

# Morpholine

**HUNTSMAN**

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### Quality Policy

Huntsman Corporation is committed to providing products and services that consistently conform to our customers' requirements.

To fulfill this commitment, the employees of Huntsman Corporation are dedicated to "being the best" through continuous improvement.

In implementing its quality policy, Huntsman Corporation is committed to the use of statistical methods.

### Product Safety Policy

It is the product safety policy of Huntsman Corporation to provide our customers with information on the safe handling and use of our products. The Material Safety Data Sheet (MSDS) should always be read and understood thoroughly before handling the product, and adequate safety procedures should be followed. Information on the toxicity, environmental, and industrial hygiene aspects of our products may be found in the MSDS.

## INTRODUCTION

Morpholine, CAS Number 110-91-8, is a colorless, mobile, hygroscopic liquid with a characteristic amine-like odor. It is completely miscible with water and a large number of organic solvents, and is itself a solvent for a large variety of organic materials, including resins, dyes, waxes, shellac, and casein.

Morpholine is an extremely versatile chemical with many important applications. It is used as an intermediate in the manufacture of rubber chemicals and optical brighteners. It is also used extensively as a corrosion inhibitor in steam boiler systems.

Fatty acid derivatives of morpholine are used as emulsifiers in the manufacture of waxes and polishes. Other derivatives have found applications as bactericides, pharmaceutical chemicals, and antioxidants for lubricating oils. Morpholine derivatives are particularly useful in the textile industry, where they are employed as textile lubricants and sizing emulsifiers.

Chemically, morpholine is an amino ether. The ether function of the molecule is typically inert and most of the reactions of morpholine involve the secondary amine group.

## SALES SPECIFICATIONS/ANALYTICAL PROCEDURES

### Sales Specifications

The following sales specifications are subject to change without notice. Appropriate analytical procedures for these specifications may be found to the right.

		<b>Method of Determination</b>
Appearance	Clear liquid, substantially free from suspended matter	ST-30.1
Color, Pt-Co scale	15 max.	ST-30.12
Morpholine, wt. %	99.0 min.	ST-35.77
Water, wt. %	0.3 max.	ST-31.53 Procedure 6

### Analytical Procedures

Abbreviated forms of the standard methods of test for use with morpholine specifications are presented here. Copies of the methods in detail are available from our Technical Services Section in Austin, Texas, upon request.

APPEARANCE (Method No. ST-30.1) is determined by visual inspection of DIGLYCOLAMINE agent in a 100-ml tall-form Nessler tube.

COLOR (Method No. ST-30.12) is determined visually in a 40-ml tube with APHA color disc standards, or in a 100-ml tall-form Nessler tube with liquid platinum cobalt (APHA) standards.

MORPHOLINE ASSAY (Method No. ST-35.77) is used to determine morpholine and impurities by gas chromatography.

WATER (Method No. ST-31.53) is determined by the standard Karl Fischer method, the end point being detected electrometrically.

### Rubber Chemicals

A major use of morpholine is as an intermediate in the production of delayed-action type rubber accelerators. Accelerators are added to rubber before fabrication to increase the rate of vulcanization. Since during fabrication there is a danger of prevulcanization, particularly if high temperatures are involved or if furnace black rather than channel black is present, delayed-action accelerators are highly desirable.

Morpholine-based delayed-action accelerators are usually made by reacting morpholine with 2-mercaptobenzothiazole. Several other morpholine-based accelerators have been reported in the literature.

### Catalysts

Morpholine has been employed as a catalyst for the condensation of aldehydes and ketones which contain active methyl or methylene groups. The condensates may be hydrogenated to polyhydroxy compounds which can be sulfated to form surface-active agents.

Small quantities of morpholine are used in the emulsion polymerization of monomers, such as butadiene and isoprene, as well as their copolymerization with styrene, acrylonitrile, and the like.

Morpholine has been used as a temperature sensitive polymerization inhibitor. Small amounts permit complete impregnation of porous materials with molten vinylpyrrolidene-type monomers just above their melting points, but still allow complete polymerization at slightly higher temperatures.

Morpholine has also been used as a gelling agent in the preparation of alumina catalysts for the treatment of hydrocarbons. Catalysts of fine particle size suitable for fluidized solid techniques result from this procedure.

### Corrosion Inhibitors

Morpholine is widely used as a neutralizing amine in combating carbonic acid corrosion in condensate return lines of steam boiler systems. The morpholine volatilizes with the steam from the boiler and condenses when the steam does, thereby affording protection to the lines, which otherwise would be subjected to corrosion by the carbonic acid present in the steam condensate.

Morpholine vapors protect silver and other metals against corrosion and tarnish by acid fumes, such as sulfur dioxide and hydrogen sulfide. The morpholine is supplied by evaporation from solution in a solid, such as camphor, or by sublimation from morpholinium N,N'-oxydiethylenecarbamate.

Morpholine is a component of a corrosion inhibitor system that prevents decomposition of a chlorinated hydrocarbon in a composition containing the chlorinated hydrocarbon and a large amount of water.

Corrosion of metal aerosol containers and valves can be prevented by the use of low levels of morpholine.

Morpholine is one of several amines employed as phosphates for inhibiting the corrosive action of grease-proof paper on steel and other metals. Di-4-morpholinyl polysulfides have been claimed as corrosion inhibitors to be added to mineral lubricating oils. Turbine oils, especially, are quickly contaminated with water, and to protect the machinery against rusting, 4,4'-alkyldenedimorpholines and poly (4-morpholinylmethyl) phenols have been used. Storage tanks, pipes, and other devices for handling petroleum distillates must be protected against corrosion, and for this purpose 4,4'-butylmercaptomorpholine, morpholinium mahogany sulfonates, and morpholine in conjunction with ammonium mahogany sulfonates have been suggested.

### Separating Agents

The physical and chemical properties of morpholine make it useful in various purification procedures. Marked differences in the solubility of the methyl amines in morpholine have led to a convenient extractive method for separating these volatile amines. The addition of morpholine to styrene-containing hydrocarbon mixtures makes possible the isolation of substantially pure styrene by azeotropic distillation. It is claimed that aldehyde or keto derivatives of morpholine, e.g., 4-formylmorpholine, are useful for separating low-viscosity components from mineral, animal, vegetable, and fish oils. It is reported that morpholine is the preferred amine to use in an oil-amine mixture for scrubbing organic sulfur compounds from fuel gas. Morpholine is also used in the purification of acetylene and certain olefins.

### Optical Brighteners

Morpholine is an important intermediate in the manufacture of optical brighteners. Optical brighteners are employed by the soap and detergent industry in the compounding of detergents. The diaminostilbene triazine type brightener with morpholine as a substituent on one of the triazine rings is particularly effective on cellulose. Having greater stability to chlorine bleaches than other types of brighteners, they are particularly suitable for home laundry detergents.

### Pharmaceutical Chemicals

The physiological activity of the morpholine nucleus is attested by the number of pharmaceutical applications which have been found for it.

The hydroperiodide is suitable for incorporation in ointments for the treatment of skin disorders, such as athlete's foot.

A number of morpholine derivatives have been described as analgesics and local anesthetics. The 4-benzyl morpholines are particularly effective. 4-(4-Bromobenzyl) morpholine, for instance, is reported to be only 25% as toxic as procaine, but almost equal to it in activity.

Several morpholine-derived chemicals are useful as respiratory and vasomotor stimulants. The N,N'-ethylenebis (N-alkyl-4-morpholinecarboxamides) are especially valuable, since the ratio of active dose to toxic dose is low. The dibutyl derivative, for example, shows 12 times the activity of nikethamide.

Other pharmaceutical fields in which morpholine has found application include cholaretics, antispasmodics, analeptics, and antimalarials. In addition, the use of morpholine as a peptizing agent for preparing aqueous dispersions of phenothiazines for anthelmintic purposes has been claimed. Likewise, the use of morpholine in preparing soluble salts of certain sulfanilamides has been patented, and various derivatives are claimed to have therapeutic value.

### **Bactericides, Fungicides, and Herbicides**

A number of morpholine derivatives have been shown to possess bactericidal activity. For example, morpholinium salts of certain acylated sulfonamides possess strong bacteriostatic or bactericidal properties, and morpholine hydroperiodide has been used as a water disinfectant.

The reaction of morpholine with 3,4,5-trichloro-2,6-pyridinedicarbonitrile yields a product which is useful in the control of fungi.

Morpholine is used in preparing compounds that are excellent herbicides and that can be applied either to the soil before the weeds emerge or to the growing plants.

### **Antioxidants**

In addition to its use as a corrosion inhibitor, 4-*t*-butylmercaptomorpholine has been employed as an antioxidant for lubricating oils. Di-4-morpholinyl monosulfide has been claimed as a lubricating oil stabilizer, and multifunctional oil additives that possess antioxidant properties can be prepared from wax-phenols, formaldehyde, and morpholine.

Small quantities of morpholine and 1-ascorbic acid are claimed to show marked synergistic antioxidant properties for use in fatty products. The morpholine salt of gallic acid is an oil-soluble antioxidant for glyceridic oils and a stabilizer for vitamin A and carotene, and 4-alkyl morpholines have been found to act as stabilizers for 2-chlorothiophene.

### **Wax Emulsifiers and Surface-Active Agents**

When morpholine is reacted with fatty acids, it forms soaps possessing excellent emulsifying properties. The oleic soap is a particularly important emulsifier used in the formulation of self-polishing waxes and polishes. One of the main advantages of morpholine-based emulsifiers is the similar boiling points of morpholine and water. When the loosely bound fatty acid-morpholine compound breaks down, the morpholine component evaporates at approximately the same rate as the water. Consequently, the resultant wax film is left dry and void of morpholine, and is then highly water resistant. This is a very desirable feature in household and automobile waxes and polishes.

The reaction products of morpholine and tung oil or linseed oil have been found to be good emulsifying and dispersing agents. Also, the quaternary alkyl ammonium sulfates of Mannich bases from morpholine and mono- or polyhydric phenols have been patented as emulsifying and wetting agents.

A number of other morpholine-containing compounds have been used as wetting agents, and it is said that morpholinium linoleate is an especially good surface tension depressor for use in rust-preventive compositions because it tends to harden the rust-preventive film.

