Aquatrade Water Treatment Chemicals (Pty) Ltd

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1 Identification

GHS Product Identifier

MORPHOLINE

Other means of identification

CAS:	110-91-8
EC:	203-815-1
RTECS:	QD6475000
ICSC:	0302
NSC:	9376
UN:	2054
Chemical Family:	Amines
Synonyms:	MORPHOLINE 1-Oxa-4-azacyclohexane Tetrahydro-1,4-oxazine Diethylene oximide Diethylenimide oxide Diethyleneimide oxide Drewamine Diethylene imidoxide Tetrahydro-2H-1,4-oxazine Tetrahydro-p-oxazine
Proper Shipping Name:	MORPHOLINE
Chemical Formula:	C_4H_9NO
Molecular weight:	87.122 g/mol

Recommended use of the chemical and restriction on use

Morpholine is used as a separating agent for volatile amines; an intermediate for textile lubricants; in the synthesis of rubber accelerators and pharmaceuticals. It is also used as a solvent, as a boiler water additive, and in the formulation of waxes, polishers, and cleaners.

Solvent for resins, waxes, casein, dyes.

Rubber accelerator, solvent, additive to boiler water, waxes and polishes, optical brightener for detergents, corrosion inhibitor, preservation of book paper, organic intermediate (catalyst, antioxidants, pharmaceuticals, bactericides, etc.).

Morpholine is used in the USA by the cosmetic industry. Data submitted to the US Food and Drug Administration in 1981 and 1986 and in 1991 show that, at least in the USA, morpholine is still used in cosmetic products. In 1981, morpholine was used in 38 cosmetic preparations, the majority (32) being mascara. It is also used in eyeliner, eye shadow and skin care preparations.

Chemical intermediate for disulfide and sulfenamide rubber accelerators, N,N'-dithiomorpholine heat stabilizer, dimorpholine polysulfide corrosion inhibitor, di-4-morpholinyl monosulfide antioxidant, morpholine oleate, a wax component, pharmaceuticals, softening and whitening agents, N-hexadecylmorpholine, an intermediate for bactericides, photographic developer, salts of sulfonated azo dyes, morpholine p-toluenesulfonic acid salt; solvent for extractions.

It has been used as emulsifier in silicone emulsions & in various greases, textile lubricants, pesticide concentrates, cosmetic creams & shampoos, & has been incorporated in curing agents & in textile dyes. Its derivatives are important in preparation of pharmaceuticals.

Industry Uses

- Adhesives and sealant chemicals
- Corrosion inhibitors and anti-scaling agents
- Functional fluids (closed systems)
- Functional fluids (open systems)
- Intermediates

Consumer Uses

- Adhesives and sealants
- Building/construction materials not covered elsewhere
- Water treatment products

Supplier's details

AQUATRADE WATER TREATMENT CHEMICALS (PTY) LTD

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Emergency phone number

E le Sar:	+27 82 921 0643 (Available Mon - Fri, GMT 5:00 to 20:00)
Spilltech:	+27 861 000 366 (Available 24/7)

2 Hazard(s) identification

Classification of the substance or mixture

Classification according to Regulation (EC) No 1272/2008

Flammable Liquid and Vapor (Category 3), H226
Acute Toxicity, Oral (Category 4), H302
Acute Toxicity, Dermal (Category 3), H311
Skin Corrosion/Skin Irritation (Category 1), H314
Acute Toxicity, Inhalation (Category 3), H331

Full text of H statements : see section 16

GHS label elements

Danger

Flammable liquid and vapour

Harmful if swallowed

Toxic in contact with skin

Causes severe skin burns and eye damage

Toxic if inhaled

Take precautionary measures against static discharge.

Do not breathe dust/fume/gas/mist/vapours/spray.

Wash thoroughly after handling.

Do not eat, drink or smoke when using this product.

Use only outdoors or in a well-ventilated area.

Wear protective gloves/protective clothing/eye protection/face protection.

IF SWALLOWED: call a POISON CENTER or doctor/physician IF you feel unwell.

IF SWALLOWED: Rinse mouth. Do NOT induce vomiting.

IF ON SKIN: Wash with plenty of soap and water.

IF ON SKIN (or hair): Remove/Take off Immediately all contaminated clothing. Rinse SKIN with water/shower.

IF INHALED: Remove victim to fresh air and Keep at rest in a position comfortable for breathing.

IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.

Immediately call a POISON CENTER or doctor/physician.

Specific treatment (see P330+P351+P352 on this label).

Take off contaminated clothing and wash it before reuse.

Wash contaminated clothing before reuse.

In case of fire: Use water spray, dry powder, foam, carbon dioxide to extinguish.

Store locked up.

Dispose of contents and container in accordance with local, regional, national, international regulations.

Keep away from heat/sparks/open flames/hot surfaces. — No smoking. Keep container tightly closed.

Ground/bond container and receiving equipment. Use explosion-proof electrical/ventilating/lighting equipment. Use only non-sparking tools.

Store in a well-ventilated place. Keep container tightly closed. Keep cool.

Other hazards which do not result in classification

Morpholine is readily biodegradable according to OECD criteria, therefore the substance is not P or vP. Regarding the bioaccumulation potential, the experimentally determined BCF is < 2.8 L/kg; The substance is not expected to significantly bioaccumulate in organisms and is, therefore, not B or vB. The substance is not T since, the lowest available chronic value is > 0.01 mg/L (Daphnia: 21-d EC10 = 8.134 mg/L) and the substance holds no official classification.

3 Composition/information on ingredients

Description	**CAS Number**	**EINECS Number**	**%**	**Note**
Morpholine	110-91-8		0 - 99	

4 First-aid measures

Description of necessary first-aid measures

Call 112 or 10177 or your local emergency help number immediately, for emergency assistance. Call the Poison Control Center at +27 21 931 6129 – Tygerberg or +27 21 658 5308 – Red Cross, Email: poisonsinformation@uct.ac.za, Website: https://www.afritox.co.za for further instructions. Provide them with information such as the compound taken, quantity and time of ingestion, age, weight and general health status of affected individual. Carefully remove the individual from the exposure area.

Inhalation

1. Move to fresh air.
2. Oxygen or artificial respiration if needed.
3. Victim to lie down in the recovery position, cover and keep him warm.
4. Call a physician immediately.

Skin

1. Take off contaminated clothing and shoes immediately.
2. Wash off immediately with plenty of water.
3. Keep warm and in a quiet place.
4. Call a physician or poison control centre immediately.
5. Wash contaminated clothing before re-use.

Eye Contact

1. Rinse immediately with plenty of water, also under the eyelids, for at least 15 minutes.
2. In the case of difficulty of opening the lids, administer an analgesic eye wash (oxybuprocaine).
3. Call a physician or poison control centre immediately.

4. Take victim immediately to hospital.

Ingestion

1. Call a physician or poison control centre immediately.
2. Take victim immediately to hospital.
3. In case of symptoms that indicate difficulty in swallowing including vomiting or decreased alertness, **DO NOT** give anything by way of mouth.
4. If swallowed, rinse mouth with water (only if the person is conscious).
5. Unless instructed by a healthcare professional, **DO NOT** induce vomiting in the affected individual. Following an ingestion of the substance, immediately give milk to drink
6. Artificial respiration and/or oxygen may be necessary.
7. Always try to take the compound bottle/container to the ER.

Most important symptoms/effects, acute and delayed

Symptoms

Irritation eyes, skin, nose, respiratory system; visual disturbance; cough; In Animals: liver, kidney damage

Inhalation Symptoms

Burning sensation. Cough. Laboured breathing. Shortness of breath. Symptoms may be delayed. See Notes.

Skin Symptoms

MAY BE ABSORBED! Redness. Pain. Skin burns. Blisters.

Eye Symptoms

Redness. Pain. Blurred vision. Severe deep burns.

Ingestion Symptoms

Abdominal pain. Burning sensation. Cough. Diarrhoea. Nausea. Shock or collapse. Vomiting.

Target Organs

Eyes, skin, respiratory system, liver, kidneys.

Indication of immediate medical attention and special treatment needed, if necessary

Antidote and Emergency Treatment

Immediate first aid: Ensure that adequate decontamination has been carried out. If patient is not breathing, start artificial respiration, preferably with a demand valve resuscitator, bag-valve-mask device, or pocket mask, as trained. Perform CPR if necessary. Immediately flush contaminated eyes with gently flowing water. **DO NOT** induce vomiting. If vomiting occurs, lean patient forward or place on the left side (head-down position, if possible) to maintain an open airway and prevent aspiration. Keep patient quiet and maintain normal body temperature. Obtain medical attention.

Basic treatment

Establish a patent airway (oropharyngeal or nasopharyngeal airway, if needed). Suction if necessary. Watch for signs of respiratory insufficiency and assist ventilations if necessary. Administer oxygen by nonrebreather mask at 10 to 15 L/min. Monitor for pulmonary edema and treat if necessary. Monitor for shock and treat if necessary. Anticipate seizures and treat if necessary. For eye contamination, flush eyes immediately with water. Irrigate each eye continuously with 0.9% saline (NS) during transport. **DO NOT** use emetics. For ingestion, rinse mouth and administer 5 mL/kg up to 200 ml of water for dilution if the patent can swallow, has a strong gag reflex, and does not drool. Administer activated charcoal. Cover skin burns with dry sterile dressings after decontamination.

Advanced treatment

Consider orotracheal or nasotracheal intubation for airway control in the patient who is unconscious, has severe pulmonary edema, or is in severe respiratory distress. Positive-pressure ventilation techniques with a bag-valve-mask device may be beneficial. Consider drug therapy for pulmonary edema. Monitor cardiac rhythm and treat arrhythmias as necessary. Start IV administration of D5W /SRP: "To keep open", minimal flow rate/. Use 0.9% saline (NS) or lactated Ringer's (LR) if signs of hypovolemia are present. For hypotension with signs of hypovolemia, administer fluid cautiously. If patient is unresponsive to these measures, vasopressors may be helpful. Watch for signs of fluid overload. Administer 1% solution methylene blue if patient is symptomatic with severe hypoxia, cyanosis, and cardiac compromise not responding to oxygen. Treat seizures with diazepam or lorazepam. Use proparacaine hydrochloride to assist eye irrigation.

Medical Surveillance
The following medical procedures should be made available to each employee who is exposed to morpholine at potentially hazardous levels:

1. Initial Medical Screening: Employees should be screened for history of certain medical conditions which might place the employee at increased risk from morpholine exposure. These include chronic respiratory disease, liver disease, kidney disease, eye disease and skin disease.
2. Periodic Medical Examination: Any employee developing the above-listed conditions should be referred for further medical examination.

5 Fire-fighting measures

Suitable extinguishing media

Excerpt from ERG Guide 132 [Substances - Flammable Liquids - Corrosive]
FIRE
Some of these materials may react violently with water.

Small Fire

- Dry chemical, CO2, water spray or alcohol-resistant foam.

Large Fire

- Water spray, fog or alcohol-resistant foam.
- Move containers from fire area if you can do it without risk.
- Dike fire-control water for later disposal; do not scatter the material.
- **DO NOT** get water inside containers.

Fire involving Tanks or Car/Trailer Loads

- Fight fire from maximum distance or use unmanned hose holders or monitor nozzles.
- Cool containers with flooding quantities of water until well after fire is out.
- Withdraw immediately in case of rising sound from venting safety devices or discoloration of tank.
- ALWAYS stay away from tanks engulfed in fire.
- For massive fire, use unmanned hose holders or monitor nozzles; if this is impossible, withdraw from area and let fire burn.

Specific hazards arising from the chemical

FIRE OR EXPLOSION

- Flammable/combustible material.
- May be ignited by heat, sparks or flames.
- Vapors may form explosive mixtures with air.
- Vapors may travel to source of ignition and flash back.
- Most vapors are heavier than air. They will spread along ground and collect in low or confined areas (sewers, basements, tanks).
- Vapor explosion hazard indoors, outdoors or in sewers.
- Those substances designated with a (P) may polymerize explosively when heated or involved in a fire.
- Runoff to sewer may create fire or explosion hazard.
- Containers may explode when heated.
- Many liquids are lighter than water.

HEALTH

- May cause toxic effects if inhaled or ingested/swallowed.
- Contact with substance may cause severe burns to skin and eyes.
- Fire will produce irritating, corrosive and/or toxic gases.
- Vapors may cause dizziness or suffocation.
- Runoff from fire control or dilution water may cause pollution.

