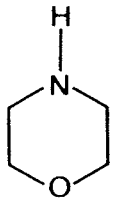
MORPHOLINE

1. Chemical and Physical Data

1.1 Synonyms

Chem. Abstr. Services Reg. No.: 110-91-8
Chem. Abstr. Name: Morpholine
Synonyms: Diethylene imidoxide; diethylene oximide; diethylenimide oxide; 1-oxa-4-azacyclohexane; tetrahydro-*para*-isoxazine; tetrahydro-1,4-isoxazine; tetrahydro-1,4-oxazine; tetrahydro-(2*H*)-1,4-oxazine; tetrahydro-(4*H*)-1,4-oxazine; tetrahydro-*para*-oxazine

1.2 Structural and molecular formulae and molecular weight



C_4H_9NO Mol. wt: 87.12

1.3 Chemical and physical properties of the pure substance

(*a*) *Description*: Clear, colourless, hygroscopic liquid with ammonia-like odour (Weast, 1985; Texaco Chemical Co., 1986)

(*b*) *Boiling-point*: 128.3°C, 24.8°C at 10 mm Hg (Weast, 1985)

(*c*) *Freezing-point*: -4.7°C (Weast, 1985); -4.9°C (Texaco Chemical Co., 1986)

(*d*) *Viscosity*: 2.23 cp at 20°C (Texaco Chemical Co., 1986)

(*e*) *Flash-point*: 35°C (closed cup) (Mjos, 1978; Texaco Chemical Co., 1986)

(*f*) *Spectroscopy data*: Nuclear magnetic resonance, infrared and mass spectral data have been reported (Sadtler Research Laboratories, 1980; Pouchert, 1981, 1983; Ohnishi, 1984; Hunt *et al.*, 1985; Pouchert, 1985).

(*g*) *Solubility*: Soluble in water, acetone, benzene, carbon tetrachloride, diethyl ether, ethanol, methanol, *n*-heptane, propylene glycol methyl ether and ethylene glycol (Weast, 1985; Dow Chemical Co., 1985; Texaco Chemical Co., 1986)

(*h*) *Refractive index*: 1.4548 at 20°C (Weast, 1985); 1.4545 at 20°C (Texaco Chemical Co., 1986)

(*i*) *Volatility*: Vapour pressure, 7 mm Hg at 20°C (Texaco Chemical Co., 1986)

(*j*) *Reactivity*: As a base (pK_B, 5.64), reacts readily with most acids to form corresponding salts; reacts with carbon dioxide under anhydrous conditions to form carbamates and with carbon disulfide to form dithiocarbamates (Mjos, 1978; Dow Chemical Co., 1985; Texaco Chemical Co., 1986). Nitrosation is known to occur, leading to the formation of *N*-nitrosomorpholine (see IARC, 1978).

(*k*) *Specific gravity*: 1.0005 at 20°/4°C (Weast, 1985); 1.002 at 20°/20°C (Texaco Chemical Co., 1986)

(*l*) *Octanol/water partition coefficient*: log P, -1.08 (Hansch & Leo, 1979)

(*m*) *Conversion factor*: $mg/m^3 = 3.56 \times ppm$[1]

1.4 Technical products and impurities

Trade names: BASF 238; Drewamine

Morpholine is generally marketed as a high-purity product with the following specifications: assay (min), 99.0%; distillation range, 126.0–130.0°C; specific gravity (20°/20°C), 1.001–1.004; water (max), 0.2–0.5% (Air Products and Chemicals, Inc., 1985; Dow Chemical Co., 1985; Texaco Chemical Co., 1986). It is also available in 40% and 88% solutions with water.

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(*a*) *Production*

The major process for the production of morpholine until the early 1970s was the acid-catalysed dehydration of diethanolamine. This process has largely been replaced by a process based on the reaction of diethylene glycol with ammonia at high temperatures and pressures, with or without a catalyst (Mannsville Chemical Products Corp., 1981).

Typically, diethylene glycol and ammonia are combined in the presence of hydrogen and a catalyst at a temperature between 150–400°C and a pressure between 3–40 MPa (30–400 atm). The hydrogenation catalyst may be any one of a number of metals. Excess ammonia is stripped from the crude reaction mixture, and morpholine is obtained by fractional distillation (Mjos, 1978).