The morpholine salt of a polymeric maleamic acid has been used in compositions for coating paper, cloth, etc. Small quantities of morpholine have been incorporated in fireproofing materials, and the stability of certain asphalt emulsions has been improved by the addition of morpholine. This amine has also been used as an equalizing and dispersing agent in dye baths and printing pastes, and its quaternary alkyl ammonium sulfates have been patented as general surface-active agents.

### Miscellaneous Applications

Morpholine derivatives have found application in the textile industry. Thus, a biquaternary compound derived from 4,4'-ethylenedimorpholine is suitable as a softening agent for natural or regenerated cellulose. In viscose spinning, small amounts of quaternary morpholine derivatives, introduced into either the viscose solution or regenerating bath, prevent fouling of the spinnerets during extrusion. Compounds of this type are also useful as textile lubricants and sizing emulsifiers. A superior whitening agent for textiles includes morpholine in the formula, and  $\alpha$ -4-morpholinylacrylic esters have been claimed as textile adjuvants.

A compound prepared from sulfur dioxide and morpholine is useful in photographic developers, and a small amount of morpholine in the recipe improves the keeping qualities of a fine grain developer.

Morpholinium salts of sulfonated azo dye components are used in dry mixtures for the production of dye images by electrolytic recording methods.

Morpholine is used in an ink eradicator formulation that is used to remove a graphic arts ink. The eradicator

enables the user to modify his original graphic representation almost immediately.

A strongly basic ion-exchange resin can be prepared by treating a polymerized 4,4'-diallylmorpholinium bromide with alkali, and it is reported that a quaternary morpholinium ethosulfate is useful as a hair conditioner and deodorant in popular wave formulations. The ethosulfate is also found in shampoos and mouthwashes. A process for citric acid by fermentation includes a small quantity of morpholine in the mash, and it has been found that dimorpholinium oxalate is an excellent precipitant for trivalent gold. A rapid test for acrylates and acrylonitrile depends upon reaction with morpholine as a first step.

Morpholine may be used alone to thermally stabilize cellulose materials. Electric graded kraft papers treated with morpholine will retain a higher degree of their original tensile strength after subjection to heat aging.

Morpholine is used to prevent the deterioration of paper, especially in books. The paper is impregnated with gaseous morpholine, thereby raising the pH of the paper and removing the acidic conditions which cause its deterioration.

The following physical properties are for the pure compound.

Autoignition temperature, °F	590	Molar polarization, $P_{\infty}$ in benzene	75.3
Boiling point, 760 mm Hg, °C	128.3	Molecular weight	87.12
Conductivity, mho/cm x $10^{10}$	6	pK <sub>b</sub>	5.64
Density, 20°C, g/cc	0.999	Refractive index, n <sub>D</sub> , 20°C	1.4545
Dielectric constant, esu	7.176	Specific gravity, 20/20°C	1.0017
Dipole moment, Debyes	1.58	Surface tension, 20°C, dynes/cm	37.5
Flash point, TCC, °F	95	Vapor pressure, 20°C, mm Hg	7
Freezing point, °C	-4.9	Viscosity, 20°C, centipoises	2.23
Heat capacity, 25°C, cal/mol/deg	41.6	Weight, 20°C, lb/gal	8.3
Heat of vaporization, 45-129°C, cal/mol	9510		

### Solubility

The solvent power of morpholine is said to exceed that of benzene, pyridine, and dioxane. Listed below are the solubilities of some common materials in morpholine.

Substance	g Solute in 100 g Morpholine at 25°C	Substance	g Solute in 100 g Morpholine at 25°C	Substance	g Solute in 100 g Morpholine at 25°C
Acetone	∞	2-Ethylbutanol	∞	Paraffin wax (hot)	>5
Beeswax	<1	Ethylene glycol	∞	Pine oil	∞
Benzene	∞	Ethyl ether	∞	Polyvinyl acetate	>5
Benzyl cellulose	>5	Methyl glycol ether	∞	Polyvinyl butyral	>5
Butyl ether	∞	n-Heptane	∞	Polyvinyl chloride	>5
Carbon tetrachloride	∞	2-Hexanone	∞	Resin	>5
Castor oil	∞	Linseed oil	∞	Shellac	>5
Cellulose acetate	>5	Methanol	∞	Sulfur	<5
Cellulose nitrate	>5	Methylamine (gaseous)	33	Toluene	∞
Copal gum	>5	Methylcyclohexanol	∞	Trimethylamine (gaseous)	34
Dimethylamine (gaseous)	109	Naphtha	>5	Turpentine	∞
Ester gum	>55	Paraffin oil	<1	Water	∞
Ethanol	∞			Xylene	∞

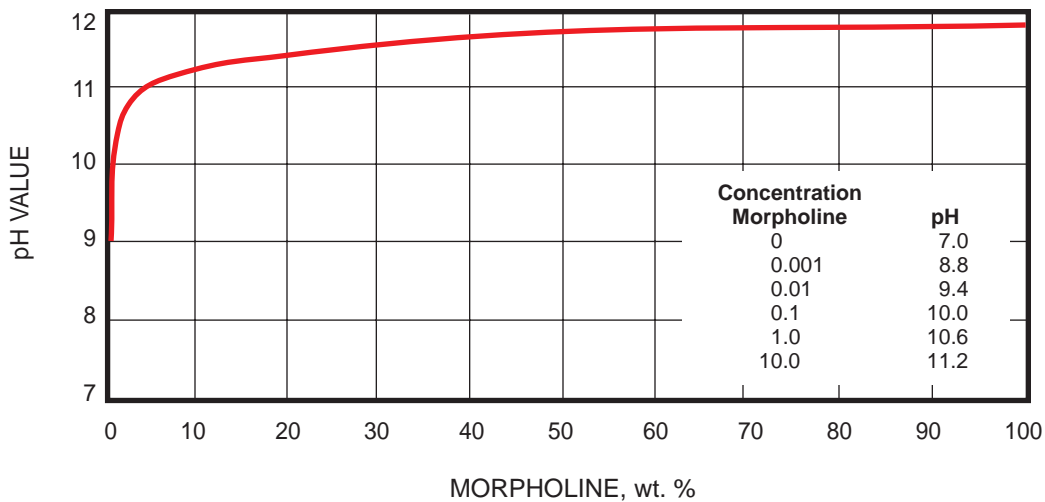


# PHYSICAL PROPERTIES

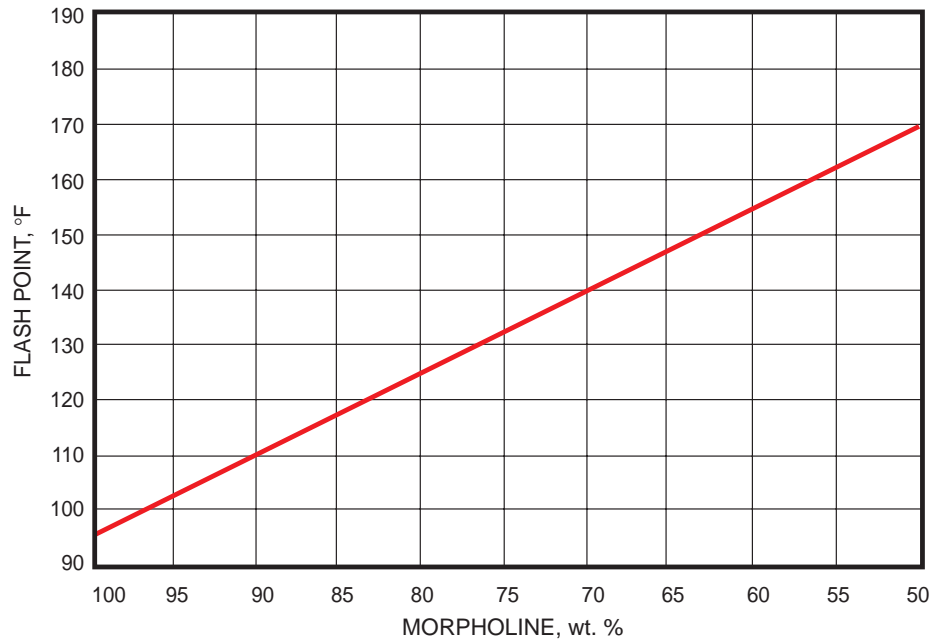
Additional physical properties pertinent to the handling and use of morpholine are presented in the pages that follow.

Property	Figure
pH Value of Aqueous Morpholine .....	1
Flash Point of Aqueous Morpholine .....	2
Freezing Point of Aqueous Morpholine .....	3
Refractive Index of Aqueous Morpholine at 20°C .....	4
Specific Gravity of Aqueous Morpholine at 20°C .....	5
Specific Gravity of Morpholine Versus Temperature .....	6
Surface Tension of Aqueous Morpholine at 20°C .....	7
Vapor-Liquid Equilibria for Aqueous Morpholine at Atmospheric Pressure .....	8
Vapor Pressure Versus Temperature of Morpholine .....	9
Viscosity of Aqueous Morpholine at 20°C .....	10

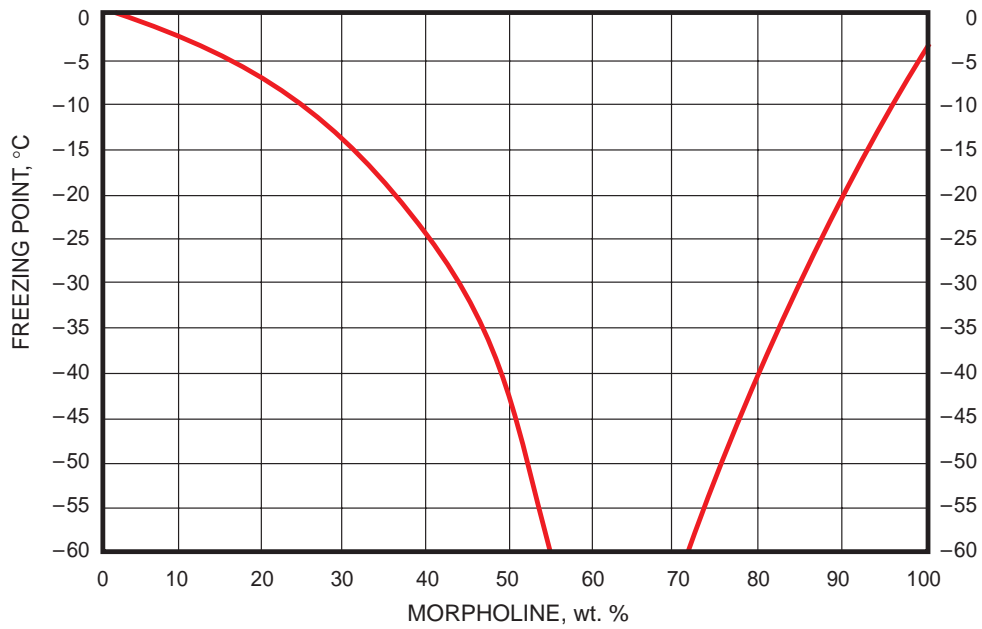
**Figure 1**  
**pH Value of Aqueous Morpholine**