Special protective actions for fire-fighters

In the event of fire, wear self-contained breathing apparatus. Use personal protective equipment. Wear chemical resistant oversuit. Cool containers / tanks with water spray.

6 Accidental release measures

Personal precautions, protective equipment and emergency procedures

Isolation and Evacuation
Excerpt from ERG Guide 132 [Substances - Flammable Liquids - Corrosive]
Spill or Leak

- Fully encapsulating, vapor-protective clothing should be worn for spills and leaks with no fire.
- ELIMINATE all ignition sources (no smoking, flares, sparks or flames in immediate area).
- All equipment used when handling the product must be grounded.
- **DO NOT** touch or walk through spilled material.
- Stop leak if you can do it without risk.
- Prevent entry into waterways, sewers, basements or confined areas.
- A vapor-suppressing foam may be used to reduce vapors.
- Absorb with earth, sand or other non-combustible material and transfer to containers (except for Hydrazine).
- Use clean, non-sparking tools to collect absorbed material.

Large Spill

- Dike far ahead of liquid spill for later disposal.
- Water spray may reduce vapor, but may not prevent ignition in closed spaces.

Environmental precautions

DO NOT release into the environment. **DO NOT** flush into surface water or sanitary sewer system. If the product contaminates rivers and lakes or drains inform respective authorities.

Environmental considerations - land spill
Dig a pit, pond, lagoon, holding area to contain liquid or solid material. If time permits, pits, ponds, lagoons, soak holes, or holding areas should be sealed with an impermeable flexible membrane liner. Dike surface flow using soil, sand bags, foamed polyurethane, or foamed concrete. Absorb bulk liquid with fly ash, cement powder, or commercial sorbents.

Environmental considerations - water spill
Use natural barriers or oil spill control booms to limit spill travel. Remove trapped material with suction hoses.

Environmental considerations - air spill
Apply water spray or mist to knock down vapors.

Methods and materials for containment and cleaning up

Spill handling
Evacuate and restrict persons not wearing protective equipment from area of spill or leak until cleanup is complete. Remove all ignition sources. Establish forced ventilation to keep levels below explosive limit. Absorb liquids in vermiculite, dry sand, earth, peat, carbon, or a similar material and deposit in sealed containers. Keep this chemical out of a confined space, such as a sewer, because of the possibility of an explosion, unless the sewer is designed to prevent the build-up of explosive concentrations. It may be necessary to contain and dispose of this chemical as a hazardous waste. If material or contaminated runoff enters waterways, notify downstream users of potentially contaminated waters. Contact your Department of Environmental Protection or your regional office of the federal EPA for specific recommendations.

For small quantities, absorb on paper towels. Evaporate in a safe place (such as a fume hood). Allow sufficient time for evaporating vapors to completely clear the hood ductwork. Burn the paper in a suitable location away from combustible materials. Large quantities can be collected and atomized in a suitable combustion chamber equipped with an appropriate effluent gas cleaning device. Morpholine should not be allowed to enter a confined space, such as a sewer, because of the possibility of an explosion.

Spill or leak procedures
Eliminate all ignition sources. Stop or control the leak, if this can be done without undue risk. Use water spray to cool and disperse vapors, protect personnel, and dilute spills to form nonflammable mixtures. Control runoff and isolate discharged material for proper disposal.

Spread over with the 9:1 mixture of sand and soda ash. After mixing, transfer into a paper carton, stuffed with ruffled paper. Burn in an open furnace with the utmost care or in the furnace with afterburner and scrubber.

7 Handling and storage

Precautions for safe handling

Precautions for safe handling

Ensure thorough ventilation of stores and work areas. Product should be worked up in closed equipment as far as possible. Handle in accordance with good industrial hygiene and safety practice. When using **DO NOT** eat, drink or smoke. Hands and/or face should be washed before breaks and at the end of the shift.

Protection against fire and explosion

Vapours may form explosive mixture with air. Prevent electrostatic charge - sources of ignition should be kept well clear - fire extinguishers should be kept handy.

Conditions for safe storage, including any incompatibilities

Conditions for safe storage, including any incompatibilities

Segregate from acids and acid forming substances. Segregate from oxidants. Segregate from esters Segregate from lactones.

Suitable materials for containers

Carbon steel (Iron), Stainless steel 1.4301 (V2), Stainless steel 1.4541, Stainless steel 1.4401, Stainless steel 1.4571, Low density polyethylene (LDPE), High density polyethylene (HDPE), glass.
Further information on storage conditions: Containers should be stored tightly sealed in a dry place.

Storage stability

Storage duration: 24 Months
From the data on storage duration in this safety data sheet no agreed statement regarding the warrantee of application properties can be deduced.

SANS 10263-0 Warehousing

8.4.3.2 Where **flammable** or **corrosive** substances are stored, the floor shall slope away from the storage area (primary collection area) to a secondary catch basin or sump of capacity at least 10 % of the total available storage volume of the fire section concerned. The secondary catch basin shall be within the fire section, and shall be such that it can be well ventilated. Care shall be taken in the design of such areas to prevent contamination of the soil or ground water.

8.4.3.9 A flame propagation inhibitor shall be installed at overflow points when **flammable** gases or **flammable** liquids are stored.

8.4.4.3 Outdoor secondary and tertiary basins may be connected by means of open gutters or closed pipelines. Where **flammable** liquids are stored, however, closed pipelines shall be connected by means such as siphons or flame-arrestor gauzes, which prevent "flashback" of burning liquid.

8.6.2 In areas where **flammable** or explosive substances are stored, appropriate measures shall be taken to prevent the accumulation of electrostatic charges or to discharge these under controlled circumstances. The relevant provisions of SANS 10123 shall apply (see also 5.1.2)

8.8.1 Ventilation

8.8.1.1 General

Every covered storage area shall be provided with either adequate natural ventilation or forced draught ventilation in accordance with Part 0 of SANS 10400:1990 that ensures at least five changes of air per hour. In general, poor ventilation occurs if vents are positioned near the floor, and good general ventilation occurs where vents are positioned both near the floor and near or in the roof. It shall be possible to shut off a forced draught ventilation system by means of a main switch in the event of a fire or the escape of poisonous or **corrosive** gases. Where highly **flammable** gases or **flammable** liquids are stored, effective extraction shall be provided, at or near floor level, and the ventilation shall be so efficient as to prevent the formation of an explosive atmosphere. A ventilation rate of up to 12 air changes per hour could be required in certain cases. Appropriate monitoring using an explosimeter is recommended. Where forced draught ventilation is applied, it shall operate continuously during periods of normal operation, and might even need to operate during periods when the warehouse is unmanned.

8.8.2.1 Air conditioning shall preferably be of the ducted air type, with the air-conditioning plant situated well away from the storage area. Individual electric air conditioners shall not be used in areas where **flammable** materials are stored. Where it is necessary to humidify the storage area, this shall be done by direct spraying of steam or water vapour. Dehumidification could be required where a large quantity of substances that react violently with water are stored. Where room humidity is critical, appropriate monitoring shall be carried out

8.8.3 Where room heating is required to ensure product integrity, it shall be so designed as to ensure that the temperature in the warehouse does not fall below 5 °C. Heating systems shall preferably be based on hot water or steam, with the heat source and pipes, radiators or similar equipment that are likely to become hot, so positioned as to prevent direct heating of the stored product. Direct electrical room heating equipment, or portable gas-fired or oil-fired room heaters shall not be used in areas where **flammable** materials are stored. Where a maximum allowable temperature applies, appropriate monitoring systems shall be used. Facilities for heating a circulating medium shall be located outside the storage area or in a separate room. Where building insulation is used, it shall be of a non-combustible material such as mineral wool or glass fibre.

8.10.4 Where electric lighting is installed in a warehouse that is to be used for **flammable** or explosive products, it shall be protected in accordance with the relevant provisions of SANS 10108 for the class and division of hazardous location that the warehouse represents.

8.10.5 No switches may be installed inside a stock warehouse that is to be used for **flammable** or explosive products. Main switches shall be positioned outside the warehouse and shall be protected against the weather.

8.11.3 Wherever practicable, electrical equipment other than for permanent lighting, such as power points, power tools or hand lights, shall not be installed in a warehouse that is used for **flammable** or explosive products. Where such electrical equipment is used, it shall be protected in accordance with the provisions of SANS 10108 for the appropriate class and division of hazardous location that the warehouse represents.

9.7.2 Every type of storage area inside a warehouse shall be clearly demarcated, for example separate storage areas for poisons, **flammables** and **corrosives** shall display the relevant hazard class diamond (see table 1). The dimensions of the hazard class diamonds shall be at least 250 mm x 250 mm.

10.2.1.2 A warehouse in which any one of the following storage limits is exceeded shall be equipped with a hydrant system in addition to portable or mobile extinguishers:

a) 30 t of **flammable** toxic or combustible toxic materials;
b) 100 t of **flammable** materials; and
c) 250 t of combustible materials.

10.2.1.3 The firefighting water supply shall be such as to ensure an adequate response to all conceivable fires, and shall have a continuous flow rate of at least 1 200 L/min per hydrant in small warehouses. In larger warehouses in which highly **flammable** substances are stored and that are equipped with automatic sprinkler facilities, a capacity in the range 3 200 L/min to 6 000 L/min is likely to be required. Where it is necessary to achieve the required capacity, existing water supply systems shall be supplemented by water from a reservoir or firefighting pond. In all cases, the water supply shall be capable of being maintained for at least 120 min.

12.8.5 Storage of **flammable** liquids of class 3, toxic substances of division 6.1 and **corrosives** of class 8

Nitro-methane class 3, UN No. 1261, shall be separated from substances of class 6.1, and cyanides of division 6.1 shall be separated from acids of class 8. Concentrated acids and bases shall be segregated by at least 1 m. Packaged **flammable** liquids of class 3, toxic substances of division 6.1 and **corrosives** of class 8 that are of category 3 can be stored in the same area, provided that

a) they are kept above floor level, and
b) liquid dangerous goods of one class are not stored above dangerous goods of another class.

12.8.8.1 **Flammable** materials (see division 2.1, and classes 3 and 4 in SANS 10228) will greatly increase the risk of a toxicant fire if stored in the same area as toxicants, therefore:

a) **Flammable** non-toxic materials shall be separated from **flammable** toxicants and from aerosols.
b) **Flammable** toxicants shall be separated from non-**flammable** toxicants.
c) **Flammable** materials shall be segregated from oxidizing substances and **corrosives**.

12.8.8.2 Oxidizing substances and organic peroxides (see class 5 in SANS 10228) can react violently with other products, and in particular with reducing substances and certain organic substances.

Oxidizing substances and organic peroxides shall be segregated from reducing substances, toxic substances and infectious substances, and from aerosol dispensers, **flammables** and **corrosives**.

12.8.8.3 Toxic and infectious substances (see class 6 in SANS 10228) can contaminate firefighting water in the event of a fire, therefore:

a) Toxic and infectious substances shall be separated from other **flammable** products and aerosols.
b) Toxic and infectious substances shall be segregated from oxidizing substances, organic peroxides and **corrosives**.
c) **Flammable** toxic and infectious substances shall be separated from non-flammable toxic and infectious substances (see 12.8.8.1).

12.8.8.4 **Corrosives** (see class 8 in SANS 10228) that leak or spill from their packaging can cause serious damage to other packages, with potentially hazardous consequences.

Corrosives shall be segregated from toxic substances, infectious substances, aerosols, **flammables**, oxidizing substances and organic peroxides.

12.13.8.4 No work that requires hot cutting or welding, or that is likely to generate heat or sparks, shall be carried out within 10 m of any **flammable** or combustible material or packaging. If such work can only be carried out in a place where products are stored, all **flammable** or combustible items shall be removed to a distance of at least 10 m from the working area and the site shall be inspected to ensure that there is no possibility of fire, explosion or contamination from leaks, vapours, dust, rags or other materials. Work shall not start unless the atmosphere has been tested for the presence of **flammable** vapours and a satisfactory result of the test has been noted on the work permit. A shield shall be created around the work area. Fire-proof blankets shall be so arranged as to prevent sparks from falling to the ground, particularly if welding is being done overhead. Care shall be taken that drains in the area are covered to prevent the entry of weld splatter or the ignition of vapours. During welding or cutting operations, at least one person shall stand by with a fire extinguisher.