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[1]Calculated from: mg/m^3 = (molecular weight/24.45) × ppm, assuming standard temperature (25°C) and pressure (760 mmg Hg)

Production of morpholine in the USA in 1981 was estimated to be in the range of 13 000 tonnes – about 40% higher than output ten years earlier. Imports to the USA may have been about 1100–1600 tonnes per year in the late 1970s; in 1981, they were reported to be in the range of 700 tonnes. About 1400 tonnes per year are exported from the USA (Mannsville Chemical Products Corp., 1981).

Data on production of morpholine elsewhere in the world were not available to the Working Group.

(*b*) *Use*

Morpholine is typically used as follows: rubber chemicals, 40%; corrosion inhibitors, 30%; waxes and polishes, 5%; optical brighteners, 5%; and miscellaneous, 20% (Mannsville Chemical Products Corp., 1981).

(i) *Rubber chemicals*

Morpholine is an important intermediate for rubber-processing chemicals, especially in the production of delayed-action rubber accelerators, which are added during the vulcanization process to reduce the possibility of prevulcanization during the mixing stages of fabrication. Morpholine-derived sulfur compounds give a high rate of cure during vulcanization, with a reduced tendency to overcure. These include morpholinium *N,N*-oxydiethylenedithiocarbamate and 2-(*N*-morpholinothio)benzothiazole. Morpholine derivatives, such as *N,N'*-dithiodimorpholine and *N,N'*-tetrathiodimorpholine, are also used to stabilize halogenated butyl rubber against heat-ageing effects (Mjos, 1978; Dow Chemical Co., 1985).

(ii) *Corrosion control*

Morpholine is used to control corrosion in steam condensate systems. It neutralizes carbon dioxide and other corrosive acid components in steam and condensate, aids in maintaining the proper pH throughout the system, has a suitable vapour pressure and aqueous solubility, and is stable at temperatures up to 288°C. Morpholine and its salts with fatty acids from animal and vegetable oils may be used as corrosion inhibitors for steel or tin plate to be used in contact with food. Morpholine has been used as a corrosion inhibitor in the natural gas and pipeline industry (Dow Chemical Co., 1985).

(iii) *Waxes and polishes*

Morpholine reacts readily with fatty acids, forming emulsifying agents, which are used in the formulation of water-resistant waxes and polishes for automobiles, floors, leather and furniture. As the film of polish emulsion gradually dries, morpholine evaporates to form a film highly resistant to waterspotting and deterioration. An example of this type of polish is a carnauba wax formulation with the following composition (in parts by weight): carnauba wax, 11.2; oleic acid, 2.4; morpholine, 2.2; water, 67.0. A typical silicone automobile polish-cleaner is composed as follows (in parts by weight): silicone fluid, 4.0; oleic acid, 2.5; morpholine, 1.5; Stoddard solvent (see the monograph on some petroleum solvents, p.), 19; kerosene (deodourized), 2; water, 57; abrasive, 14. The following formulation is representative of silicone-containing furniture polishes (in parts by weight): silicone fluid, 5.0; VM & P naphtha (see the monograph on some petroleum solvents, p. 43) (high flash), 30.0; oleic acid, 2.5; morpholine, 1.5; water, 60.6; water-soluble resin, 0.4 (Dow Chemical Co., 1985).

(iv) *Optical brighteners*

Morpholine is an important intermediate in the manufacture of optical brighteners. The diaminostilbene triazine type brightener with morpholine as a substituent on one of the triazine rings is used in home laundry detergents since it is stable to chlorine bleaches (Texaco Chemical Co., 1986).

(v) *Miscellaneous*

Morpholine and its salts have been reported to be used as components of protective coatings applied on fruits and vegetables (Ohnishi, 1984; US Food and Drug Administration, 1988).

The compound has been used in the preparation of pharmaceuticals, including such diverse products as analgesics, local anaesthetics, respiratory and circulatory stimulants, antispasmodics and soluble sulfanilamides (Dow Chemical Co., 1985).