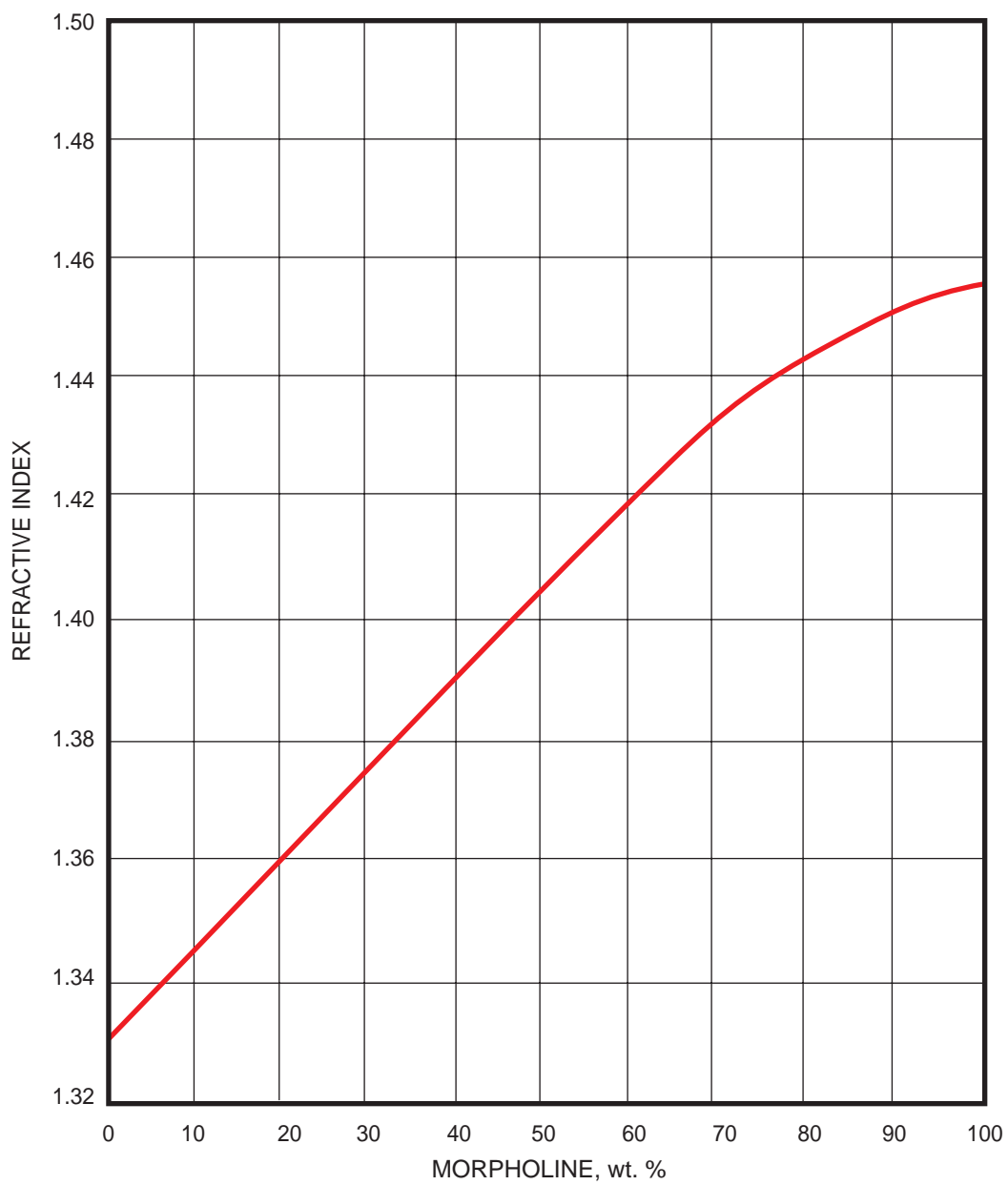
**Figure 2**  
**Flash Point of Aqueous Morpholine**



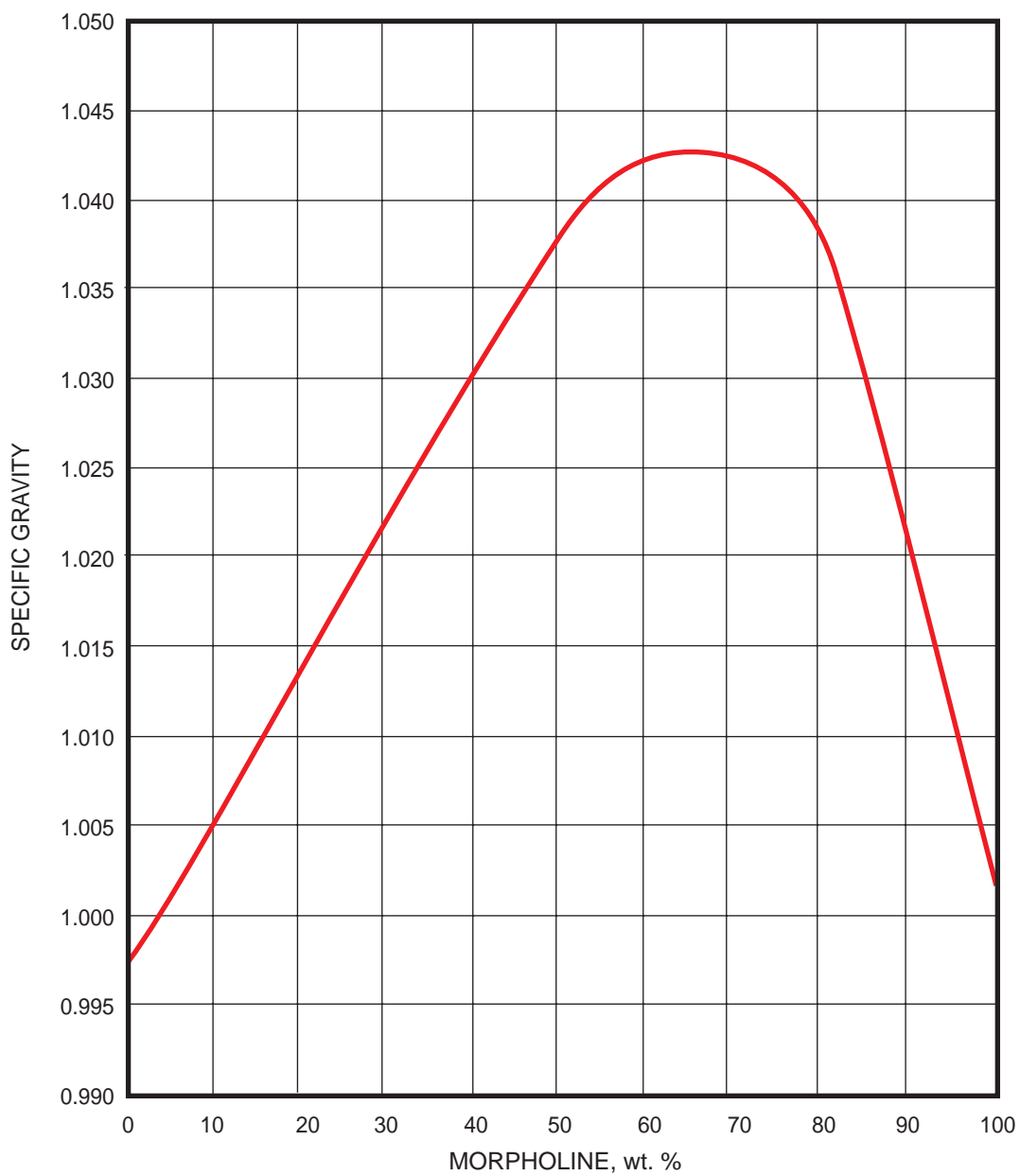
**Figure 3**  
**Freezing Point of Aqueous Morpholine**