12.14.1.5 Paints, **flammable** liquids and polishes for use on the premises shall, when not in use, be kept in metal containers, preferably outside the building. A separate metal container shall be provided for rags or cotton waste used in connection with polishes and cleaning fluids.

The provisions of above apply to the storage of the following quantities of dangerous goods.

Flammable liquids Class 3	
Category 1: closed-cup flashpoint < 23 °C and initial boiling point d 35 °C	> 100 l
Category 2: closed-cup flash point < 23 °C and initial boiling point > 35 °C	> 500 l
Category 3: closed-cup flash point 23 °C and 60 °C	> 1 000 l
Corrosives (acids and bases) Class 8	
Category 1	> 50 kg
Category 2	> 200 kg
Category 3	> 1 000 kg

8 Exposure controls/personal protection

Control parameters

REL	TWA 20 ppm (70 mg/m3) ST 30 ppm (105 mg/m3) [skin]
PEL	TWA 20 ppm (70 mg/m3) [skin] See Appendix G
PEL-TWA	20 ppm (70 mg/m^3)
REL-TWA	20 ppm (70 mg/m^3)
REL-STEL	30 ppm (105 mg/m^3)

Immediately Dangerous to Life or Health

IDLH 1400 ppm Based on 10% of the lower explosive limit. (NIOSH, 2016)

1400 ppm [Based on 10% of the lower explosion limit for safety considerations even though the relevant toxicological data indicated that irreversible health efects or impairment of escape existed only at higher concentrations.]

Threshold Limit Values
8 hr Time Weighted Avg (TWA) 20 ppm. Skin.

Excursion Limit Recommendation: Excursions in worker exposure levels may exceed 3 times the TLV-TWA for no more than a total of 30 minutes during a work day, and under no circumstances should they exceed 5 times the TLV-TWA, provided that the TLV-TWA is not exceeded.

A4; Not classifiable as a human carcinogen.

20 ppm as TWA; (skin); A4 (not classifiable as a human carcinogen).

36 mg/m3, 10 ppm; peak limitation category: I(2); pregnancy risk group: D.

Appropriate engineering controls

Very toxic chemicals, or those that are reproductive hazards or sensitizers, require expert advice on control measures if a less toxic chemical cannot be substituted. Control measures include:

i. enclosing chemical processes for severely irritating and corrosive chemicals,
ii. using local exhaust ventilation for chemicals that may be harmful with a single exposure, and
iii. using general ventilation to control exposures to skin and eye irritants.

The following work practices are also recommended
Label process containers.
Provide employees with hazard information and training.
Monitor airborne chemical concentrations.
Use engineering controls if concentrations exceed recommended exposure levels.
Provide eye wash fountains and emergency showers.
Wash or shower if skin comes in contact with a hazardous material.
Always wash at the end of the workshift.
Change into clean clothing if clothing becomes contaminated.
DO NOT take contaminated clothing home.
Get special training to wash contaminated clothing.
DO NOT eat, smoke, or drink in areas where chemicals are being handled, processed or stored.
Wash hands carefully before eating, smoking, drinking, applying cosmetics or using the toilet.

In addition, the following may be useful or required
Before entering a confined space where Morpholine may be present, check to make sure that an explosive concentration does not exist.

Individual protection measures

The selection of PPE is dependent on a detailed risk assessment. The risk assessment should consider the work situation, the physical form of the chemical, the handling methods, and environmental factors. Recommendations below is advisory only and must be evaluated by an industrial hygienist and safety officer familiar with the specific situation of anticipated use by our customers. It should not be construed as offering an approval for any specific use scenario.

Hand protection
Chemical resistant protective gloves (EN 374)

Suitable materials also with prolonged, direct contact (Recommended: Protective index 6, corresponding > 480 minutes of permeation time according to EN 374):
butyl rubber (butyl) - 0.7 mm coating thickness
fluoroelastomer (FKM) - 0.7 mm coating thickness
Polyethylene-Laminate (PE laminate) - ca. 0.1 mm coating thickness

Suitable materials for short-term contact (recommended: At least protective index 2, corresponding > 30 minutes of permeation time according to EN 374)
nitrile rubber (NBR) - 0.4 mm coating thickness
polyvinylchloride (PVC) - 0.7 mm coating thickness
chloroprene rubber (CR) - 0.5 mm coating thickness

Supplementary note: The specifications are based on tests, literature data and information of glove manufacturers or are derived from similar substances by analogy. Due to many conditions (e.g. temperature) it must be considered, that the practical usage of a chemical-protective glove in practice may be much shorter than the permeation time determined through testing.

Manufacturer's directions for use should be observed because of great diversity of types.

Eye protection
Wear indirect-vent, impact and splash resistant goggles when working with liquids.
Wear a face shield along with goggles when working with corrosive, highly irritating or toxic substances.
DO NOT wear contact lenses when working with this substance.

Body protection
Avoid skin contact with Morpholine. Wear personal protective equipment made from material which can not be permeated or degraded by this substance. Safety equipment suppliers and manufacturers can provide recommendations on the most protective glove and clothing material for your operation.

Safety equipment manufacturers recommend Butyl, Silver Shield®/4H®, and Barrier® as glove materials, and Tychem® BR, Responder®, and TK, or the equivalent, as protective clothing materials.

All protective clothing (suits, gloves, footwear, headgear) should be clean, available each day, and put on before work.

Respiratory protection
Improper use of respirators is dangerous. Respirators should only be used if the employer has implemented a written program that takes into account workplace conditions, requirements for worker training, respirator fit testing, and medical exams, as described in the OSHA Respiratory Protection Standard (29 CFR 1910.134).

Where the potential exists for exposure over 20 ppm, use a NIOSH approved full facepiece respirator with an organic vapor cartridge. Increased protection is obtained from full facepiece powered-air purifying respirators.
Leave the area immediately if

1. while wearing a filter or cartridge respirator you can smell, taste, or otherwise detect Morpholine,
2. while wearing particulate filters abnormal resistance to breathing is experienced, or
3. eye irritation occurs while wearing a full facepiece respirator. Check to make sure the respirator-to-face seal is still good. If it is, replace the filter or cartridge. If the seal is no longer good, you may need a new respirator.

Consider all potential sources of exposure in your workplace. You may need a combination of filters, prefilters or cartridges to protect against different forms of a chemical (such as vapor and mist) or against a mixture of chemicals.

Where the potential exists for exposure over 200 ppm, use a NIOSH approved supplied-air respirator with a full facepiece operated in a pressure-demand or other positive-pressure mode. For increased protection use in combination with an auxiliary self-contained breathing apparatus or an emergency escape air cylinder.

Exposure to 1,400 ppm is immediately dangerous to life and health. If the possibility of exposure above 1,400 ppm exists, use a NIOSH approved self-contained breathing apparatus with a full facepiece operated in a pressure- demand or other positive-pressure mode equipped with an emergency escape air cylinder.

General safety and hygiene measures
Handle in accordance with good industrial hygiene and safety practice. **Avoid** contact with the skin, eyes and clothing. **Avoid** inhalation of vapour. When using, do not eat, drink or smoke. Hands and/or face should be washed before breaks and at the end of the shift. Gloves must be inspected regularly and prior to each use. Replace if necessary (e.g. pinhole leaks). Take off immediately all contaminated clothing. Wash contaminated clothing before reuse. Store work clothing separately.

9 Physical and chemical properties

Physical and chemical properties

Physical state at 20°C and 1013 hPa:	Colourless hygroscopic liquid
Odour:	Ammonia, fish-like
pH:	Strong base
Melting / freezing point at 101 325 Pa:	-4.9 °C
Boiling point at 101 325 Pa:	128.3 °C
Relative density at 20C:	1.001
Vapour pressure:	9.8 hPa @ 20.3 °C
Partition Coefficient:	-0.84 @ 25°C and pH 10.3 -2.55 @ 25°C and pH 7
Water solubility:	completely miscible in water
Surface tension:	not surface active
Flash point at 101 325 Pa:	32 °C
Autoflammability / Self-ignition temperature:	255 °C @ 101 325 Pa
Flammability:	Flammable liquids, Category 3 (flammable liquids and vapour) of EU CLP: flash point >= 23 °C and <= 60 °C
Explosiveness:	non explosive
Oxidising properties:	no
Dissociation constant:	pKa: 8.49 @ 25 °C
Viscosity:	2.23 mPa • s (dynamic) @ 20 °C

NOTE: The physical data presented above are typical values and should not be construed as a specification.

10 Stability and reactivity

Reactivity

Highly flammable. Water soluble. Sensitive to moisture. No hazardous reactions if stored and handled as prescribed/indicated.

MORPHOLINE neutralizes acids in exothermic reactions to form salts plus water. May be incompatible with isocyanates, halogenated organics, peroxides, phenols (acidic), epoxides, anhydrides, and acid halides. May generate hydrogen, a flammable gas, in combination with strong reducing agents such as hydrides. Sensitive to moisture. Reacts readily with oxidizing agents (NTP, 1992).

Corrosion to metals
Corrosive effects to metal are not anticipated.
Formation of flammable gases: Remarks: Forms no flammable gases in the presence of water.

Reactive Group
Amines, Phosphines, and Pyridines

Chemical stability

The product is stable if stored and handled as prescribed/indicated.

Possibility of hazardous reactions

Strong exothermic reaction with acids.

Conditions to avoid

Avoid all sources of ignition: heat, sparks, open flame.

Incompatible materials

Oxidizing agents, acids, nitrosating agents, **Avoid** contact with reactive components such as acids and organic components, for example ester and lactone., **Avoid** contact with monomers that can induce in alkaline medium polymerization.

Hazardous decomposition products

Carbon monoxide, Carbon dioxide, toxic gases/vapours

11 Toxicological information

Toxicological (health) effects

Date	System	Route/Organism	Dose	Effect
Skin and Eye Irritation				
Sep-13		eye /rabbit	2 mg	severe
Sep-13		skin /rabbit	500 mg open irritation test	moderate
Mutation Data				
Sep-13	Cytogenetic Analysis	inhalation/rat	0.07 mg/L/122D-intermittent	
Sep-13	morphological transform	fibroblast/mouse	125 mg/L	
Sep-13	morphological transform	lymphocyte/mouse	1 µL/L	
Sep-13	mutation in mammalian somatic cells	lymphocyte/mouse	1 gm/L	
Sep-13	sister chromatid exchange	ovary/hamster	160 mg/L	
Tumorigenic Data				
Sep-13		oral/mouse	lowest published toxic dose: 2560 mg/kg/1Y-continuous	Tumorigenic: Neoplastic by RTECS criteria
Acute Toxicity Data				
Sep-13		inhalation/mammal (species unspecified)	lethal concentration (50 percent kill): 12000 mg/m3	
Sep-13		inhalation/mouse	lowest published toxic concentration: 0.1 gm/m3/2H	Lung, Thorax, or Respiration: Other changes
Sep-13		inhalation/mouse	lethal concentration (50 percent kill): 1320 mg/m3/2H	Eye: Lacrimation
Sep-13		inhalation/mouse	lethal concentration (50 percent kill): 12000 mg/m3	Behavioral: Alteration of classical conditioning
Sep-13		inhalation/mouse	lethal concentration (50 percent kill): 1.35 gm/m3	
Sep-13		inhalation/mouse	Lowest published lethal concentration: 1.98 gm/m3/2H	
Sep-13		inhalation/mouse	Lowest published lethal concentration: 1.67 gm/m3/2H	Blood: Hemorrhage
Sep-13		inhalation/mouse	Lowest published lethal concentration: 0.45 gm/m3/2H	Behavioral: Irritability
			lethal concentration (50 percent kill): 8000	

