vaporization of blowing agents and the foam rises within the moving channel. During the initial phase of foam rise there is a blowoff of chemicals (e.g., TDI) from the foam. To reduce worker exposure to the potentially harmful vapors, the first stage of the continuous foaming process is done in an enclosed ventilated area; however, due to the speed with which many manufacturers run production, the developing foam is enclosed within this area for only a few minutes. Directly after this stage, the foam is cut and moved along conveyors to a storage area. During this latter phase of production, plant workers are continuously exposed to any vapors emitted from the cut foam. Maximum temperatures are not reached in the foam until about 10 hours after production, resulting in the migration of additives such as the catalysts from the foam during the cutting and storage process. The residual amine odor can also extend into the final cutting and fabrication points of the facility, thereby exposing additional workers to the catalyst. There have been extreme pressures on catalyst suppliers to the polyester polyol flexible slabstock industry to produce lower odor versions of the catalysts, which has led to the invention of morpholine derivatives including dimorpholinodiethyl ether (Muha *et al.*, 1997).

It should be noted that morpholine derivatives with a less intense odor may produce greater worker comfort but will not reduce worker exposure unless the substituted product has significantly lower vapor pressure or additional engineering controls are instituted.

In the presence of an appropriate catalyst, urethane hot melts have rapid rates of cure. While widely used, hot melt urethanes have not been problem free. Toxicity issues may become especially important in the application of hot melt adhesives to substrates using spraying and other dispensing methods. Because of these concerns, the use of urethane hot-melts has been banned from some industrial sites. Several approaches have been developed to address the toxicity issue, including the use of dimorpholinodiethyl ether, a replacement for tin catalyst. The amount of dimorpholinodiethyl ether added to the mixture is typically about 0.2% by weight (Tangen & Waid, 2004).

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The use of dimorpholinodiethyl ether as a catalyst in reactive polyurethane hot melt adhesives provides adhesives which are not free of volatile organic compounds (VOCs). Industrial dimorpholinodiethyl ether is reported to contain about 76% VOCs. During application at elevated temperatures, fugitive catalyst can escape from the adhesive. In addition to the environmental problems created, the loss of catalyst makes the curing rate less consistent. This is particularly pronounced in open roll coater applications where the adhesives are constantly exposed to high temperatures and a strong, open ventilation air flow (Li & Lohrey, 2003).

Additional workers may be exposed to unreacted catalyst while preparing final products from plastics and foams being machined into final products. Slabstock foam products are primarily used in furniture seat cushions and bedding materials; molded foam is used in automotive seats, packaging, and a wide range of specialty products (EPA, 1996).

Environmental Occurrence:

Dimorpholinodiethyl ether is not a natural product. No information on its presence in the air or industrial effluents from its production or uses was found in the available literature although it would be expected that emissions to air, water, and soil from production, use, and disposal or recycling would be possible.

Regulatory Status:

No standards or guidelines have been set by NIOSH or the Occupational Safety and Health Administration (OSHA) for occupational exposure to or workplace allowable levels of DMDEE. DMDEE was not on the American Conference of Governmental Industrial Hygienists (ACGIH) list of compounds for which recommendations for a Threshold Limit Value (TLV) or Biological Exposure Index (BEI) are made.

The release of toxic air pollutants, primarily methylene chloride, from the flexible polyurethane foam industry has received substantial attention from the Occupational Safety and Health Administration (OSHA) and the Environmental Protection Agency (EPA).

OSHA has required the approximately 40 loop slitter adhesive users to alter adhesive compositions. In 2003, EPA required new or reconstructed facilities that use flame lamination processes to reduce air toxic emissions by 90%; approximately three facilities were affected (EPA, 1996; EPA, 2003). Since these regulations were intended to reduce methylene chloride emissions, it is unclear whether they reduced or increased the emissions of dimorpholinodiethyl ether.

TOXICOLOGICAL INFORMATION

Human Data:

No epidemiological studies or case reports investigating the association of dimorpholinodiethyl ether and health effects in humans were identified in the available literature.

Huntsman notes that JEFFCAT catalysts (including dimorpholinodiethyl ether) are slightly to moderately toxic by ingestion in single doses and by single skin applications. The principal hazards arising from working with these products according to Huntsman are associated with similar organic amines, namely, corrosive action on skin and eyes. Prolonged skin contact with JEFFCAT catalysts can produce severe irritation and skin sensitivity in susceptible persons upon repeated exposure or prolonged contact (Huntsman, 1998).

Animal Data:

Acute, Subchronic, and Chronic Studies. No information was identified in the available literature.

Metabolism. No information on the metabolism of dimorpholinodiethyl ether was identified in the available literature.

The predictive program, METEOR described metabolism through oxidative deamination and oxidative O-dealkylation to multiple products as plausible pathways (Lhasa Ltd., 2004).

Other Biological Effects. No information on any other biological effects was identified for dimorpholinodiethyl ether in the available literature.

Structure-ActivityAnalysis:

Two SAR-based computer software programs were used as tools to assess the toxicity of dimorpholinodiethyl ether. One program, TOPKAT uses robust, cross-validated models based on experimental data to calculate a probability value from 0.0-1.0 that a chemical will be positive for a certain endpoint. This program also incorporates a validity diagnostic that indicates if the predicted toxicity values may be accepted with confidence. Another SAR-based model, DEREK, uses structure alerts to predict the toxicity of a compound. TOPKAT described the weight of evidence probability of carcinogenicity of dimorpholinodiethyl ether as 1.0 with all validation criteria satisfied. TOPKAT was unable to predict a probability of Ames mutagenicity. Additional TOPKAT computations are given in Table 2. DEREK found no structure alerts upon which to make a determination of the toxicity of dimorpholinodiethyl ether (Accelerys, 2004; Lhasa Ltd., 2004).

Table 2. Toxicity Predictions for Dimorpholinodiethyl Ether Using TOPKAT

Toxicity Endpoint	Toxicity Prediction
Carcinogenicity (male rat, NTP model)	0.988 - Probable
Carcinogenicity (female rat, NTP model)	0.000 - Unlikely
Carcinogenicity (male mouse, NTP model)	0.995 - Probable
Carcinogenicity (female mouse, NTP model)	0.999 - Probable
Developmental Toxicity	Unable to make prediction
Skin Irritation	Unable to make prediction
Skin Sensitization (Neg. vs. Sensitive)	0.059 – Unlikely

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