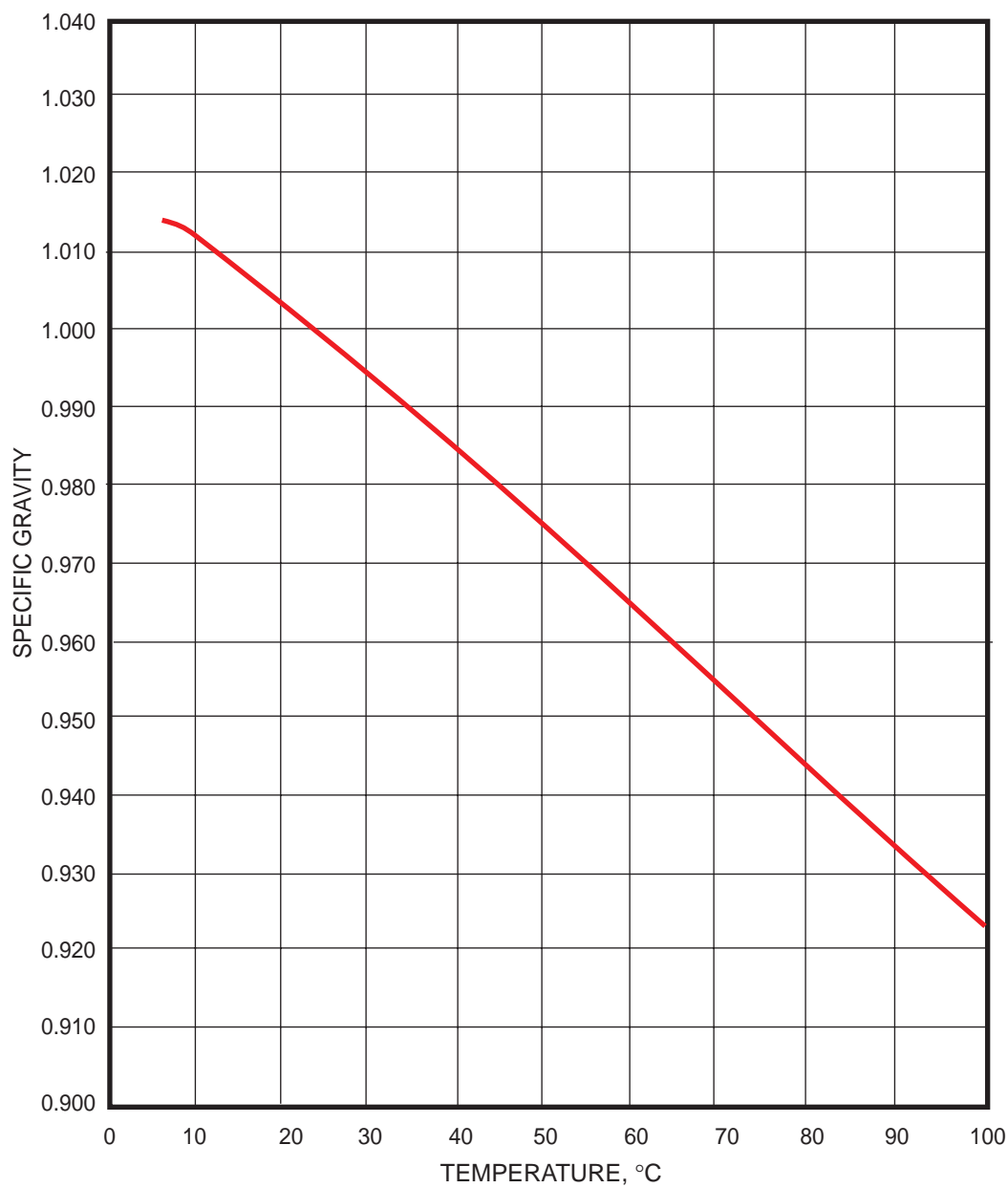
**Figure 4**  
**Refractive Index of Aqueous Morpholine at 20°C**



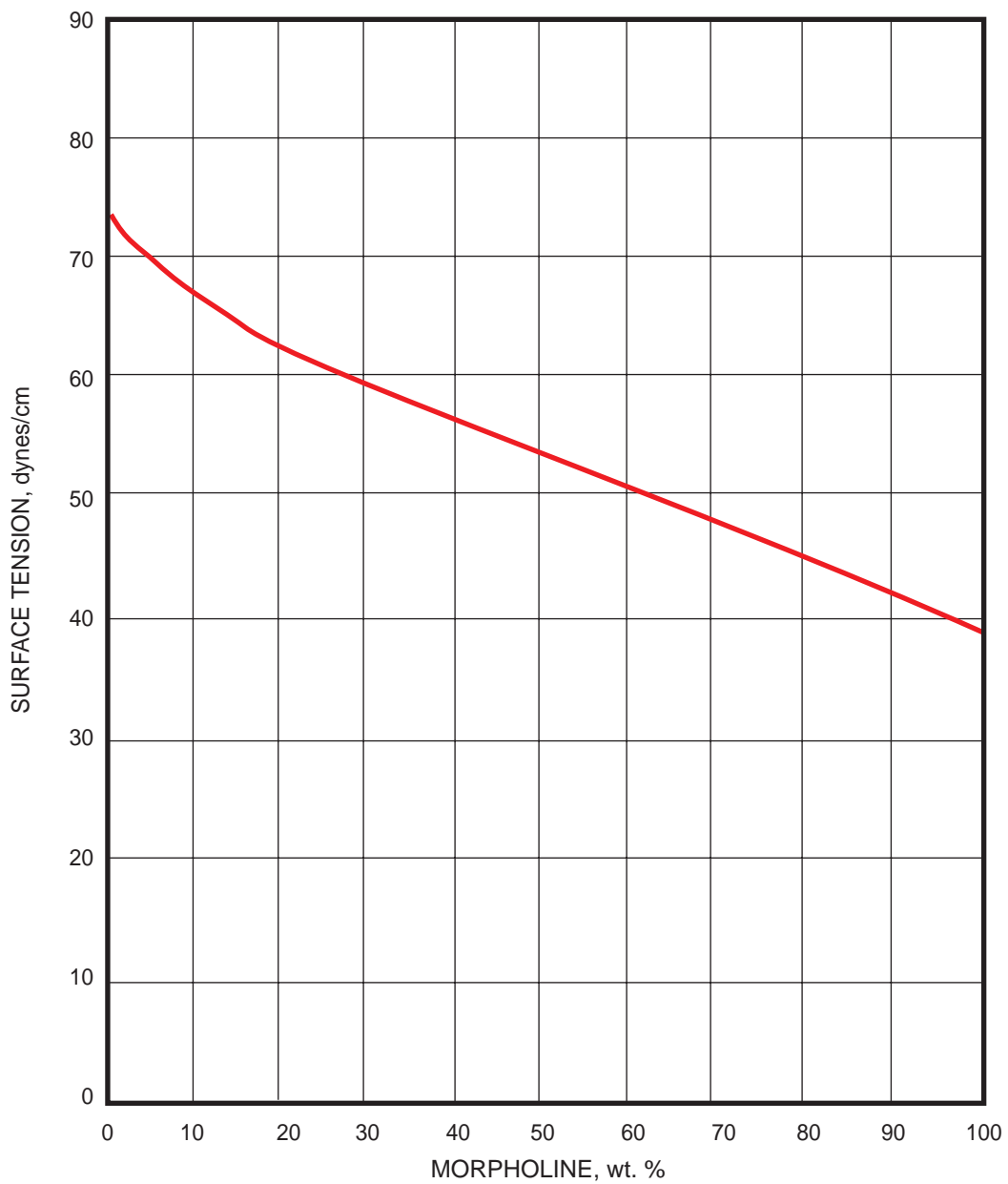
**Figure 5**  
**Specific Gravity of Aqueous Morpholine at 20°C**



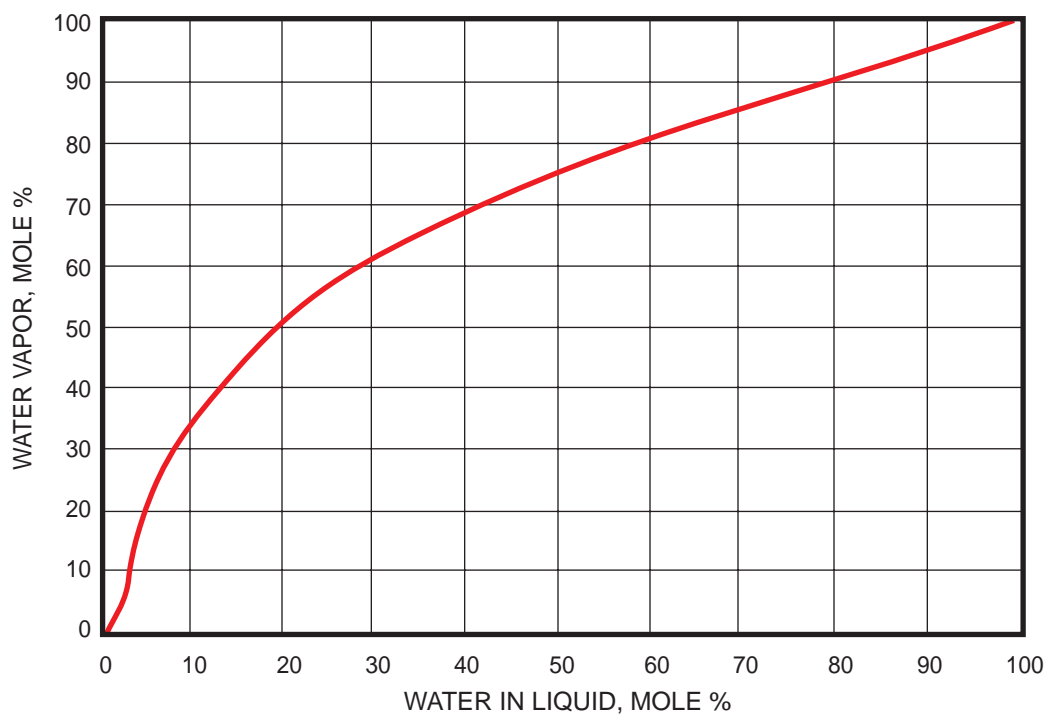
**Figure 6**  
**Specific Gravity of Morpholine Versus Temperature**