Sep-13		inhalation/rat	ppm/8H	NULL
Sep-13		intraperitoneal/mouse	lethal dose (50 percent kill): 413 mg/kg	Reproductive: Paternal effects: Testes, epididymis, sperm duct
Sep-13		ocular/rabbit	lowest published toxic dose: 100 pph	Eye: Conjunctiva irritation
Sep-13		oral/guinea pig	lowest published lethal dose: 100 mg/kg	Olfaction: Other olfaction effects
Sep-13		oral/mammal (species unspecified)	lethal dose (50 percent kill): 1220 mg/kg	
Sep-13		oral/mouse	lethal dose (50 percent kill): 1200 mg/kg	
Sep-13		oral/mouse	lowest published lethal dose: 1200 mg/kg	
Sep-13		oral/mouse	lethal dose (50 percent kill): 525 mg/kg	Behavioral: Sleep
Sep-13		oral/rat	lowest published toxic dose: 500 mg/kg	
Sep-13		oral/rat	lethal dose (16 percent kill): 700 mg/kg	Reproductive: Paternal effects: Spermatogenesis (including genetic material, sperm morphology, motility, and count)
Sep-13		oral/rat	lethal dose (50 percent kill): 1738 mg/kg	Kidney, Ureter, and Bladder: Changes in blood vessels or in circulation of kidney
Sep-13		oral/rat	lowest published lethal dose: 1500 mg/kg	NULL
Sep-13		oral/rat	lowest published lethal dose: 2300 mg/kg	Brain and Coverings: Changes in circulation
Sep-13		skin/rabbit	lethal dose (50 percent kill): 500 µL/kg	
Sep-13		subcutaneous/mouse	lethal dose (50 percent kill): 458 mg/kg	
Sep-13		unreported route/rat	lowest published lethal dose: 1600 mg/kg	
Other Multiple Dose Data				
Sep-13		inhalation/guinea pig	lowest published toxic concentration: 70 mg/m3/4H/17W-intermittent	Liver: Liver function tests impaired
Sep-13		inhalation/guinea pig	lowest published toxic concentration: 0.07 gm/m3/2W- intermittent	Peripheral Nerve and Sensation: Recording from peripheral motor nerve
Sep-13		inhalation/guinea pig	lowest published toxic concentration: 0.07 gm/m3/30D-intermittent	Blood: Other changes
			lowest published toxic concentration: 0.008	

Sep-13		inhalation/guinea pig	gm/m3/61D- intermittent	Liver: Liver function tests impaired
Sep-13		inhalation/rat	lowest published toxic concentration: 70 mg/m3/4H/17W- intermittent	Vascular: BP lowering not characterized in autonomic section
Sep-13		inhalation/rat	lowest published toxic dose: 250 ppm/6H/13W- intermittent	Lung, Thorax, or Respiration: Fibrosis, focal (pneumoconiosis)
Sep-13		inhalation/rat	lowest published toxic concentration: 0.07 gm/m3/2W- intermittent	Peripheral Nerve and Sensation: Recording from peripheral motor nerve
Sep-13		inhalation/rat	lowest published toxic concentration: 0.07 gm/m3/30D- intermittent	Blood: Changes in other cell count (unspecified)
Sep-13		inhalation/rat	lowest published toxic concentration: 0.008 gm/m3/61D- intermittent	Vascular: BP lowering not characterized in autonomic section
Sep-13		inhalation/rat	lowest published toxic concentration: 0.07 gm/m3/122D- intermittent	Liver: Other changes
Sep-13		inhalation/rat	lowest published toxic concentration: 0.008 gm/m3/122D- intermittent	Blood: Changes in spleen
Sep-13		oral/guinea pig	lowest published toxic dose: 13500 mg/kg/30D- intermittent	Gastrointestinal: Necrotic changes
Sep-13		oral/rat	lowest published toxic dose: 24 gm/kg/30D- intermittent	Gastrointestinal: Necrotic changes
Sep-13		skin/guinea pig	lowest published toxic dose: 27 gm/kg/30D- intermittent	Kidney, Ureter, and Bladder: Changes in both tubules and glomeruli
Sep-13		skin/rabbit	lowest published toxic dose: 9 gm/kg/10D- intermittent	Liver: Fatty liver degeneration

Information on the likely routes of exposure

Workers - Hazard via inhalation route

Systemic effects

Long term exposure

Hazard assessment conclusion:	DNEL (Derived No Effect Level)
Value:	91 mg/m³
Most sensitive endpoint:	repeated dose toxicity

DNEL related information

Overall assessment factor (AF):	2
Modified dose descriptor starting point:	NOAEC

Acute/short term exposure

Hazard assessment conclusion:	medium hazard (no threshold derived)

Local effects
Long term exposure
Hazard assessment conclusion: DNEL (Derived No Effect Level)
Value: 36 mg/m³
Most sensitive endpoint: irritation (respiratory tract)
Acute/short term exposure
Hazard assessment conclusion: DNEL (Derived No Effect Level)
Value: 72 mg/m³
Most sensitive endpoint: irritation (respiratory tract)

Workers - Hazard via dermal route
Systemic effects
Long term exposure
Hazard assessment conclusion: DNEL (Derived No Effect Level)
Value: 1.04 mg/kg bw/day
Most sensitive endpoint: repeated dose toxicity
DNEL related information
Overall assessment factor (AF): 480
Modified dose descriptor starting point: LOAEL
Acute/short term exposure
Hazard assessment conclusion: medium hazard (no threshold derived)
Local effects
Long term exposure
Hazard assessment conclusion: medium hazard (no threshold derived)
Acute/short term exposure
Hazard assessment conclusion: medium hazard (no threshold derived)

Workers - Hazard for the eyes
Local effects
Hazard assessment conclusion: medium hazard (no threshold derived)

General Population - Hazard via inhalation route
Systemic effects
Long term exposure
Hazard assessment conclusion: hazard unknown but no further hazard information necessary as no exposure expected
Acute/short term exposure
Hazard assessment conclusion: hazard unknown but no further hazard information necessary as no exposure expected
Local effects
Long term exposure
Hazard assessment conclusion: hazard unknown but no further hazard information necessary as no exposure expected
Acute/short term exposure
Hazard assessment conclusion: hazard unknown but no further hazard information necessary as no exposure expected

General Population - Hazard via dermal route
Systemic effects
Long term exposure
Hazard assessment conclusion: hazard unknown but no further hazard information necessary as no exposure expected
Acute/short term exposure
Hazard assessment conclusion: hazard unknown but no further hazard information necessary as no exposure expected
Local effects
Long term exposure
Hazard assessment conclusion: hazard unknown but no further hazard information necessary as no exposure expected

Acute/short term exposure
Hazard assessment conclusion: hazard unknown but no further hazard information necessary as no exposure expected

General Population - Hazard via oral route
Systemic effects
Long term exposure

Hazard assessment conclusion:	DNEL (Derived No Effect Level)
Value:	6.3 mg/kg bw/day
Most sensitive endpoint:	repeated dose toxicity

DNEL related information

Overall assessment factor (AF):	80
Modified dose descriptor starting point:	LOAEL

Acute/short term exposure
Hazard assessment conclusion: hazard unknown but no further hazard information necessary as no exposure expected

General Population - Hazard for the eyes
Local effects
Hazard assessment conclusion: hazard unknown but no further hazard information necessary as no exposure expected

Symptoms related to the physical, chemical and toxicological characteristics

Symptoms
Irritation eyes, skin, nose, respiratory system; visual disturbance; cough; In Animals: liver, kidney damage

Inhalation Symptoms
Burning sensation. Cough. Laboured breathing. Shortness of breath. Symptoms may be delayed. See Notes.

Skin Symptoms
MAY BE ABSORBED! Redness. Pain. Skin burns. Blisters.

Eye Symptoms
Redness. Pain. Blurred vision. Severe deep burns.

Ingestion Symptoms
Abdominal pain. Burning sensation. Cough. Diarrhoea. Nausea. Shock or collapse. Vomiting.

Target Organs
Eyes, skin, respiratory system, liver, kidneys

Delayed and immediate effects and also chronic effects from short and long term exposure

Toxicokinetics, metabolism and distribution
Kinetics and metabolism of Morpholine
The pharmacokinetic profile, protein binding and metabolism of morpholine were studied in different species after single administration. The available studies in rat demonstrate that morpholine is rapidly and quantitatively absorbed. Morpholine has been reported to be resistant to metabolism in the rat (Tanaka et al., 1978; Sohn et al., 1982), dog (Rhodes and Case, 1977), and rabbit (Van Stee et al., 1981). In contrast, Sohn et al. (1982) reported that morpholine is extensively metabolized by N-methylation and N-oxidation in the guinea pig. Morpholine is metabolized to a much smaller extent by N-methylation in the rat and hamster (Sohn et al., 1982). Reports also suggested that morpholine is preferentially distributed to the rabbit kidney (Van Stee et al., 1981) and the rat kidney and intestine (Tanaka, 1978). Morpholine is primarily excreted unchanged in the urine.

Absorption
Toxicity experiments on rodents have shown that morpholine is absorbed after oral, dermal and inhalation exposure (c.f. Shea, 1939; Smyth et al., 1954).

Distribution
Tanaka et al. (1978) determined the distribution of 14C-labelled morpholine in male Wistar rats (3 animals/group, 250 to

300 g) after oral (200 mg/kg bw) and intravenous administration (150 mg/kg bw). The radioactivity was determined in the dried, powdered organs. Large amounts of 14C morpholine were only found in muscle and intestine regardless of route of administration. In rats sacrificed 2 hours after oral administration of morpholine HCl, 29% of the radioactivity was found in the intestine and 26% in muscle tissue. Similarly, 2 hours after intravenous injections, 19 and 27 % of the dose was found in the intestine and muscle tissue, respectively. Elimination of radioactivity from other organs, tissues and blood was very rapid in cases of both oral and i.v. administration.

Female New Zealand White rabbits were exposed to morpholine (905 mg/m³) for 5 hours by nose-only inhalation (Tombropoulos, 1979). At the end of the exposure, the animals were sacrificed and the tissue and body fluids analysed. Concentrations of Morpholine were highest in urine (324 mg/L) and kidney (118 mg/kg bw), the other tissues having concentrations below 50 mg/kg bw.

Van Stee et al. (1981) injected six male New Zealand White rabbits intravenously with 5 mmol [14C]-labelled morpholine/kg bw (435 mg/kg bw). The distribution of radioactivity after 30 min showed the highest concentrations in the renal medulla (36 mmol/kg bw) and cortex (15.4 mmol/kg bw), followed by lung (5.1 mmol/kg bw), liver (4.7 mmol/kg bw) and blood (2.3 mmol/L). Morpholine was not bound to serum proteins. Furthermore, the subcellular binding interactions of morpholine were investigated (Naylor Dana Institute, 1983). Uniform distribution of 14C in TCA-insoluble fractions indicated a non-specific binding and/or incorporation of morpholine. No significant amounts of covalently bound 14C were detected in the subcellular fractions of the liver.

Metabolism

Morpholine is eliminated mainly in a non-metabolized form in the urine of the rat, mouse, hamster and rabbit (Griffiths, 1968; Tanaka et al., 1978; Van Stee et al., 1981; Sohn et al., 1982). However, Sohn et al. (1982) reported that morpholine is metabolized by N-methylation followed by N-oxidation in the guinea-pig. After an intraperitoneal injection of 125 mg/kg bw [14C]-labelled Morpholine in guinea-pigs, 20 % of the radioactivity was found in the urine as N-methylmorpholine- N-oxide. The Morpholine ring can be cleaved in mammalian systems: in several studies on the metabolism of morpholine derivatives in the rat, ring cleavage products have been reported (Tatsumi et al., 1975; Hecht & Young, 1981; Kamimura et al., 1987).

Elimination and excretion

Expired air:

Following intraperitoneal injection, the elimination of 14C from labelled morpholine through expired air is minimal. In rats, only about 0.5 % of the dose of radioactively labeled morpholine was exhaled as 14C carbon dioxide (Sohn et al., 1981). In rabbits, only 0.0008 % of the administered morpholine dose was 14C carbon dioxide (Van Stee et al., 1981).

Urine:

Elimination studies on male Wistar rats (200-350 g) were carried out by administering morpholine HCl (500 mg/kg bw) or [14C]-labelled morpholine HCl (200 mg/kg bw) orally and morpholine-HCl (250 mg/kg bw) intravenously. In all cases, over 85 % of the total dose was excreted in urine within 24 hours. A further portion, up to 5 %, was excreted during the next three days. 14C morpholine palmitate was eliminated slightly slower, but the urinary excretion within 3 days following oral administration amounted to 90 % of the dose (Tanaka et al., 1978). Of the radioactive morpholine administered to rats, 62 to 77.5 % was excreted in the urine after 24 hours (Griffiths, 1968; Ohnishi, 1984).

The time-course of urinary excretion of 14C by Sprague-Dawley rats, Syrian golden hamsters, and strain II guinea pigs treated with 14C Morpholine was compared by Sohn et al. (1982). In all three species over 80 % of the dose was excreted in 3 days, while the rate of urinary excretion within the first 6 hours was greatest in the hamster and least in the guinea pig.