Morpholine derivatives have been used widely in the textile industry, as softening agents for cellulosic fibres, ingredients of rayon spinning baths, sizing emulsifiers, textile lubricants, whitening agents and dyes (Dow Chemical Co., 1985).

Cosmetic products that may incorporate morpholine-based compounds include hair conditioners, deodorants, shampoos, mouthwashes and cosmetic creams. Stabilizers and antioxidants for lubricating oils, soluble oils for cutting tools and carbon remover compounds have been prepared from morpholine. This compound has a high selectivity and solvency for aromatics and can be used to extract benzene (see IARC, 1982), toluene (see monograph, p. 79) and xylene (see monograph, p. 125) economically from petroleum feedstock. Other products synthesized from morpholine include ion-exchange resins, dyes for electrolytic recording inks and photographic chemicals (Dow Chemical Co., 1985).

(*c*) *Regulatory status and guidelines*

Morpholine can be used as a component of food, provided that: (i) it is used as the salt(s) of one or more of the fatty acids meeting certain requirements, as a component of protective coatings applied to fresh fruits and vegetables; and (ii) it is used at a level not in excess of that reasonably required to produce its intended effect (US Food and Drug Administration, 1988).

Morpholine is allowed as a boiler-water additive either alone or in combination with other substances at up to 10 ppm (36 mg/m^3) concentration in steam, when the steam may contact food, excluding milk or milk products. Morpholine and morpholine fatty acid salts derived from animal or vegetable oils are allowed for use as corrosion inhibitors for steel and tin plate. Additional regulations cover its use as a component of adhesives, as a defoaming agent component for use in the manufacture of paper and paperboard and as a component of animal glue (US Food and Drug Administration, 1987).

Occupational exposure limits for morpholine in 18 countries are presented in Table 1.

Table 1. Occupational exposure limits for morpholine[a]

Country	Year	Concentration[b] (mg/m^3)	Interpretation[c]
Australia	1984	S 70	TWA
Austria	1985	70	TWA
Belgium	1985	S 70	TWA
Denmark	1988	S 70	TWA
Finland	1987	S 70	TWA
		S 105	STEL (15 min)
France	1986	70	TWA
		105	STEL (15 min)
Germany, Federal Republic of	1988	S 70	TWA
Indonesia	1985	S 70	TWA
Netherlands	1986	S 70	TWA
Norway	1981	S 70	TWA
Romania	1985	S 40	Average
		S 60	Maximum
Sweden	1987	70	TWA
		110	STEL (15 min)
Switzerland	1985	S 70	TWA
UK	1987	S 70	TWA
		S 105	STEL (10 min)
USA[d]			
OSHA	1987	70	TWA
ACGIH	1988	S 70	TWA
		S 105	STEL (15 min)
USSR	1986	S 0.5	Ceiling
Venezuela	1985	S 70	TWA
		S 105	STEL
Yugoslavia	1984	S 70	TWA

[a]From Direktoratet for Arbeidstilsynet (1981); International Labour Office (1984); Arbeidsinspectie (1986); Institut National de Recherche et de Sécurité (1986); Cook (1987); Health and Safety Executive (1987); National Swedish Board of Occupational Safety and Health (1987); Työsuojelahallitus (1987); US Occupational Safety and Health Administration (1987); American Conference of Governmental Industrial Hygienists (1988); Arbejdstilsynet (1988); Deutsche Forschungsgemeinschaft (1988)

[b]S, skin notation

[c]TWA, 8-h time-weighted average; STEL, short-term exposure limit

[d]OSHA, Occupational Safety and Health Administration; ACGIH, American Conference of Governmental Hygienists

2.2 Occurrence

(*a*) *Natural occurrence*

Morpholine is not known to occur as a natural product.

(*b*) *Occupational exposure*

On the basis of a US National Occupational Exposure Survey, the National Institute for Occupational Safety and Health (1983) estimated that 117 000 workers were potentially exposed to morpholine in the USA in 1981–83.

Eight-hour time-weighted average personal exposures of up to 0.4 ppm (1.4 mg/m^3) morpholine were reported in a plant that manufactured a rubber accelerator, 4-morpholinyl-2-benzothiazole disulfide (Taft & Stroman, 1979).