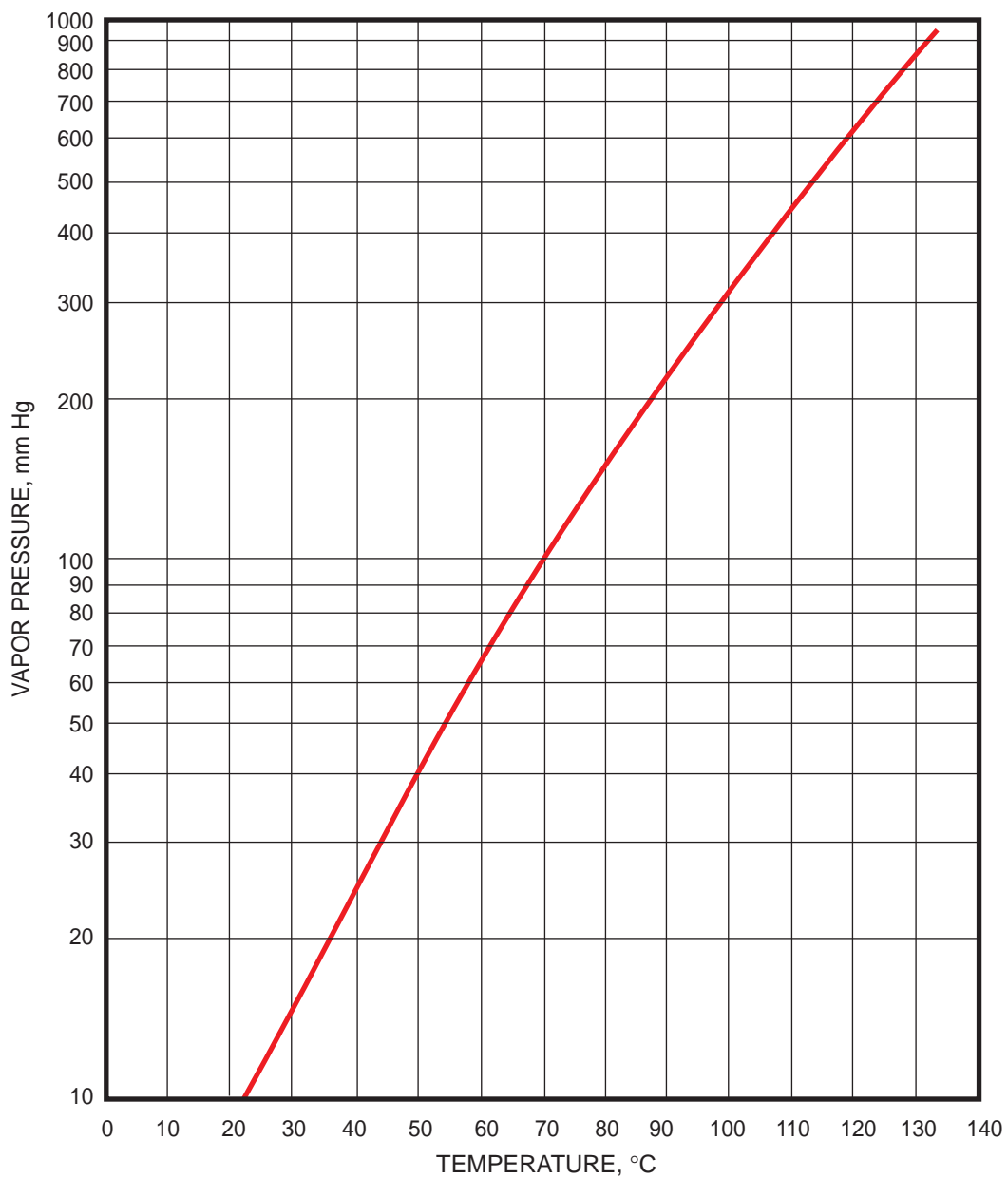
**Figure 7**  
**Surface Tension of Aqueous Morpholine at 20°C**



**Figure 8**  
**Vapor-Liquid Equilibria for Aqueous Morpholine at Atmospheric Pressure**

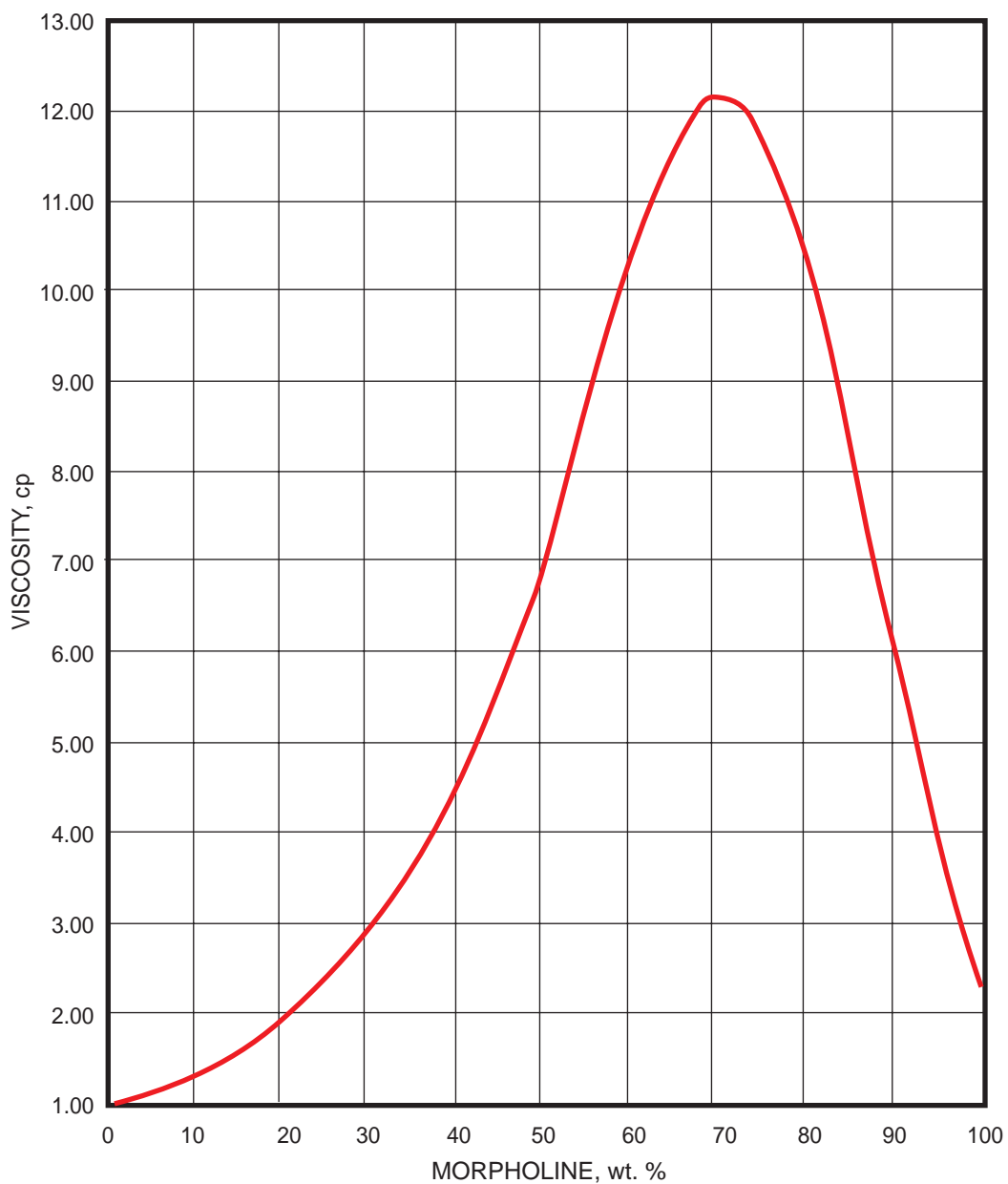


**Figure 9**  
**Vapor Pressure Versus Temperature of Morpholine**





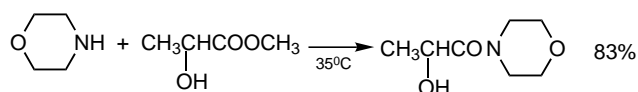
**Figure 10**  
**Viscosity of Aqueous Morpholine at 20°C**



Because of the chemical inertness of ethers in general, most of the chemical reactions of morpholine involve the secondary amine function of the molecule. An outline of the chemistry of morpholine is given in the following sections. Reaction yields are given where they are available.

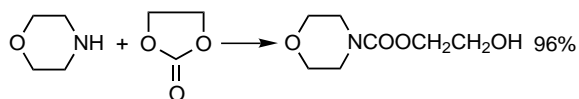
### Reaction with Acids and Acid Derivatives

Like most secondary amines, morpholine reacts with carboxylic acids and their anhydrides, chlorides, and esters to give the corresponding morpholides.

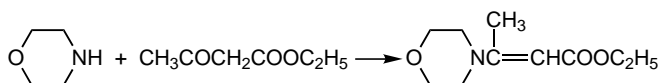
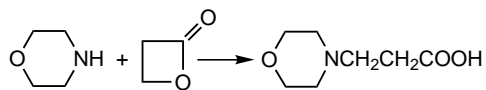


It is interesting that in the particular case cited, other secondary amines, such as diethylamine or diphenylamine, were essentially unreactive.

Ethylene carbonate reacts smoothly with morpholine at temperatures below 100°C to give β-hydroxyethyl N,N'-oxydiethylenecarbamate.

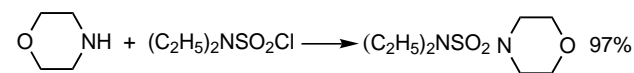
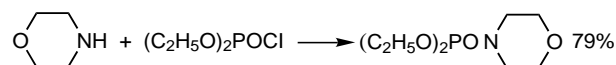


A morpholide is not formed, however, with β-propiolactone or ethyl acetoacetate.



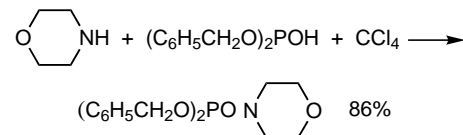
The last reaction is an important one, for it offers a clean-cut route to mono-substituted acetoacetic esters via alkylation of the β-4-morpholinylcrotonic ester. Alkyl halides or sulfates are satisfactory alkylation reagents. The mechanism of alkylation of ethyl β-4-morpholinylcrotonate permits the attack of only one alkyl group and treatment of the adduct with hot water leads to the mono-alkyl acetoacetic ester.

Although reaction of morpholine with dialkyl sulfates and trialkyl phosphates results in 4-alkyl morpholines, the related acid chlorides lead to morpholides.

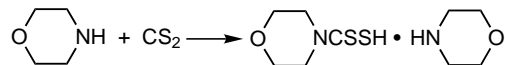


It is expected that ethyl chlorosulfonate would react with morpholine in a similar manner.

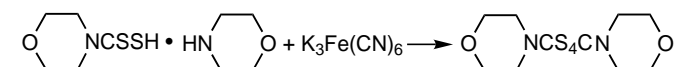
Dibenzyl phosphite undergoes oxidation when treated with morpholine and carbon tetrachloride and yields the corresponding phosphoramidate.