Van Stee et al. (1981) infused rabbits intravenously with 14C morpholine (5 mmol/kg bw) which had been neutralized with HCl. After 4 hours, 18.5 % of the dose was excreted in the urine. When the pH of the urine was lowered from 7.8 - 7.9 to 7.1 - 7.2 by administration of ammonium chloride (10 g/L) in drinking-water prior to the Morpholine injection, the urinary excretion more than doubled (to 43 %). These data suggest that the urinary excretion of morpholine is enhanced by its neutralization with acid.

14C Morpholine was administered to dogs by an unspecified route. 70 to 80 % of the radioactive morpholine was excreted in the urine, with no other detectable metabolites (Rhodes & Case, 1977).

Faeces:

Rats dosed orally or intravenously with morpholine HCl excreted not more than 1.7 % of the dose in the faeces (Griffiths, 1968; Tanaka et al., 1978). However, when dosed orally with morpholine palmitate (Tanaka et al., 1978; Ohnishi, 1984), up to 7% was excreted in faeces.

Retention and turnover
Plasma concentration-time curves of 14C after intraperitoneal injections of 14C Morpholine (125 mg/kg bw in 0.9% NaCl) in Sprague-Dawley rats, Syrian golden hamsters, and strain II guinea pigs declined biexponentially. Marked differences were noted between the guinea pig and the other two species with respect to plasma levels (as well as the metabolism of Morpholine). Whereas rates of the first phase of elimination from plasma in rats and hamsters were similar (half-lives of 115 and 120 min, respectively), the half-life in guinea-pigs was significantly longer (300 min) (Sohn et al., 1982).

Additional information on Morpholine – nitrosation
In the presence of nitrite, Morpholine can be nitrosated to the carcinogenic N-nitrosomorpholine (NMOR). For instance, NMOR was found in the stomach of rodents whose feed contained nitrite and Morpholine (Sander et al., 1968; Inui et al., 1978; Kitano et al., 1979). Hecht & Morrison (1984) developed a method to monitor the in vivo formation of NMOR by measuring N-nitroso(2 -hydroxyethyl)glycine, its major urinary metabolite. The formation of NMOR was measured in F-344 rats over wide range of doses of Morpholine (38.3 - 0.92 µmol) and sodium nitrite (191 - 4.8 µmol). According to estimates by the authors, 0.5 to 12 % of the administered Morpholine, depending on the dose, was nitrosated. Furthermore, in vitro experiments have demonstrated that nitrosation of Morpholine is also possible in human saliva and in gastric juices (Ziebarth, 1997; Ziebarth, 1973; Boyland et al., 1971).

Acute Toxicity

Acute toxicity: via oral route
Endpoint conclusion
Dose descriptor: LD_{50} 1 900 mg/kg bw
Acute toxicity: via inhalation route
Endpoint conclusion
Dose descriptor: LC_{50} 8 000 mg/m³
Acute toxicity: via dermal route
Endpoint conclusion
Dose descriptor: LD_{50} 500 mg/kg bw
Additional information
Acute toxicity: oral
The acute oral toxicity of Morpholine in the rat was examined in several toxicity studies. In general, oral administration of Morpholine to rats resulted in LD50 values within the range of 1000 to 2000 mg/kg bw (BASF AG, 1969; Shea, 1939; Smyth et al., 1954; Börzsönyi et al., 1981; Huntsman, 1981). Gastrointestinal and nasal haemorrhage were reported as clinical findings following oral Morpholine administration. When Morpholine was administered to 7 male rats at a neutral pH, no deaths occurred at 1000 mg/kg bw (Börzsönyi et al., 1981). In a supporting study on guinea-pigs (Shea, 1939) a lower LD50 of 900 mg/kg bw was observed.

The Huntsman study (1981) indicating LD50=1680 mg/kg bw) is the key-study here. The BASF study from 1967, where a LD50 of ca.1900 mg/kg bw was derived, has been identified as a second key-study. These studies represent the most reliable study. A reliable source of test material was used and the test was done according to a well described BASF method which was in compliance with the principles of OECD Guideline 401. The same holds true for the Huntsman study.

Acute toxicity: dermal
In the key study on acute dermal toxicity (Smyth et al., 1954), necrosis on the clipped skin of albino rabbits was noted within 24 hours of application of undiluted Morpholine. Mortality observed within 14 days after dermal exposure to Morpholine resulted in an LD50 of 0.5 mL/kg bw. Due to the given specific density of Morpholine (1.0 g/cm³) a LD50 of 500 mg/kg bw was derived. In a supporting study (Shea, 1939), the single dermal exposure of rabbits to undiluted, unneutralized Morpholine resulted in irreversible skin injuries and death of some animals.

Acute toxicity: inhalation
Exposure to Morpholine at vapour saturation concentrations resulted in 100% lethality after 5.5 h (BASF AG, 1967). Irritating and corrosive properties were noted. In studies using lower Morpholine concentrations, Lam & Van Stee (1978) obtained LC50 values of 8.2 and 7.8 mg/L for male and female rats, respectively (exposure period was not specified; Fed. Proc., 37: 679, abstract no. 2459: A re-evaluation of the toxicity of morpholine). Other authors reported no deaths at a three times higher dose level (24 mg/L) after an exposure period of 4 hours (ILO, 1972). 9/10 rats died after a single exposure to 18.1 mg/L for 6 hours (Huntsman, 1981). With regard to other species, reported LC50 values for mice are consistently in the range of ca. 5 - 7 mg/L (Lam and Van Stee, 1978). Based on these findings and using a conservative approach (here: reflecting the results of Lam & Van Stee, 1978), a LC50 value of ca. 8.0 mg/L for rat is postulated and used for further calculations.

Justification for classification or non-classification
Classification, Labeling, and Packaging Regulation (EC) No 1272/2008

Based on the results for acute oral (LD_{50} rat ca. 1900 mg/kg bw), acute dermal (LD_{50} rabbit 500 mg/kg bw) and inhalation toxicity (LC_{50} ca. rat 8 mg/L) morpholine is classified as follows: acute toxicity: cat. 4, H302, harmful if swallowed, cat. 3, H311, toxic in contact with skin, and cat. 3, H331, toxic if inhaled (according to Regulation 1272/2008/EC).

Irritation / corrosion

Skin irritation / corrosion
Endpoint conclusion: adverse effect observed (corrosive)
Eye irritation
Endpoint conclusion: adverse effect observed (irritating)
Respiratory irritation
Endpoint conclusion: adverse effect observed (irritating)
Additional information

Skin irritation

With regard to the key- and supporting studies from Huntsman, Morpholine was considered to be highly corrosive (Huntsman 1997, Key-study) and was identified as corrosive dependent on the applied criteria (Huntsman 1986, Huntsman 1993, Huntsman 1997). The corrosive potential of Morpholine was measured by applying 0.1 g mixture (0.1, 0.5, 2, 5 and 10% Morpholine in petrolatum) to guinea-pig skin for 24 h (Wang and Suskind 1988). Observations were made 1, 24 and 48 h after removal of the test materials, and no noticeable effects were found in this supporting study.

In an in-house study classified as second key study, two rabbits were treated for 1, 5, 15 min or 20 h using occlusive conditions. An application site of 2.5 x 2.5 cm was covered with the liquid test substance. The animals were observed for 3 weeks and skin changes were recorded daily account. The application of the test substance for 1 min caused in 1 animal hemorrhagic areas and leathery-like necrosis at the end of the observation period. The application for 5 min caused after 24 h parchment-like necrosis in one animal and hemorrhagic areas after 24 h and leathery-like necrosis after 8 days. The application of the test substance for 15 min caused hemorrhagic areas, edema and parchment-like necrosis after 24 h which declined to leathery-like necrosis after 8 days. Leathery-like necrosis is considered as a full-thickness necrosis (BASF AG XVI). In a further study, noticed as supporting study, rabbits were treated with aqueous solutions of 2, 20, 40 and 60% Morpholine and the skin reactions were evaluated after 0.5, 24, 48 and 72 h. A 2% solution of Morpholine caused skin irritation after 72 h, whereas 40% and 60% solutions immediately caused reddening of the skin (Loden, 1985).

Eye irritation

Eye injury in rabbits was reported in several acute studies. Noticed in an in-house study classified as key study, one drop of undiluted Morpholine in rabbit eyes, repeated once after 5 min, caused oedema, opacity, staphyloma and corrosion of the eye mucous membranes within 24 h (BASF AG XVI). In a further key study it was demonstrated that 0.1 mL of undiluted Morpholine resulted in necrosis in and around the eyes (Koch1985); acting like a corrosive substance. Before these investigations, eye injury in rabbits was tested also by Smyth et al. (1954), who reported severe eye burns with 0.5 mL of a 1% solution Morpholine. With regard to other test animals, in-life clinical examinations in rats exposed to up to 0.54 g/m^3 (150 ppm) Morpholine revealed increased incidences in inflammation of the cornea at week 103 of a chronic inhalation study (Huntsman 2147-102, cf. 7.5.3). Findings included keratitis, oedema, abrasion, scarring, and ulceration with or without neovascularization and corneal epithelial hyperplasia. A high incidence of retinal degeneration was observed, primarily in female animals, which was probably an age-related light-induced retinal degeneration.

Respiratory irritation

Studies of acute inhalation toxicity of Morpholine revealed irritation of the mucous membranes. In a key study there is indication that the test substance causes local irritation to exposed tissues including respiratory tract (BASF AG XVI/352, cf. 7.2.2). A supporting study noticed irritation of nose and eyes (mucous membranes) after exposure of rats to Morpholine for 6 hours to whole body at a nominal concentration of 5000 ppm equivalent to ca. 18.1 mg/L; 9/10 animals died after one treatment (Huntsman 2147-100, cf. 7.2.2).

Effects on skin irritation/corrosion: corrosive
Effects on eye irritation: corrosive
Effects on respiratory irritation: irritating

Justification for classification or non-classification
Classification, Labeling, and Packaging Regulation (EC) No 1272/2008

The available experimental test data are reliable and suitable for the purpose of classification under Regulation (EC) No 1272/2008. Based on these information the test item is considered to be classified for skin and eye irritation cat. 1A and cat. 1, respectively under Regulation (EC) No. 1272/2008, as amended for the tenth time in Regulation (EU) No 2017/776.

However, as the substance is already listed in Annex VI of Regulation (EC) No 1272/2008 concerning skin and eye irritation (cat. 1B, H314), the harmonized classification is used.

Sensitisation

Skin sensitisation

Endpoint conclusion:	no adverse effect observed (not sensitising)

Additional information:
Since morpholine is alkaline and is corrosive to skin and mucous membranes, a sensitisation study does not need to be conducted in accordance with column 2 of REACH Annex VII.

However, the sensitizing potential of morpholine was tested on 10 guinea pigs by Buehler's method (Wang & Suskind, 1988). Morpholine (2 % in vaseline) proved not to be skin sensitizing. In an in vitro experiment with limited reliability it was investigated whether or not morpholine, being a haptene, reacts with amino acids, thereby unfolding a sensitizing action. No reaction occurred with either lysine, cysteine or glycine (Wang & Tabor, 1988).

Migrated from Short description of key information:
In accordance with column 2 of REACH Annex VII, a sensitisation study does not need to be conducted because the substance is classified for skin corrosivity. Given as supplementary information, no skin sensitization was seen in an animal study with guinea pigs tested with a 2% solution of morpholine.

Respiratory sensitisation

Endpoint conclusion

Additional information: Migrated from Short description of key information:
There are no human data available indicating a respiratory sensitisation potential.

Justification for classification or non-classification

Classification, Labeling, and Packaging Regulation (EC) No 1272/2008

Morpholine is classified for skin corrosivity. Thus, in accordance with column 2 of REACH Annex VII, a sensitisation study does not need to be conducted. There are data available indicating no dermal sensitisation potential of Morpholine. Based on the results of the skin sensitisation study (no skin reactions after challenge with a 2% solution of test substance in vaseline), morpholine is not subject to classification as dermally sensitizing substance according to Regulation 1272/2008/EC.