(*c*) *Food and beverages*

Morpholine has been detected in many samples of foodstuffs. In six fish samples, the following concentrations were determined (μmol/100 g) [mg/kg]: tinned tuna, ≤0.7 [≤0.6]; frozen ocean perch, 10 [9]; frozen cod, < 0.3 [< 0.3]; spotted trout, 7 [6]; small mouth bass, ≤0.8 [≤0.7]; salmon, 1.2 [1.0]. Two meat samples also contained morpholine: baked ham, 0.6 μmol/100 g [0.5 mg/kg];; sausages, 0.5 μmol/100 g [0.4 mg/kg]. Six beverage samples had the following concentrations (μmol/100 g) [mg/kg]: evaporated milk, 0.2 [0.2]; coffee, 1 [1]; tea, < 0.1 [< 0.1]; tinned beer, 0.5 [0.4]; bottled beer, ≤0.3 [≤0.2]; wine, ≤0.8 [≤0.7] (Singer & Lijinsky, 1976).

Morpholine was also detected at an average concentration of 0.2 mg/kg in five samples of baked ham. None was detected (limit of detection, 0.01 mg/kg) in fish sausage, cod roe, spinach or fermented soya bean (Hamano *et al.*, 1981). Morpholine was tentatively identified by gas chromatographic retention time in an extract of cooked bacon (Rounbehler & Fine, 1982).

The morpholine concentrations in paper and paperboard food packages ranged from 0.10 to 0.84 mg/kg, with a mean of 0.38 mg/kg. Those materials that contained *N*-nitrosomorpholine (see IARC, 1978) usually contained higher concentrations of morpholine. Morpholine was detected at a concentration of 0.018 mg/kg in flour packaged in a paper sack that contained morpholine (Hotchkiss & Vecchio, 1983).

Residual levels of morpholine in the rinds of commercial citrus fruits ranged from undetectable (< 0.02 mg/kg) to 71.1 mg/kg. Levels in the flesh of citrus fruits and in marmalade were much lower, from undetectable to 0.7 mg/kg (Ohnishi, 1984).

2.3 Analysis

Singer and Lijinsky (1976) analysed foodstuffs for naturally occurring secondary amines by gas–liquid chromatography–mass spectrometry of *para*-toluenesulfonamide (tosylamide) derivatives. Tosylamides were prepared by steam distillation of the homogenized sample, extraction and reaction with *para*-toluenesulfonyl chloride under alkaline conditions. The lower quantifiable limit for morpholine in foods and beverages by this method, using dual flame-ionization/Coulson detectors, was approximately 0.1–0.3 mg/kg.

Secondary amines in foods have also been quantified by gas chromatography (GC) of benzene sulfonamide derivatives. Derivatives were prepared by extraction of the homogenized sample with acidified methanol, followed by a series of solvent exchanges and reaction

with benzenesulfonyl chloride under alkaline conditions. Using this method, the detection limit for morpholine, analysed by capillary GC with a flame photometric detector, was 0.01 mg/kg (Hamano *et al.*, 1981).

Morpholine has been detected (lower limit of detection, 0.02 mg/kg) in citrus fruits by steam distillation, column chromatography and GC analysis as the free amine with a flame-ionization detector (FID). Identity of the GC peak was confirmed by mass spectrometry (Ohnishi, 1984).

GC–FID, after a multi-step extraction and solvent exchange procedure, has been used to quantify morpholine in blood plasma, urine and biological tissues (Tombropoulos, 1979).

The sensitivity and selectivity of the thermal energy analyser (TEA) in the GC analysis of nitrosamines has been used to advantage in the determination of *N*-nitrosomorpholine and morpholine in foods and food packaging materials. Morpholine itself has been determined by nitrosation of extracts or distillates prior to GC–TEA analysis (lower limit of detection, approximately 0.003 mg/kg). A modified TEA, which converts any organic nitrogen to the nitrosyl radical, has been used to analyse directly for morpholine in foods and beverages (Rounbehler *et al.*, 1980; Rounbehler & Fine, 1982).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals[1,2]

(*a*) *Oral administration*

Mouse: As part of a toxicity study to investigate the nitrosation of morpholine, groups of 20 male and 20 female random-bred Swiss mice, six to 11 weeks of age, were fed a diet containing 6.33 g/kg morpholine (purified) for 28 weeks and observed for a further 12 weeks. A group of 80 males and 80 females received no treatment. Surviving mice were killed in week 40. Lung adenomas were counted grossly, and the numbers of adenoma-bearing mice and the total numbers of lung adenomas per mouse were comparable in the treated and untreated groups: 5/38 and 20/144 mice had five and 26 adenomas (both sexes pooled), respectively. There was a significant increase in the incidence of extrapulmonary tumours in treated mice (Greenblatt *et al.*, 1971). [The Working Group noted the short duration of the study.]