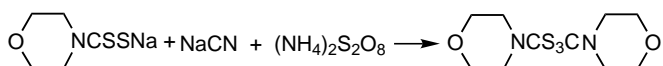
Morpholine reacts with carbon dioxide to form a carbamate that sublimes unchanged at about 95 to 100°C. Carbon disulfide gives the corresponding dithiocarbamate.



The action of potassium ferricyanide on the dithiocarbamate yields N,N,N',N'-bis(oxydiethylene) thiuram disulfide.



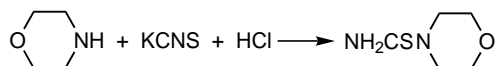
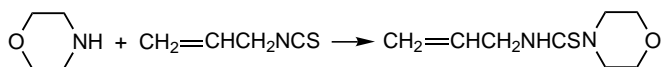
In the presence of certain water-soluble cyanides and oxidizing agents, N,N,N',N'-bis (oxydiethylene) thiuram sulfide is obtained from the dithiocarbamate salts.



The monosulfide can also be obtained by treating the disulfide with potassium cyanide.

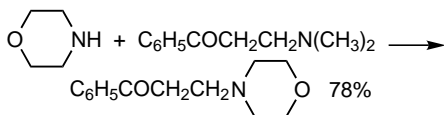
#### Reaction with Isocyanates and Isothiocyanates

Reactions of morpholine with isocyanates give the corresponding substituted ureas, and isothiocyanates yield thioureas.

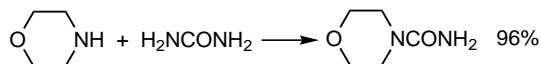


#### Reaction with Amines and Amides

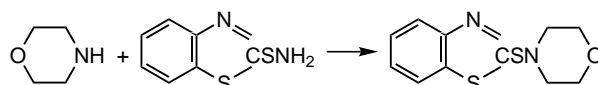
Mannich bases, such as  $\beta$ -dimethylaminopropiophenone, and Betti bases, e.g., 1- $\alpha$ -dimethylaminobenzyl-2-naphthol, undergo amine exchange when heated with morpholine.



The amine function of certain amides, too, can be caused to exchange with morpholine. Heating the latter with urea in a nitrogen atmosphere gives 4-morpholinecarboxamide.

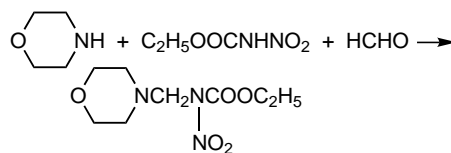
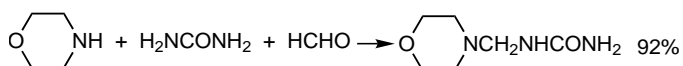
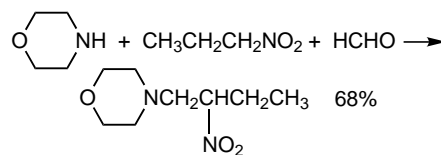
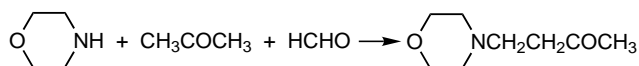
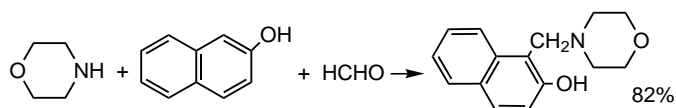


Morpholine also reacts with 2-benzothiazolesulfenamide to give the substituted sulfenamide.



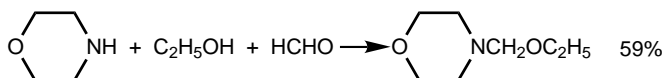
#### The Mannich and Related Reactions

Morpholine has been found to enter into the Mannich reaction in the broadest sense. Thus, phenols, ketones, nitroalkanes, and amides react with morpholine and formaldehyde to give corresponding 4-morpholinylmethyl compounds.



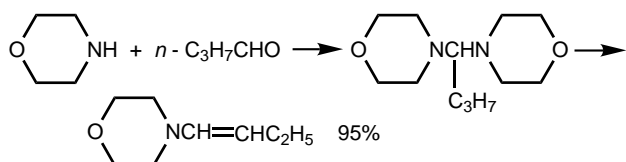
No reaction occurs with a simple aliphatic nitrile, but if the effect of the nitrile group is augmented by that of a phenyl group, reaction does occur. Thus, phenylacetone nitrile reacts, but acetonitrile does not.

Alcohols enter this reaction to give 4-morpholinyl-methyl ethers.



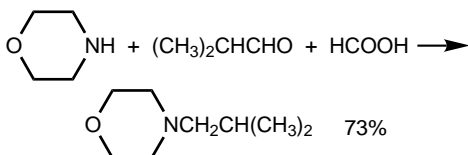
### Reaction with Aldehydes

Two molecules of morpholine condense with an aldehyde to form a 4,4'-alkylidenedimorpholine. When the aldehyde bears an alpha hydrogen atom, the appropriate enamines form upon gentle heating.



### The Leuckart-Wallach Reaction

The addition of formic acid to a mixture of morpholine and aldehyde leads to reductive alkylation of the morpholine. This is the Leuckart-Wallach reaction.

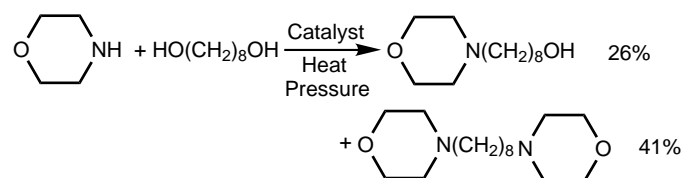
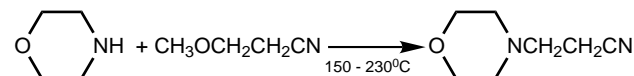
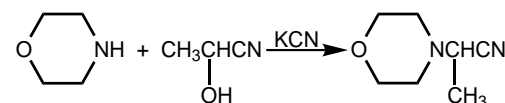
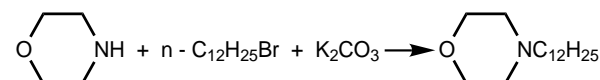
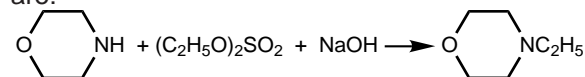


Some ketones, e.g., cyclohexanone, can be used instead of aldehydes.

### Alkylation

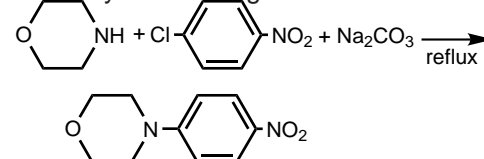
In addition to the Mannich and Leuckart-Wallach reactions, morpholine can be alkylated by several other methods. Dialkyl sulfates, trialkyl phosphates, alkyl halides, and cyanhydrins are effective reagents for

preparing 4-substituted morpholines. Certain activated ethers also react with morpholine to give morpholine derivatives and, under vigorous conditions, polymethylene glycols have been found to give low yields of ω-4-morpholinylalkanols and 4,4'-polymethylenemorpholines. Examples of these reactions are:



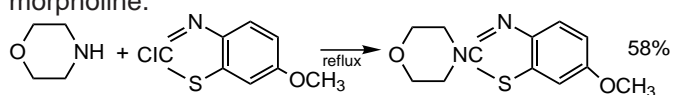
### Arylation

Morpholine can be arylated by aryl halides that possess relatively labile halogens.



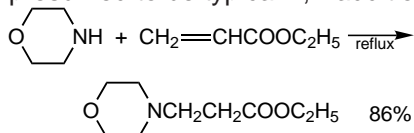
Morpholine reacts more slowly than does piperidine in this respect, but it is equally favored by the absence of by-products and the morpholine derivatives are, in general, higher melting.

Aryl halides characterized by reduced aromaticity, e.g., halogenated anthraquinones or 2-chloro-6-methoxy-benzothiazole, also arylate morpholine.

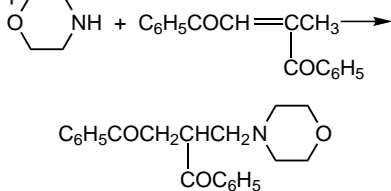


#### Addition to Unsaturation

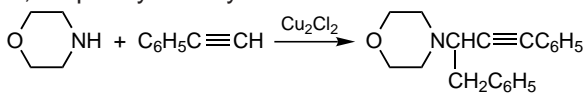
Like most secondary amines, morpholine adds to  $\alpha$ ,  $\beta$ -unsaturated ketones, esters, and nitriles in a manner presumed to be typical 1,4-addition.



In certain instances, however, apparently as a consequence of enolization, reaction occurs at an allylic position rather than at the normal olefinic linkage.

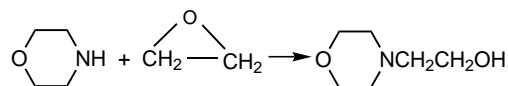


In the presence of cuprous chloride, morpholine reacts with phenylacetylene to give 3-(4-morpholinyl)-1,4-diphenyl-1-butyne.

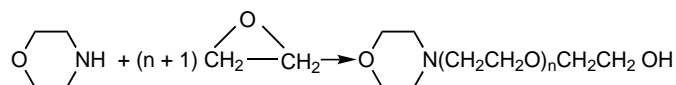


#### Reaction with Epoxides and Imines

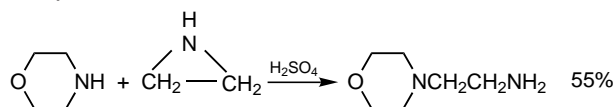
Morpholine reacts with alkylene oxides to give the corresponding  $\beta$ -4-morpholinylalkanols.



Polyoxyethylene derivatives also can be obtained.



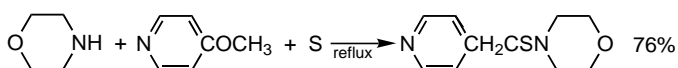
Ethylenimine and morpholine yield 4-(2-aminoethyl)-morpholine.