Repeated dose toxicity

Repeated dose toxicity: via oral route - systemic effects

Endpoint conclusion

Dose descriptor:	LOAEL	500 mg/kg bw/day

Repeated dose toxicity: inhalation - systemic effects

Endpoint conclusion

Dose descriptor:	NOAEC	36 mg/m³

Additional information

Repeated dose toxicity: oral:

In a repeated dose toxicity study on Sprague-Dawley rats, Morpholine was added to feed for eight weeks (Sander & Bürkle, 1969). Seven rats took in a daily average of 500 m/kg bw. This dosage did not kill the animals. After 270 days had elapsed, the only symptom noted was moderate adiposis of the liver. The oral toxicity of Morpholine was evaluated before (Shea, 1939). In a subacute study on rats damage to liver, kidneys and stomach mucosa first appeared after intake of approx. 160 mg/kg bw. Intake of 800 mg/kg bw caused the death of 10 out of 20 rats within 20 days. At the end of 30 days, only 1 rat was still alive. Eventual effects caused by subchronic oral intake of Morpholine depended markedly on the individual dose and route of administration.

In a subchronic study Morpholine oleic acid salt (MOAS) was applied to mice for 13 weeks (Shibata, 1987). The dose levels of MOAS used were 0, 0.15, 0.3, 0.6, 1.25, and 2.5 % in drinking water (approximately 0, 70, 140, 200, 400 and 700 mg/kg bw/d). It seems that a dose equivalent to approx. 200 mg/kg bw/day impaired renal activity, as evidenced by the rise in the blood urea and the specific gravity of the urine. Approximately 700 mg/kg bw/day caused swelling of the proximal renal tubules (no further treatment-related histopathological alterations were observed in organs of either sex). Due to the given data, a LOAEL of 500 mg/kg bw/day is derived for oral repeated toxicity.

Repeated dose toxicity: dermal
Shea (1939) assessed the dermal toxicity and skin absorption of Morpholine in one investigation using rabbits. Unneutralized, diluted Morpholine (1 part Morpholine, 2 parts water) was applied at a daily dose of 900 mg/kg bw to the clipped skin. All rabbits (7/7) died before the eleventh dose. Necrosis of the treated skin, and inflammation and congestion of the underlying organs were evident upon gross examination. Microscopic lesions of the liver and effects on kidneys and spleen were observed.

Repeated dose toxicity: inhalation
Rats were exposed by inhalation to 18,000 ppm Morpholine. Exposures were nominal 8 hours a day for five days. Irritation of the eyes, nose and thoracic walls were registered. Some animals died during the study period. In animals that died after 5 days repeated exposure to ca. 65 g/m³ Morpholine, lung haemorrhage, severe damage to the secreting tubules of the kidney, and fatty degeneration of the liver were noted (Shea1939).

Twenty male Wistar rats were exposed intermittently to 300 ppm (12.5 µM/L) Morpholine vapour 5 days a week for 6 h daily during 4-15 weeks. The animals were killed after 4, 8, 12 or 15 weeks, and brain and perirenal fat samples taken. The specimens were analyzed for Morpholine content by gas chromatography. All exposed rats appeared similar to controls; weight gain of treated animals was similar to that of nontreated controls. Concentrations of Morpholine in the brain increased towards the end of the exposure period. Fat morpholine concentrations were a fraction of those detected in brain; a decreasing trend was discernible after 8 exposure weeks. Axonal succinate dehydrogenase activity of the test group was below the control group after 15 weeks. The muscle acetylcholine esterase activities were above the control level in the test group after 8 weeks and decreased to the level of the control group after 15 weeks. With regard to the concentrations in the brain, the authors (Savolainen & Rosenberg, 1983) postulated that the “metabolic clearance is saturated” in case of Morpholine.

The induction of lysosomal enzymes by Morpholine were examined in rabbits. Two acid hydrolases, alpha-mannosidase and acid phosphatase, were induced in the lung alveolar macrophages during the course of inhalation exposure (905 mg/m³, 250 ppm, 6 h/day, 5 days/week for a total of 33 exposures). The induction was also observed when macrophages were cultured in the presence of Morpholine (Tombropoulos, 1983).

Grodeckaja and Karamzina (1973) evaluated thyroid function as an indicator of Morpholine toxicity. In an inhalation study male rats were exposed to 0.08 g Morpholine/m³, 4 hours/day for 2, 4, or 8 days. Then iodine-131 was administered and thyroid gland uptake of iodine-131 was measured over 48 hours. Treated rats accumulated a larger amount of iodine-131 compared to control animals after 4 days exposure, indicating increased thyroid gland activity. Microscopic examination of the thyroid gland indicated hypersecretion by thyroid cells. As a main result increased thyroid activity was observed in rats.

In a two-year chronic inhalation study (Huntsman, 1983), male and female rats that inhaled Morpholine at concentrations of 0, 10, 50, or 150 ppm (0, 36, 181 or 543 mg/m³), 6 hours/day, 5 days/week for 104 weeks showed normal growth, survival, hematology, and clinical chemistries.The incidence of neoplasia in morpholine-exposed rats was not altered significantly compared to the concurrent controls. Rats exposed at the 150 ppm concentration developed focal erosion and focal squamous metaplasia of the epithelium of the anterior nasal cavity. Obvious evidence of chronic nasal irritation and inflammation with neutrophilic infiltration was documented in these same tissues. Ocular injury, including retinal degeneration, corneal irritation, uveitis, and corneal damage, were demonstrated only in rats exposed at 150 ppm. The distribution of ocular changes recorded in the groups exposed at 10 or 50 ppm Morpholine was similar to that seen in the controls. Chronic exposure of rats to morpholine for 2 years at concentrations of 150 ppm or less revealed no carcinogenic potential or chronic systemic toxicity. Consistent with its known irritating properties, Morpholine produced only local irritation, which was limited almost exclusively to high-dose animals.

In a previous subchronic inhalation study (Conaway, 1984), rats inhaled Morpholine at concentrations of 0, 25, 100, and 250 ppm. None of the animals died or were sacrificed in extremis during the study. No treatment-related trends or findings were apparent in either sex for haematology, clinical chemistry and gross pathology. Exposure to Morpholine at 250 ppm for 13 weeks confirmed the result, seen at week 7, of focal erosion of the maxillary turbinates accompanied by the presence of necrotic cell debris and focal squamous metaplasia. Lesions were then noted involving the nasal septum and anterior nasal cavities. Lesions of chronic murine pneumonia were also increased in severity in rats of the high-level group. A maximum tolerated dose (MTD) of 150 ppm was established on the basis of the nasal irritation. The subchronic study of Conaway (1984) is based on a range-finding study, Rats inhaling morpholine at 3.62 or 18.1 g/m³ for 9 days, 6 h per day, died within the exposure period (Huntsman, 1981d). At lower concentrations (1.81 g/m³), weight loss and irritation to nose and eyes, as well as two deaths, were reported. It was concluded that the maximal tolerated dose for rats is about or just below 0.3 g/m³.

This author demonstrated also in a subchronic inhalation study with rats that none of the animals died or were sacrificed in extremis during the study and no treatment-related findings were apparent in either sex for haematology, clinical chemistry and gross pathology. Thus, a maximum tolerated dose (MTD) of 150 ppm was established on the basis of nasal irritation (Huntsman, 1981c).

The 2-year chronic inhalation study of Huntsman (1983) is considered to be the best available base for setting of relevant toxicological parameters.Based on this study, a systemic NOEC of 181 mg/m³ (50 ppm) and a local NOEC of 36 mg/m³ for repeated dose toxicity is derived.

Repeated dose toxicity: inhalation - systemic effects (target organ) respiratory: nose

Justification for classification or non-classification
Classification, Labeling, and Packaging Regulation (EC) No 1272/2008
Based on the results of the chronic dose toxicity study with special regard to specific target organ toxicity after repeated inhalation exposure, morpholine is not subject to classification and labelling according to Regulation 1272/2008/EC.

Genetic toxicity
Genetic toxicity testing of Morpholine produced mostly negative findings as well as borderline positive findings.

Morpholine was tested for mutagenicity in vitro in the Ames test with and without metabolic activation. In the key reverse gene mutation assay (BASF AG, 1981), Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 and Escherichia coli WP2 were exposed to 0, 15.8, 50, 158, 500, 1580, 5000, 15800, 31600 or 50000 µg/plate in the standard plate test (plate incorporation method). Higher doses were tested, but were too cytotoxic. Slight increases in the number of revertants were observed at 50000 µg/plate with TA100 in the presence and absence of S9 mix and with WP2 uvrA only with metabolic activation. Morpholine exposure at 0.5, 1.0, 1.5 or 2.5 mL/20 L by means of the desiccator method did not reveal mutagenicity of Morpholine at any dose. Morpholine (or possibly an impurity) was weakly mutagenic in the Ames test at a concentration of 50000 µg/plate. However, the observed increase in the number of mutants at this relatively high dose was not more than 2-fold. Therefore, this test result is considered as ambiguous. The positive controls induced the appropriate responses in the corresponding strains. An Ames test reported by Haworth et al. (1983) was considered as supporting study as well as a test by Huntsman (1979). Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 were exposed to Morpholine at concentrations of 0, 109, 363, 1090, 3633 or 10900 µg/plate in the preincubation assay. Morpholine was tested up to slightly cytotoxic concentrations (10900 µg/plate). The positive controls induced the appropriate responses in the corresponding strains. In this study (and in the study by Huntsman, 1979), there was no evidence of a concentration-related positive response of induced mutant colonies over background.

In a key mouse lymphoma mutation assay with L5176Y TK +/- cells (Huntsman, 1979), the mutagenic potential of Morpholine was assessed in vitro at concentrations up to 1.25 µL/mL in the presence and absence of metabolic activation (S9 mix). This assay was repeated and in an additional assay concentrations from 1.2 to 2 µL/mL were tested. The positive controls induced the appropriate responses. The test material induced small increases in the mutation frequency over the applied concentration range of 0.625 to 1.25 µL/mL under non-activation conditions. These treatments were highly toxic and the mutant frequency increases (approximately 2.5 -fold) were at the limit of detectability for this assay with microsomal activation; concentrations up to 1.0 - 1.25 µL/mL were not very toxic and not detectably mutagenic; concentrations from 1.2 - 1.5 µl/mL were excessively lethal. Under the conditions of this study, Morpholine was considered to be very weakly mutagenic in the assay without metabolic activation. In a supporting study (Huntsman, 1979), Morpholine is considered to be active in the BALB/3T3 in vitro transformation assay.

In a key in vitro sister chromatid exchange assay (Huntsman, 1980), Chinese hamster ovary cells were treated with Morpholine at concentrations of 3.13, 6.25, 12.50, 25.00, 50.00 or 100.00 nL/mL in the presence and absence of mammalian metabolic activation (S9 mix). Positive control items induced the appropriate responses. The maximum increases in sister chromatid exchange noted were only 25 % and 22 % with and without S9 mix, respectively. In the absence of a positive dose response these results indicated a very weak, or negative, response. Morpholine did not cause a meaningful increase in sister chromatid exchange under the conditions of this assay.

Morpholine was tested in vitro in a rat hepatocyte primary culture (HPC/DNA Repair Assay) at concentrations of 0.00001, 0.0001, 0.001, 0.01, 0.1 or 1% (Huntsman, 1982). Positive control items induced the appropriate responses in this key study. Under the conditions of this assay, Morpholine did not induce DNA repair over background at the highest non-toxic doses and lower doses.

In an in vivo transplacental mutagenesis study (Inui et al., 1979), sodium nitrite with Morpholine or Morpholine (500 mg/kg bw) alone were administered by single oral gavage to pregnant Syrian golden hamsters on day 11 or 12 of pregnancy. Twenty-four hours after treatment, the hamster embryos were excised and examined for chromosomal aberrations, micronucleus formation, morphological or malignant transformation and drug resistance mutation. Cells exposed in utero to Morpholine showed no increases in the numbers of chromosomal aberrations, micronuclei, 8-azaguanine- or ouabain-resistant mutants, or transformation rates. The number of resistant colonies was markedly increased after administration of sodium nitrite together with Morpholine only, showing that Morpholine alone displayed no mutagenic activity in vivo under the conditions of this study.

Short description of key information:
Morpholine was not mutagenic in several key or supporting in vitro mutagenicity studies (Hawoth et al., 1983; Huntsman, 1980; Huntsman, 1982) and in a key in vivo mutagenicity study (Inui et al., 1979). However, ambiguous results or borderline mutagenicity were noted in a key Ames test (BASF AG, 1981) and a key mouse lymphoma mutation assay (Huntsman, 1979), respectively, at high and/or cytotoxic doses. Taking the overall evidence into account and with special regard to the partially equivocal findings at high doses in vitro, Morpholine is not considered to be mutagenic.