Groups of 50 male and 50 female B6C3F1 mice, six weeks old, received 0, 0.25 or 1.0% morpholine oleic acid salt [purity unspecified] in the drinking-water for 96 weeks followed by

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[1]Studies on the carcinogenicity of morpholine in combination with nitrite and of *N*-nitrosomorpholine were evaluated previously, in Volume 17 of the *IARC Monographs* (1978); *N*-nitrosomorpholine is carcinogenic to experimental animals.

[2]The Working Group was aware of a study in progress in rats by oral administration of morpholine (IARC, 1988).

eight weeks on tap water. Survival was not affected, but body weight was significantly reduced in high-dose males and in females of both treatment groups. No significant increase in the incidence of any tumour occurred in treated animals. The incidence of squamous epithelial hyperplasia of the forestomach was increased in high-dose males (Shibata *et al.*, 1987a).

Rat: In a long-term study to investigate the nitrosation of morpholine, groups of pregnant Sprague-Dawley rats and their offspring, treated from conception, were fed reagent-grade morpholine at 0 or 1000 mg/kg of diet and an F_2 generation was treated similarly. Median survival was 117 weeks for treated and 109 weeks for control rats. In the group of 104 rats treated with morpholine (F_1 and F_2 generations combined), three developed liver-cell carcinomas, two lung angiosarcomas and two malignant brain gliomas. A group of 156 untreated controls (F_1 and F_2 combined) did not develop these tumours. The diet was stated to contain no detectable nitrite or *N*-nitrosomorpholine, and the rats were given only distilled drinking-water. The authors noted that the liver and lung tumours might be the result of the interaction of morpholine with nitrite of unknown origin to form *N*-nitrosomorpholine (Newberne & Shank, 1973; Shank & Newberne, 1976).

Hamster: In a long-term study to investigate the nitrosation of morpholine, groups of pregnant random-bred Syrian golden hamsters were treated from conception with reagent-grade morpholine at 0 or 1000 mg/kg of diet. Animals were killed at 110 weeks of age. Median survival time was 72 weeks for controls and 68 weeks for animals treated with morpholine. One liver-cell tumour and four angiosarcomas were observed among 23 control animals, but none of these tumours were seen in 22 treated animals of both sexes combined (Shank & Newberne, 1976). [The Working Group noted the small number of animals used.]

(*b*) *Inhalation*

Rat: Groups of 70 male and 70 female Sprague-Dawley rats, approximately nine weeks of age, were exposed by inhalation to 0, 10, 50 or 150 ppm (0, 36, 178 or 534 mg/m^3) morpholine (purity, 99.16%) for 6 h per day on five days per week for up to 104 weeks. Levels of nitrates and nitrites in the drinking-water were reported to be < 0.1 mg/l and 0.01 mg/l, respectively. An interim kill of ten males and ten females per group at was done 53 weeks. The experiment was terminated in week 105. Survival at termination in control, low-, mid- and high-dose groups was 40, 44, 33 and 32 males and 35, 27, 32 and 35 females. Exposure to morpholine was associated with dose-related increases in inflammation of the cornea, inflammation and squamous metaplasia of the turbinate epithelium, and necrosis of the turbinate bones in the nasal cavity in rats of both sexes. No significant increase in the incidence of tumours was seen in rats of either sex (Harbison *et al.*, 1989). [The Working Group noted that only tissues from the respiratory tract and eyes were examined histologically for mid- and low-dose groups.]