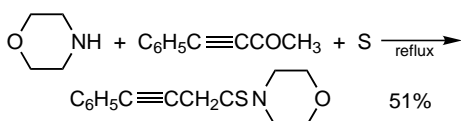
#### Willgerodt Reaction

As originally reported, yellow ammonium sulfide was employed in the Willgerodt reaction to convert aryl alkyl ketones to  $\omega$ -aryl fatty acid amides. The volatility of ammonium polysulfide required that the reaction be carried out in a closed vessel at 150°C. The disadvantage was overcome when morpholine and sulfur were substituted for the volatile sulfide. Since then, the reaction has been the subject of considerable investigation, much of it employing morpholine, although other high-boiling amines can be used.

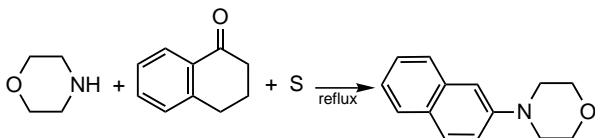
The nucleus may be heterocyclic as well as homocyclic. Thus, 4-acetylpyridine gives 4-pyridylthioacetomorpholine.



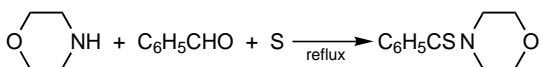
Acetylphenylacetylene and benzalacetone have been found to behave as typical aryl alkyl ketone, giving  $\gamma$ -phenylethylthioacetomorpholide and  $\gamma$ -phenylvinylthioacetomorpholide, respectively.



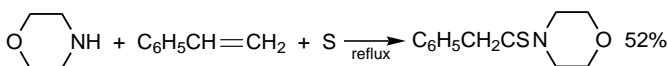
When  $\alpha$ -tetralone is the ketone employed, no thiomorpholide is possible without ring rupture and the product is 4-(2-naphthyl)-morpholine.



In addition to aryl alkyl ketones, the reaction has been found to be applicable to aldehydes, alcohols, mercaptans, amines, olefins, and acetylenes. Thus, benzaldehyde, benzylamine, and benzylmercaptan give benzothiomorpholide when refluxed with equivalent quantities of morpholine and sulfur.

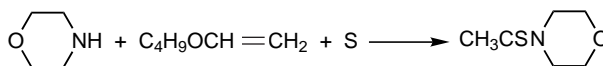


Styrene and vinylnaphthalene yield the corresponding aryl acetothiomorpholides under the conditions of the Willgerdt reaction.



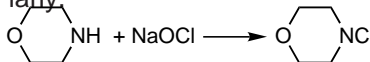
Acetylene gives 54% dithioöxalomorpholide and 45% acetothiomorpholide.

Aryl alkyl ethers give  $\beta$ -aryloxypropiothiomorpholides when refluxed with morpholine and sulfur, but vinyl ethers and esters are cleaved at the oxygen to give thioacetomorpholide.

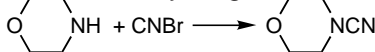


#### Reaction with Oxidizing Agents

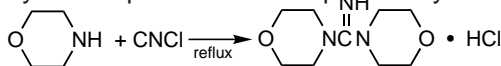
Morpholine reacts with aqueous sodium hypochlorite in the cold to give a quantitative yield of 4-chloromorpholine. Sodium hypobromite reacts similarly.



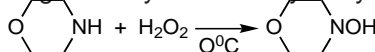
Essentially quantitative yields of 4-cyanomorpholine result when a cold ethereal solution of morpholine is treated with cyanogen bromide.



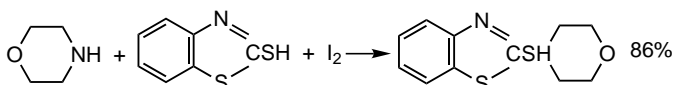
On the other hand, if a benzene solution of morpholine and cyanogen chloride is refluxed, the product is the hydrochloride of 1,1,3,3-bis(oxydiethylene)-guanidine. The hydrobromide of the same base results from reaction of 4-cyanomorpholine with morpholine hydrobromide.



Morpholine reacts with aqueous hydrogen peroxide to give low yields of 4-hydroxymorpholine.

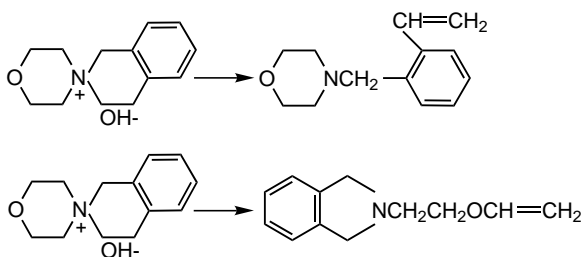


Oxidative condensation of morpholine with 2-mercapto-benzothiazole in the presence of iodine yields 2-(4-morpholinylmercapto)-benzothiazole.



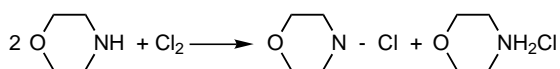
### The Hofman Degradation

Thermal decomposition of quaternary morpholinium hydroxides may result in either retention or rupture of the morpholine ring.



### Direct Chlorination

An excess of morpholine reacts with chlorine to form 4-chloromorpholine and an equivalent amount of morpholinium chloride.



### Complex Formation

The addition of certain metallic halides to hot morpholine results in the formation of addition complexes which contain two moles of morpholine per mole of metallic halide. The complexes are sensitive to moisture, but in

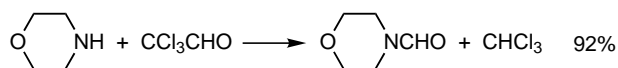
anhydrous condition some of them are stable to temperatures in excess of 200°C. The decomposition temperatures of several of the halide complexes are:

Halide Complex	Decomposition Range, °C	Halide Complex	Decomposition Range, °C
CdBr <sub>2</sub>	250-252	ZnCl <sub>2</sub>	200-210
CdI <sub>2</sub>	205-210	ZnBr <sub>2</sub>	230-240
HgBr <sub>2</sub>	131-135	SnCl <sub>4</sub>	215-235

Cuprous chloride combined in a 1:1 molecular ratio with aqueous morpholine hydrochloride at temperatures below 50°C gives a 90% yield of a complex which melts with decomposition at 110.5 to 112°C. Cupric chloride, under the same conditions, gives a complex containing two moles of morpholine hydrochloride per mole of cupric chloride. This complex melts at 160°C.

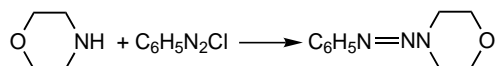
### Miscellaneous Reactions

Morpholine attacks chloral in the same fashion as does sodium hydroxide; the products are chloroform and 4-formylmorpholine.



The latter is formed in equally good yield from morpholine and formic acid.

Aryl diazonium salts treated with morpholine give 4-aryl-azomorpholines. These compounds are readily purified and are reported to be remarkably stable in the solid state.



**an General**

The handling and storage of morpholine presents no unusual problems. Huntsman Corporation's Technical Service Section is available to assist those who may desire additional information.

Commercial morpholine is liquid at room temperature, but will solidify at approximately 23°F.

The vapor pressure of morpholine is less than 7 mm of mercury at 20°C. Being an organic compound, it will undergo combustion, and it is classified as flammable by the Department of Transportation. Although not considered poisonous, morpholine is moderately toxic and should not be ingested or allowed to come in contact with the skin. In case of contact with the eyes, flush immediately with plenty of water for at least 15 minutes and obtain medical attention. (See toxicity statement on pages 26-27.)

**Maintaining Specifications**

Morpholine is hygroscopic and, if its water content is to be minimized, a dry gas pad under a few ounces of pressure should be used on storage tanks. Since morpholine is basic, it will react with acidic gases, hence carbon dioxide and natural gas containing acidic sulfur compounds cannot be used. Nitrogen is quite suitable. Nitrogen should also be used if low color is important, since absorbed atmospheric oxygen will cause morpholine to develop color.

Morpholine will react with copper to form complex salts. Because of this, the use of copper and alloys containing copper should be avoided in equipment which will contact morpholine or its aqueous solutions.

Other factors that should be considered in the installation of storage and handling facilities are the solvent properties and alkaline nature of morpholine. Storage tanks constructed according to a recognized code, using carbon steel as a material of construction, generally are satisfactory. In those cases where low color is needed, stainless steel or aluminum should be used. However, aluminum should not be used if the

temperature of the morpholine will exceed 150°F. Neither should it be used in contact with aqueous morpholine solutions at any temperature.

In areas where the temperature is expected to fall below 23°F, steam coils of a suitable area to heat the tank contents using low-pressure steam should be built into the tank about 6 inches above the floor. The coils should be constructed in such a manner as to allow the condensate to drain. Stainless steel is the preferred material of construction for the coils, particularly when low color of the morpholine is important. When steam heat is to be used continuously to prevent freezing of the morpholine, a temperature regulator that throttles either the steam or condensate should be installed.

In situations where the ambient temperature is low, insulation of the tank will probably be desirable. The temperature of the morpholine in the tank should not exceed 100°F if the low color is to be maintained.

If a dry gas pad is used, pressure relief and vacuum relief valves of suitable capacities should be installed. The dry gas system may consist of a cylinder of nitrogen and a line to the top of the storage tank. Tanks should be diked and electrically bonded and grounded.

**Transfer Lines**

Transfer lines, preferably not less than 2 inches in diameter, constructed of carbon steel and joined by welds or flanges are suitable. Screwed joints are subject to failure unless back-welded. Morpholine will leach conventional pipe dopes. However, threads can be wrapped with Teflon tape. Garlock 7021 gasket material, or its equivalent, is satisfactory for use with flanged connections in morpholine service.

If the ambient temperature is low, the transfer line should be steam-traced and insulated. Steam-tracing can be accomplished by affixing copper tubing, approximately  $\frac{3}{8}$ -inch diameter, to the underside of the line, insulating, and using low-pressure steam in the tubing. For flexible connections, stainless steel metal hose is preferred to rubber, since rubber will generally deteriorate in morpholine service.



Systems which are insulated and steam-traced should be preheated in cool weather before being put into service. Normally, 15 to 30 minutes of applying steam to the tracing will adequately warm, but not overheat, the system.