Endpoint Conclusion: No adverse effect observed (negative)

Justification for classification or non-classification
Classification, Labeling, and Packaging Regulation (EC) No 1272/2008
Considering the ambiguous or negative results observed in the Ames test, the borderline mutagenicity noted in a mouse lymphoma assay, and the negative findings in a sister chromatid exchange assay, a DNA repair assay and in a transplacental mutagenesis study including evaluation of micronuclei and chromosomal aberrations, morpholine is not subject to classification for mutagenicity according to Regulation 1272/2008/EC.

Additional information
In a key combined chronic/carcinogenicity study (Harbison et al., 1989), morpholine (99.2 %) was administered by whole body inhalation exposure to Sprague-Dawley rats at mean concentrations of 0, 36, 181 or 543 mg/m^3 (6 h/day, 5 days/week) for 52 weeks (10 animals/sex/group) or for 104 weeks (60 animals/sex/group). No treatment-related changes in mortality, body weights, organ weights, or clinical pathology parameters were observed. Ophthalmoscopic examinations at week 103 revealed signs of eye irritation. Histological findings were limited to ocular and anterior nasal cavity effects, consistent with the known irritating properties of morpholine. At the doses tested, there was no evidence of increased incidence of carcinogenesis due to chronic morpholine inhalation. Since only local effects were noted, under the conditions of this study, the NOAEC was >543 mg/m^3 for both carcinogenicity and toxicity.

Carcinogenicity
In a supporting carcinogenicity study (Kitano et al., 1997), the effects of dietary morpholine administration at a dose level of 0.5 % (approx. 220 mg/kg bw) to male Fischer 344 rats (10 or 20 animals/group) were investigated for a period of 23 weeks (i) in combination with sodium nitrite given in the drinking water following an initiation phase, (ii) without sodium nitrite following an initiation phase and (iii) in combination with sodium nitrite without initiation phase. In an additional experiment, male Fischer 344 rats (14 or 5 animals/group) received a dietary treatment with morpholine (2.0 %) for 1 hour with subsequent administration of sodium nitrite for determination of N-nitroso compounds in the stomach and to detect DNA adduct generation. Both experiments were run with concurrent control groups. Morpholine alone was not tested. The initiation treatment decreased the body weight of rats compared to non-initiated groups. The group that was initiated and received sodium nitrite in the drinking water and morpholine in the diet was significantly lower in body weight than the group that was only initiated. However, the liver and kidneys weights were increased. The combination of initiation followed by sodium nitrite and morpholine caused an increase in the number and area of GST-P positive liver foci as compared to the group that was only initiated, indicating that morpholine plus sodium nitrite, but not morpholine alone, has a tumour promoting effect. Treatment with morpholine or morpholine plus sodium nitrite did not clearly lead to an increased tumour incidence. No tumours were induced by morpholine plus sodium nitrite in the absence of initiation. The mean N-nitrosomorpholine yield in the group given morpholine plus sodium nitrite was 6720 µg. No DNA adducts related to morpholine treatment were detected immunohistochemically.

Overall, there was no evidence of carcinogenic activity of morpholine.

Justification for classification or non-classification
Classification, Labeling, and Packaging Regulation (EC) No 1272/2008
Since there is no evidence for a carcinogenic potential, morpholine is not subject to classification as being carcinogenic

according to Regulation 1272/2008/EC.

Toxicity to reproduction
Effects on fertility
Additional information
In several subchronic and subacute studies no apparent adverse effects on reproductive organs were observed in rats (Conaway et al., 1984; Sander & Bürkle, 1969; Shea, 1939). Inhalation exposure of rats to 900 mg/m³ for 13 weeks resulted in inflammation in mouth and nose; after 7 weeks, focal metaplasia and necroses in nose muscles of 8/40 animals were seen; these findings were intensified after 13 weeks and lesions of chronic murine pneumonia were registered. Organs and tissues examined at necropsy included brain, adrenals, lungs, heart, liver, spleen, kidneys, testes, ovaries, and nasal cavity (Conaway et al. 1984).

In a subchronic trial on rats damage to liver, kidneys and stomach mucosa first appeared after intake of approx. 160 mg/kg bw (Shea, 1939). Observations of rats treated with 800 mg/kg bw included lethargy, weight loss, intense irritation of the intestinal tract, and congestion of the stomach wall and membrane. Microscopic changes in the liver included cloudy swelling, marked congestion, haemorrhage, necrosis, and an increase in Kupffer and connective tissue cells. The kidneys had tubular congestion, degeneration, swelling and necrosis; desquamation of the epithelium also was noted. The spleens of the 800 mg/kg bw group had congestion and showed an increase in splenocytes and hemosiderin deposits. Necrosis of the epithelium and capillary congestion were observed in the stomach. The lungs had congestion and alveolar desquamation. Intake of 800 mg/kg bw caused the death of 10 out of 20 rats within 20 days. At the end of 30 days, only 1 rat was still alive.

Sander & Bürkle (1969) added Morpholine to feed for eight weeks. Seven rats took in a daily average of 500 mg/kg bw. This dosage did not kill the animals. After 270 days had elapsed, the only symptom noted was moderate adiposis of the liver. Damage caused by subchronic oral intake of Morpholine depended markedly on the individual dose and route of administration.

Due to its corrosivity, Morpholine treatment resulted in irritation and inflammation of the upper digestive tract on oral intake, irritation of the respiratory tract and eyes on being inhaled and, in high concentrations, irritation on contact with the skin. Possible target organs of chronic intoxication were the liver, kidneys and stomach.

Because of a high correlation, histopathology data and organ weights from repeated dose studies were used to assess male fertility (Mangelsdorf, 2003). These parameters, taken from 90 day studies, were in fact shown to be more sensitive than fertility parameters that were measured during multi-generation studies. It could also be shown that exposure for 4 weeks suffices for an assessment of male fertility, although 90 day studies have been regarded as superior in the past because they cover a complete cycle of spermatogenesis (Mangelsdorf, 2003). If such a 28 day study shows neither relevantly elevated testis or ovary weights nor histopathological alterations in those organs, the weight of the evidence is that effects on reproduction are also not expected (BAuA, 2003). A comparison of more than one hundred 90 day studies with two-generation studies that used the same test substance additionally showed that the NOAELs differed by less than the variation limit of studies, i.e. a factor of two (Janer, 2007).

Based on the argumentation of Mangelsdorf (2003), the information gained from a two-generation study can be regarded as minimal if a 90 day study has been performed. Thus, based on the data presented for Morpholine, information gained from a two-generation study are regarded as not necessary with regard to the fact that REACH allows the assessment of the reproductive toxicity of a given chemical with the help of findings from studies with repeated administration. This is in line with the idea that the information requirements under REACH are regarded as the evaluation of endpoints which does not necessarily require data from specific studies.

Short description of key information:
Since REACH allows the assessment of the reproductive toxicity of a given chemical with the help of findings from studies with repeated administration, studies available for Morpholine were incorporated to elucidate effects on fertility. No apparent adverse effects on reproductive organs were observed in rats in several subchronic and subacute studies with Morpholine.

Effects on developmental toxicity
In a developmental toxicity study with Morpholine hydrochloride (97 %) at doses of 75, 250 and 750 mg/kg bw/d applied orally to rats, no adverse fetal findings of toxicological relevance were evident. The developmental NOAEL was determined as 750 mg/kg bw/day, whereas the maternal NOAEL was 75 mg/kg body weight/day based on statistically significant haematological changes in the dams at 250 and 750 mg/kg bw/day.

Effect on developmental toxicity: via oral route
Dose descriptor: NOAEL 750 mg/kg bw/day

Additional information
Listed as read across study, Morpholine hydrochloride (97% a.i.) was administered as an aqueous solution to 25 time-mated female Wistar rats (Crl:WI[Han]) by gavage at doses of 75, 250 or 750 mg/kg bw/day on gestation days 6 through 19 in a developmental toxicity study. The control group, consisting of 25 females, was dosed with the vehicle (drinking water) in parallel. A standard dose volume of 10 mL/kg bw was used for each test group. At terminal sacrifice on GD 20, all females (25 per group) had implantation sites. The oral administration of 250 and 750 mg/kg bw/d caused a mild, regenerative anaemia in the dams, along with increased liver weights. Additionally, transiently reduced mean food consumption and bw gain as well as affection of liver cells and liver cell metabolism were noted at high dose. The oral administration of Morpholine hydrochloride to the dams up to 750 mg/kg bw/d had no influence on gestational parameters. Conception rate, mean number of corpora lutea, total implantations, resorptions and live foetuses, foetal sex ratio, and the values calculated for pre- and postimplantation losses were all unaffected. The maternal NOAEL was 75 mg/kg bw/day based on statistically significant haematological changes in the dams at 250 and 750 mg/kg bw/day. Foetal examinations revealed no influence of Morpholine hydrochloride on sex distribution of the foetuses and foetal body weights. Morpholine hydrochloride showed no direct and specific effect on the respective morphological structures. Foetal findings in this study were primarily limited to a slight increase in delayed ossification in the mid- and high-dose groups. These specific skeletal variations mirrored common minor effects on foetal morphology which are considered to be transient in nature, being obviously secondary to maternal toxicity. Thus, these findings were regarded to be of no toxicological relevance and were not classified as adverse events. The developmental NOAEL was 750 mg/kg bw/day. No adverse foetal findings of toxicological relevance were evident at any dose.The developmental toxicity study is classified as acceptable and satisfies the guideline requirement for a developmental toxicity study (OECD 414) in rat.

Justification for classification or non-classification
Classification, Labeling, and Packaging Regulation (EC) No 1272/2008
Since morpholine hydrochloride caused no developmental toxicity and teratogenicity in the rat in a developmental toxicity study according to OECD TG 414 and no apparent adverse effects on reproductive organs or fertility were observed in rats in several subchronic and subacute studies with morpholine, morpholine is considered not to cause damage to the unborn child and is not subject to classification according to Directive 67/548/EEC and Regulation 1272/2008/EC.

Numerical measures of toxicity (such as acute toxicity estimates)

Organism	Test Type	Route	Dose	Effect
rat	LD_{50}	oral	1450 mg/kg (1450 mg/kg)	
rat	LC_{50}	inhalation	8000 ppm/8H (8000 mg/kg)	
rat	LD_{Lo}	unreported	1600 mg/kg (1600 mg/kg)	
mouse	LD_{50}	oral	525 mg/kg (525 mg/kg)	BEHAVIORAL: SLEEP
mouse	LC_{50}	inhalation	1320 mg/m3/2H (1320 mg/kg)	SENSE ORGANS AND SPECIAL SENSES: LACRIMATION: EYE
mouse	LD_{50}	intraperitoneal	413 mg/kg (413 mg/kg)	
mouse	LD_{50}	subcutaneous	458 mg/kg (458 mg/kg)	
rabbit	LD_{50}	skin	500 uL/kg (0.5 mg/kg)	
guinea pig	LD_{Lo}	oral	100 mg/kg (100 mg/kg)	SENSE ORGANS AND SPECIAL SENSES: OTHER CHANGES: OLFACTION
mammal (species unspecified)	LD_{50}	oral	1220 mg/kg (1220 mg/kg)	

mammal (species unspecified)	LC_{50}	inhalation	12000 mg/m3 (12000 mg/kg)	

Interactive effects

A group of seven female Sprague-Dawley rats /were fed/ 5 g morpholine together with 5 g nitrite/kg diet for 12 weeks. After 39 weeks, all of the animals developed hepato-cellular adenomas, six out of the seven hepatocellular carcinomas, two hemangioendotheliomas of the liver, one a cyst-adenocarcinoma of the liver, and one a renal adenoma. Rats fed morpholine or nitrite alone did not develop tumors.

Pregnant rats /were fed/ on a diet containing various concentrations of morpholine, sodium nitrite, and NMOR (N-nitrosomorpholine). Hepatocellular carcinoma and hemangio-sarcomas of the liver and angiosarcoma of the lungs were the most common tumors observed in the rats. The neoplasms induced by nitrite and morpholine were morphologically similar to those induced by NMOR. High concentrations (1000 mg/kg) of morpholine and nitrite together were carcinogenic to rats. When the morpholine concentration was reduced and the nitrite concentration remained high, the incidence of hepatic cell carcinomas decreased with a linear dose-response relationship. When morpholine concentration remained high, with decreasing nitrite concentration, the number of hepatic tumors was sharply reduced. This agrees with the observation in vitro that the nitrosation of morpholine depends on the square of the nitrite concentration.