3.2 Other relevant data

(*a*) *Experimental systems*

(i) *Absorption, distribution, excretion and metabolism*

Morpholine is absorbed after oral, dermal and inhalation administration. In rats, it was distributed to all organs and was eliminated rapidly (Tanaka *et al.*, 1978). In mice, rats, hamsters, guinea-pigs and rabbits, almost all ingested or intravenously or intraperitoneally injected morpholine was excreted unchanged in the urine (Tanaka *et al.*, 1978; Van Stee *et al.*, 1981; Sohn *et al.*, 1982). In the urine of guinea-pigs, 20% of an administered dose was identified as *N*-methylmorpholine-*N*-oxide (Sohn *et al.*, 1982). In mice, rats and hamsters, *N*-nitrosomorpholine is formed following concomitant administration of morpholine and nitrite or nitrous oxide (e.g., IARC, 1978; Van Stee *et al.*, 1983). *N*-Nitrosomorpholine was formed when morpholine was added to human saliva (Wishnok & Tannenbaum, 1977).

(ii) *Toxic effects*

The oral LD_{50} for morpholine was reported to be 1.05 g/kg bw in rats (Smyth *et al.*, 1954); that for 1:4 aqueous dilutions was 1.6 g/kg bw in rats and 0.9 g/kg bw in guinea-pigs (Shea, 1939). The skin penetration LD_{50} for morpholine was reported to be 0.5 ml(g)/kg in rabbits (Smyth *et al.*, 1954). The maximal exposure time without mortality to concentrated morpholine vapour by inhalation was estimated to be about 1 h, and 6/6 rats survived at least 14 days after an 8-h exposure to 8000 ppm (28 500 mg/m^3; Smyth *et al.*, 1954). As reported in an abstract, acute inhalation studies have given LC_{50} values of 2250 ppm (8010 mg/m^3) in male and 2150 ppm (7650 mg/m^3) in female rats and of 1450 ppm (5160 mg/m^3) in male and 1900 ppm (6760 mg/m^3) in female mice (Lam & Van Stee, 1978).

Morpholine is a strong skin and eye irritant in rabbits (Smyth *et al.*, 1954) and guinea-pigs; it caused skin necrosis after dermal application of 0.9 g/kg bw diluted or undiluted, unneutralized compound to rabbits and of 0.9 g/kg bw undiluted, unneutralized compound to guinea-pigs (Shea, 1939).

Morpholine (undiluted, unneutralized) caused necrosis of the liver and tubular necrosis of the kidney in guinea-pigs after dermal application of 0.9 g/kg bw. Similar effects were observed in rabbits following dermal application of 0.9 g/kg bw dilute morpholine. A single oral administration (0.1–10 g/kg bw) of undiluted, unneutralized morpholine caused haemorrhages in the stomach and small intestine in guinea-pigs and rats; treatment of guinea-pigs for up to 30 days (0.5 g/kg bw) caused necrosis of the liver and renal tubules. Liver and kidney necrosis also occurred after exposure of rats by inhalation to 12 000 or 18 000 ppm (42 720 or 64 000 mg/m^3) for up to 42 h (Shea, 1939).

Morpholine given to rats at a level of 1 g/kg in the diet caused fatty degeneration of the liver after 270 days (Sander & Bürkle, 1969). In mice given 0.15–2.5% morpholine oleic acid salt in the drinking-water for 13 weeks, a significant increase in urine specific gravity and plasma urea nitrogen and an increase in the relative weights of the kidneys were observed in males and females in the two highest dose groups. Slight cloudy swelling of the proximal tubules of the kidneys was seen in animals of each sex given the highest dose (Shibata *et al.*, 1987b).

When rats were exposed by inhalation to 250 ppm (890 mg/m³) morpholine for 6 h per day on five days per week, there were signs of an irritant effect after one week. In some of the animals killed after seven weeks, and in almost all killed after 13 weeks, there were focal erosions and squamous metaplasia in the maxilloturbinates. Similar effects were noted in a few animals exposed to 100 ppm (356 mg/m³) for 13 weeks (Conaway *et al.*, 1984a). It was reported in an abstract that rats exposed by inhalation to 450 ppm (1600 mg/m³) morpholine for 6 h per day on five days per week for eight weeks developed changes in sensory areas (eyes, nose), had decreased body weight gains and had increased organ:body weight ratios for the lungs and kidneys (Lam & Van Stee, 1978).