Transfer piping and pumps may be equipped with an inert gas padding system so that the morpholine can be pressured out of the lines when an extended idle period is due. This practice will help to reduce losses and increases in color that would result if the morpholine was allowed to remain in the lines.

### **Pumps**

Rotary or centrifugal pumps of all-iron construction can be used with morpholine, although a centrifugal pump is preferred. Rotary pumps should be equipped with externally lubricated bearings. John Crane Type 9 Mechanical Seal is suitable. Where pump packing is needed, Garlock 234, Garlock 239, or equivalent is considered satisfactory. Provision should be made for preheating pumps that are exposed to the cold. This can be done by playing live steam on the uninsulated pump, or by having the pump wrapped with copper tubing and insulated, then applying low-pressure steam to the tubing.

### **Unloading in Cold Weather**

Thawing a tank or tank car of morpholine is accomplished by applying steam at 50 pounds maximum pressure to the coils of the tank or tank car. The liquid temperature should be kept below 100°F to avoid discoloring the product.

As the morpholine melts, solids will remain in the bottom and on the sides of the tank while the warmer liquid rises. The thawing may be accelerated by using a liquid circulating pump. As soon as the flow of steam to the coils is discontinued, they should be blown free of condensate with dry air to prevent freezing of the condensate and rupturing of the coils.

Morpholine which has frozen in drums may be thawed in a hot room at about 100°F. The thawing should be expected to require two days.

### **New Facilities and Cleaning**

Prior to putting storage vessels into service, it is sometimes desirable to purge with inert gas to remove oxygen from the tank atmosphere. Although cleaning tanks and transfer lines frequently is not recommended, it is sometimes necessary as the result of contamination or accumulation of foreign material in the system. For such cleaning, a water wash is generally satisfactory.

Tank cleaning is normally accomplished by thoroughly sluicing the interior of the tank with a water jet and following this with cloth or chamois drying. Unless excessive rust scale makes it necessary, the interior of the tank should not be wire-brushed or sand-blasted because the oxides of iron are relatively inert to morpholine. Once clean and dry, the tank should be sealed and purged with dry inert gas to avoid undue condensation and rust formation.

New systems frequently introduce line scale, rust, and the like, which will be a source of contamination and possible plugging. These solids can be effectively removed with either a "y" strainer, using a 150-200 mesh stainless steel screen, or with a commercial-type cloth filter. A good grade of woven cotton canvas, 12-ounce or heavier, is suitable as a cloth filter medium. Wool and synthetic fibers have been found to be unsatisfactory.

Most of what has just been described concerns commercial, essentially anhydrous, morpholine. Its aqueous solutions have lower freezing points and lower viscosities, so storage and handling may be simplified considerably by dilution in storage if the morpholine is to be used as an aqueous solution.

Delivery of morpholine can be made in 10,000- and 20,000-gallon tank cars. These cars are constructed of welded carbon steel, and have bottom-unloading fittings and steam coils. In areas within reasonable proximity of bulk storage points, deliveries can be made in full or compartmented, insulated, stainless-steel tank wagons with steam coils. If requested, tank wagons can be equipped with unloading pumps and hoses. Drums of morpholine can be shipped promptly from local warehouses in carload, truckload, or smaller quantities. The net weight of a drum is 460 pounds, approximately 55 gallons per drum. Drums are UN1A1 or UN1H1, nonreturnable.

Under US Department of Transportation (DOT) and Canadian Transportation of Dangerous Goods (TDG) regulations, the proper shipping name for this product is "morpholine," identification number UN 2054. This product is considered a flammable material (TDG hazard class 3.3) and requires a "FLAMMABLE" label for shipping. Please note: The Department of Transportation (DOT) classification for morpholine, UN 2054, as a

Packing Group III flammable liquid, does not address the potential dermal corrosivity hazards of morpholine. Huntsman has recently sponsored DOT dermal corrosivity studies using morpholine which indicate that morpholine should be reclassified as a Packing Group I dermal corrosive. On the basis of these studies, Huntsman has petitioned the DOT for a change in the Hazardous Materials Table entry for morpholine, from Packing Group III flammable liquid to Packing Group I corrosive liquid with a subsidiary hazard of flammability. Until the DOT rules on our petition for this change, we will continue to identify morpholine as a Packing Group III flammable liquid on our MSDS, product labels, and shipping papers, to minimize any confusion which could result from a discrepancy between our DOT Packing Group determination and the existing DOT classification for morpholine. **However, to ensure employee, customer and public safety, Huntsman will handle and transport morpholine as a Packing Group I corrosive, using appropriate shipping containers and handling procedures.**

For further information, please refer to the Material Safety Data Sheet (MSDS) for this product.

**MORPHOLINE FDA CLEARANCES UNDER 21 CFR****Direct Additives**

172.235	173.310
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**Indirect Additives**

175.105	176.210
175.300	177.1200
176.170	177.1210
176.180	178.3120
176.200	178.3300

**TOXICITY STUDIES****Acute Toxicity**

The results of acute toxicity testing using morpholine indicate that this product is moderately toxic by single oral and single dermal exposures. The oral LD<sub>50</sub> in rats and the dermal LD<sub>50</sub> in rabbits are 1.05 g/kg and 1.21 g/kg, respectively.

Acute irritation studies have shown this product to be extremely irritating/corrosive to the skin of rabbits, with a Draize dermal irritation score of 8.0 (maximum score 8.0). Rabbit eye irritation studies using morpholine have shown that this product is extremely irritating to the eyes, with a Draize ocular irritation score of >80 (maximum score 110).

**Chronic Toxicity**

A chronic inhalation (vapor) study of morpholine was conducted using Sprague-Dawley rats at exposure concentrations of 0, 10, 50, and 150 ppm for 6 hours per day, 5 days per week, over a period of 104 weeks.

Survival, body weight gains, organ weights, hematology/clinical chemistry blood parameters, gross pathol-

ogy, and histopathology were normal in the exposed groups and comparable to the control animals. There were no exposure-related adverse changes in the liver, kidney, brain, intestine, lung, or any other internal organ or tissue. The incidences of neoplasia were comparable among all groups (including controls), and were typical for the strain and age of rat used in this study. Not unexpectedly, irritation of the eyes, nose, and skin was observed during the course of this study. Chronic exposure to morpholine vapors produced inflammation of the cornea (keratitis) at the highest exposure concentration.

Nasal effects included nasal cavity irritation and necrosis at the highest exposure concentration. Posterior nasal structures (trachea, bronchial tree, and lungs) were histologically normal.

The results of this chronic exposure study demonstrate that morpholine is neither carcinogenic nor systemically toxic. These exposures did result in local (ocular, nasal, and dermal) irritation, consistent with the known irritation properties of morpholine.

**Genetic Toxicity**

A battery of *in vitro* genetic toxicity studies, employing an Ames assay, a Cell Transformation assay, an Unscheduled DNA Synthesis (UDS) assay, and a Sister Chromatid Exchange (SCE) assay, were equivocal in their responses to morpholine. Morpholine was negative in the Ames and UDS assays, and weakly positive in the Mouse Lymphoma Forward Mutation and SCE assays. Morpholine was active (positive) in the Cell Transformation assay. The interpretation of these assays may be confounded by the contribution of the pH of the test medium (after introduction of morpholine) to the observed genotoxic activity in these assays. The possible presence of nitrosating agents in the test system may

also contribute to genotoxic activity in these assays, due to the potential formation of genetically active nitrosamines.

#### **Aquatic Toxicity**

The acute toxicity (LC<sub>50</sub>) of morpholine to freshwater fish has been reported to range from 180 to 380 mg/l (*Salmo* species). The acute toxicity (LC<sub>50</sub>) to freshwater crustaceans (*Daphnia* species) has been reported to range from 100 to 119 mg/l. The toxicity threshold (EC<sub>50</sub>) to algae has been reported to be 1.7 to 28 mg/l.

#### **HUMAN HEALTH EFFECTS AND FIRST AID**

On the basis of these animal toxicity studies, the principal health hazard from accidental exposures to morpholine is a moderate to severe irritation/corrosion of the eyes, skin, and mucous membranes.

Chemical-type goggles with face shield must be worn during handling or use of the undiluted product or concentrated solutions. Contact lenses should not be worn. Protective clothing and gloves resistant to chemicals and petroleum distillates must be worn.

Should accidental eye contact occur, flush eyes with large amounts of water for at least 15 minutes, after which a physician should be consulted. During flushing of the eyes, eyelids should be held apart to permit rinsing of entire surface of eye and lids.

For skin contact, immediately flush skin with large amounts of water for at least 15 minutes. Clothing wet with the product must be removed immediately and laundered before reuse. Morpholine has been known to

produce dermal sensitization (allergic skin reaction) in sensitive exposed individuals.

If morpholine is accidentally ingested and the individual is conscious and can swallow, he or she should be given two large glasses of water, after which a physician should be consulted. Since this product is expected to produce severe irritation/corrosion of mucous membranes, vomiting should not be induced, due to the possibility of lung damage from aspiration of the product into the lungs during vomiting.

Under usual circumstances, exposure to harmful quantities of vapor should not be a health problem; however, exposure to appreciable concentrations of morpholine vapors can result in irritation to the eyes, nose, and throat, and may produce temporary and reversible hazy or blurred vision. These symptoms disappear when exposure to morpholine is terminated. Adequate ventilation should be provided where a large quantity of product is exposed, or where mists or vapors are generated. Spills in confined areas should be cleaned up promptly, using appropriate personal protective equipment.

The Threshold Limit Value (TLV) for morpholine, as established by the American Conference of Governmental Industrial Hygienists (ACGIH) is 20 ppm (71 mg/m<sup>3</sup>), calculated as an 8-hour time weighted average (TWA). The TLV for morpholine also includes a "skin" notation, warning of the potential significant contribution to the overall exposure by the cutaneous route. The Occupational Safety and Health Administration (OSHA) has established a Permissible Exposure Limit (PEL) for morpholine at 20 ppm, and a Short Term Exposure Limit (STEL) of 30 ppm. Exposures should be kept below these values to avoid symptoms of irritation to eyes, nose, and throat.

For further information, please refer to the Material Safety Data Sheet (MSDS) for this product.