After 33 exposures to 250 ppm (890 mg/m³) in air, rabbits displayed increased enzyme activities in alveolar macrophages, indicating airway damage (Tombropoulos *et al.*, 1983).

(iii) *Effects on reproduction and prenatal toxicity*

No data were available to the Working Group.

(iv) *Genetic and related effects*

Morpholine was not mutagenic to *Salmonella typhimurium* TA1535, TA1537, TA98 or TA100 either in the presence or in the absence of an exogenous metabolic activation system from Aroclor-induced rats (Haworth *et al.*, 1983). A morpholine fatty acid salt was not mutagenic to *S. typhimurium* TA1535, TA1537, TA92, TA94, TA98 or TA100 either in the presence or in the absence of an exogenous metabolic activation system (Ishidate *et al.*, 1984). It did not induce mutation in *S. typhimurium* TA1590 when used as indicator strain in a host-mediated assay in NMRI mice (Braun *et al.*, 1977), or in *S. typhimurium* TA1530 in CD-1 mice (Edwards *et al.*, 1979).

Morpholine did not induce DNA repair in primary cultures of rat hepatocytes (Conaway *et al.*, 1984b).

Morpholine did not cause chromosomal aberrations, micronuclei, morphological transformation, or 8-azaguanine- or ouabain-resistant mutants in hamster embryo cells following administration by stomach tube to mothers on day 11 or 12 of pregnancy (Inui *et al.*, 1979). A morpholine fatty acid salt did not induce chromosomal aberrations in Chinese hamster fibroblasts (Ishidate *et al.*, 1984).

In an abstract, morpholine was reported to have a weak positive effect on the induction of mutations in L5178 $TK^{+/-}$ mouse lymphoma cells without metabolic activation. In the same abstract, an increase in the frequency of morphological transformation of Balb/3T3 cells was also reported (Conaway *et al.*, 1982).

(*b*) *Humans*

(i) *Absorption, distribution, excretion and metabolism*

No data were available to the Working Group.

(ii) *Toxic effects*

Lachrymation, rhinitis and lower airway irritation have been reported in humans exposed to 'high levels' of morpholine in an industrial setting. Corneal oedema with 'hazy vision' and halo phenomena around lights have also been reported (National Research Council, 1983; Grant, 1986).

(iii) *Effects on fertility and on pregnancy outcome*

No data were available to the Working Group.

(iv) *Genetic and related effects*

No data were available to the Working Group.

3.3 Epidemiological studies of carcinogenicity to humans

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Exposures

Morpholine is a synthetic organic liquid used mainly as an intermediate in the production of rubber chemicals and optical brighteners, as a corrosion inhibitor in steam condensate systems, as an ingredient in waxes and polishes and as a component of protective coatings on fresh fruits and vegetables. Occupational exposure may occur during the production of morpholine and in its various uses, but data on exposure levels are sparse. It has been detected in samples of foodstuffs and beverages.

4.2 Experimental carcinogenicity data

Morpholine was tested for carcinogenicity by oral administration in two strains of mice, one strain of rats and one strain of hamsters. The studies in one of the strains of mice and in hamsters were considered inadequate for evaluation. In the other strain of mice, no significant increase in the incidence of tumours was seen in treated animals. In the study in rats, a few tumours of the liver and lung occurred in treated animals. Morpholine was also tested by inhalation exposure in rats; it did not increase the incidence of tumours over that in controls.

4.3 Human carcinogenicity data

No data were available to the Working Group.

4.4 Other relevant data

Morpholine is an irritant in humans and experimental animals. It caused kidney damage in experimental animals.

Morpholine did not induce micronuclei, chromosomal aberrations or mutation in hamsters. It did not induce morphological transformation, chromosomal aberrations or DNA damage in cultured animal cells. It did not induce mutations in bacteria. (See Appendix 1.)

4.5 Evaluation[1]

There is *inadequate evidence* for the carcinogenicity of morpholine in experimental animals.

No data were available from studies in humans on the carcinogenicity of morpholine.

Overall evaluation

Morpholine *is not classifiable as to its carcinogenicity to humans (Group 3).*

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