Groups of 40 male MRC Wistar rats were treated for 2 yr with either 10 g morpholine/kg diet and drinking-water containing 3 g sodium nitrite/L, or with drinking-water containing 0.15 g NMOR/L. In both cases, one group of rats was also given sodium ascorbate (22.7 g/kg diet). The results of treatment with morpholine plus nitrite or with NMOR were similar to those reported /in the feeding experiments/. When ascorbate was present, the liver tumors induced by morpholine plus nitrite had a longer induction period (93 vs 54 weeks) and a slightly lower incidence (49% vs 65%). However, ascorbate did not affect liver tumor induction by preformed NMOR. Of those treated with morpholine, nitrite, and ascorbate, 21/39 animals developed forestomach tumors. In a similar study using Syrian hamsters, a high morpholine, high nitrite diet (1000 mg/kg) induced liver cancer in some animals. In contrast, hamsters fed NMOR in the diet seemed to have greater resistance to tumor induction.

Bis(2,2-dimethyl-4-methanesulfonic acid sodium salt-1,2-dihydroquinoline)-6,6'-methane (MIDQ-DA) inhibited liver necrosis induced in rats by simultaneous admin of morpholine and sodium nitrite.

Groups of 3-5 mice were gavaged with aq soln of 2 mg morpholine and immediately exposed to 2-50 ppm levels of nitrogen dioxide in inhalation chambers for about 3 hr. After exposure, mice were frozen and pulverized, aliquots of the frozen specimens were analyzed for N-nitrosomorpholine. N-nitrosomorpholine yields in test mice were time-dependent with respect to duration of nitrogen dioxide exposure and dose-dependent with respect to nitrogen dioxide levels. These studies demonstrate the in vivo nitrosating potential of nitrogen oxides.

Morpholine (10 g/kg) in the diet and sodium nitrite (2 g/L) in the drinking water were admin for life to rats without (group 1) or with (group 2) sodium ascorbate (22.7 g/kg) in the diet. Group 2 showed a lower liver tumor incidence with a longer latency than group 1, indicating a 78% inhibition by morpholine of in vivo N-nitrosomorpholine formation. The incidence of forestomach papillomas was 3% in group 1, 38% in group 2 and 8% in control group.

Sea buckthorn juice which was diluted to be suitable for drinking blocked the nitrosation of morpholine in a model system simulating the human stomach condition. The blocking effects of the juice were 95.8%, 91.1% and 72.7% respectively when incubated for 30 min, 1, and 2 hr whereas ascorbic acid solution of the same concentration as the juice gave 88.3%, 79.9% and 52.5% of blocking respectively. The better blocking effect of the juice suggested that there might be some other blocking substances besides ascorbic acid in sea buckthorn juice.

The effects of feeding methylurea (MU) or morpholine (Mor) plus sodium nitrite (NaNO2) were investigated using a multi-organ carcinogenesis model. In experiment 1, to intiate multiple organs, groups of 10 or 20 male F344 rats were treated with 6 carcinogens targeting different organs. Starting a week after completion of this initiation phase, animals were given 0.1% MU or 0.5 Mor in their food and/or 0.15% NaNO2 in their drinking water for 23 weeks. The induction of tumors and/or preneoplastic lesions in the forstomach and esophagus was significantly increased in the group receiving MU plus NaNO2. The numbers and areas of liver glutathione S-transferase placental form (GST-P)-positive foci were significantly elevated with MU or Mor plus NaNO2. Experiment 2 was conducted to assess formation of N-nitroso compounds in the stomach, and to detect DNA adduct generation in target organs by immunohistochemical staining. Groups of 5 or 14 animals were starved overnight, then given 0.4% MU or 2.0% Mor in diet, or basal diet alone for 1 hr. Then NaNO2 or distilled water was given intragastrically. The mean gastric N-methyl-N-nitrosourea yield in the MU plus NaNO2 group was 7700 micrograms at 2 hr after combined administration. The mean N-nitrosomorpholine yield in the group given Mor plus NaNO2 was 6720 micrograms. Immunohistochemically, N7-methyldeoxyguanosine-postive nuclei were evident in the forestomach epithelium at 8 h after the combination treatment with MU plus NaNO2.

Groups of male MRC Wistrar rats were treated for 2 years either with morpholine (10 g/kg food) together with sodium nitrite (3 g/L drinking water) or with N-nitrosomorpholine (NM, 0.15 g/L drinking water). In both cases, a group of rats was given sodium ascorbate (22.7 g/kg food) in addition to these treatments. When ascorbate was present, the liver tumors induced by morpholine and nitrite showed a 1.7-fold longer induction period, a slightly lower incidence, and an absence of metastases in the lungs, indicating that ascorbate had inhibited the in vivo formation of NM. Ascorbate did not affect liver tumor induction by the preformed NM. The group treated with morpholine, nitirite, and ascorbate had a 54% incidence of forestomach tumors, including an 18% incidence of squamous cell carcinomas possibly because ascorbate promoted NM action in this organ.

The possibility of N-nitrosomorpholine formation was investigated in mice treated with morpholine and then exposed to 45 ppm nitrogen dioxide in an inhalation chamber for 2 hr. Following this treatment, the mice were frozen and pulverized in liquid nitrogen and concentrated extracts from the powders of these animals were analyzed for N-nitrosomorpholine using a thermal energy analyzer interfaced to a gas chromatograph. The data indicate the nitrogen dioxide exposure causes the nitrosation of morpholine in vivo.

Male CD-1 mice were exposed to a nominal concentration of 20 ppm of 15N-nitrogen dioxide (15NO2) for 6 hr/day for 4 days and for 2 hr on the day 5, and to 1 g morpholine/kg body wt by gavage daily for five consecutive days. N-Nitrosomorpholine (NMOR) was found in whole mice, stomach, skins with hair, and remains. The sum of individual tissue concentrations measured separately was 3421 ng/tissue, where the average skin weighed 4.3 g, the average stomach weighed 1.0 g and the average remains weighed 22.2 g. The average whole mouse weighed 27.7 g and contained a total of 3903 ng of NMOR. The concentration of NMOR was highest in the skin, next highest in the stomach, and lowest in the remains. However, the total quantity of NMOR per tissue, while highest in the skin (83%), was next highest in the remains (14.8%) and lowest in the stomach (2.2%). GC-MS analysis served to distinguish between the NMOR of 15NO2 origin and that of other origin. All of the NMOR in the whole mouse homogenates was identified as 15NMOR. In the stomach 73% was identified as 14NMOR, representing 1.6% of the total NMOR in the mouse, and 27% as 15NMOR, representing 0.6% of the total NMOR in the mouse. N-Nitrosamine formation in vivo is discussed as a possibly ongoing mammalian process.

Studies have been done in mice with morpholine in conjunction with nitrites and N-nitroso compounds. Morpholine alone did not induce lung tumors; however, other tissues were not studied. A recent feeding study with rats and hamsters, again with nitrite and N-nitrosomorpholine, included morpholine alone as a control. Rats fed morpholine alone had a low number of tumors that were similar to those in the nitrite-morpholine group. The base line controls had none.

Hamster embryos were exposed in utero to the action of sodium nitrite (NaNO2) and morpholin (Mo) administered simultaneously by stomach tube to the mothers on the 11th or 12th day of pregnancy. Embryo cells were examined for chromosomal aberrations, micronuclear formation, morphological or malignant transformation and drug resistance mutations. For detection of induced mutations, the embryo cells were cultured in normal medium for 72 hr and then transferred to medium containing 10 or 20 micrograms/mL of 8-azaguanine (8AG) or 1m7 ouabain (Oua). The number of 8AG-, Ouaresistant colonies was markedly increased after administration of NaNO2 and Mo. The embryonic fibroblasts also showed a markedly increased frequency of micronulceation and a slight increase in chromosome aberrations. This treatment also caused morphological or malignant transformation of fetal cells. After cultivation in vitro, cells from some transformed colonies produced tumors when inoculated into the cheek pouch of young golden hamsters. Orally administered N-nitroso-morpholine (N-Mo), as a positive control, had the same transplacental biological actions on embryonic fibroblasts. However, transplacentally Mo alone was ineffective. A single administration of 500 mg/kg NaNO2 had only slight biological effects. N-Mo was produced in the stomachs of animals treated simultaneously with NaNO2 and Mo. A small amount of a nitrosamine, N-nitrosodimethylamine (DMN), was detected in the stomach after a single dose of NaNO2.

Male Wistar rats exposed intermittently to 300 ppm (12.5 umol/L) morpholine vapor 5 days/wk for 6 hr daily during 4-15 wk displayed an increased brain solvent content. The morpholine-induced effects were less remarkable than the treatment combining sodium nitrite. The results point at pharmacokinetic interaction between the solvent and nitrite with its own effects on energy metabolism. No N-nitrosomorpholine was found, although other metabolic interactions could not be excluded.

Morpholine can be easily nitrosated to form N-nitrosomorpholine (NMOR), the mutagenicity of which is well documented.

Morpholine, given sequentially with nitrite or nitrate, was mutagenic in a host-mediated mutagenicity assay using Salmonella typhimurium TA1950 as a genetic indicator system.

Two mouse peritoneal cavity host-mediated assays with S. typhimurium have been performed. In one, with strain TA1530, different morpholine doses were administered orally to mice simultaneously with a standard sodium nitrite dose of 120 mg/kg. The mixtures were adjusted to pH 3.4. Significant increases in the mutant fraction were observed with morpholine doses of 4-40 mg/kg, the full range tested. In the other assay, with strain TA1950, equimolar mixtures of morpholine and sodium nitrite (1450 or 2900 umol/kg, approximately 125 or 250 mg/kg) were administered orally to mice (pH 7.0). Significant increases in the mutant fraction were observed at both dose levels. When the nitrite was administered to the mice 10 min before the morpholine treatment, no mutagenic response was induced.

Mutations were found in S. typhimurium TA1535 used to test the urine of OF1 mice after morpholine (250 mg/kg bw) had been administered in the presence of nitrate (2000 mg/kg). Lower levels of nitrate (333 and 666 mg/kg) caused no mutations.

Where specific chemical data are not available

No further information available.

Mixtures

No further information available.

Mixture versus ingredient information

No further information available.

Other information

None.

12 Ecological information

Toxicity

Hazard for aquatic organisms

Freshwater

Hazard assessment conclusion:	PNEC aqua (freshwater)
PNEC value:	0.163 mg/L
Assessment factor:	50
Extrapolation method:	assessment factor
PNEC freshwater (intermittent releases):	0.09 mg/L

Marine water

Hazard assessment conclusion:	PNEC aqua (marine water)
PNEC value:	0.016 mg/L
Assessment factor:	500
Extrapolation method:	assessment factor

STP

Hazard assessment conclusion:	PNEC STP
PNEC value:	10 mg/L
Assessment factor:	100
Extrapolation method:	assessment factor

Sediment (freshwater)

Hazard assessment conclusion:	PNEC sediment (freshwater)
PNEC value:	1.83 mg/kg sediment dw
Extrapolation method:	equilibrium partitioning method

Sediment (marine water)

Hazard assessment conclusion:	PNEC sediment (marine water)
PNEC value:	0.183 mg/kg sediment dw
Extrapolation method:	equilibrium partitioning method

Hazard for air

Air

Hazard assessment conclusion:	no hazard identified

Hazard for terrestrial organisms

Soil

Hazard assessment conclusion:	PNEC soil
PNEC value:	0.269 mg/kg soil dw
Extrapolation method:	equilibrium partitioning method

Hazard for predators

Secondary poisoning

Hazard assessment conclusion:	no potential for bioaccumulation

Official classification regarding environmental hazards

Aquatic compartment

In accordance with Regulation (EC) 1272/2008 Annex VI Table 3.1, the substance is not officially classified.
In accordance with Regulation (EC) 1272/2008 Annex VI Table 3.2, the substance is not officially classified.

Aquatic compartment

Following GHS, the substance is not to be classified as acutely hazardous to the aquatic environment. Based on the available acute and chronic data, the substance is not to be classified as chronically hazardous to the aquatic environment.
Rationale:
The substance is not to be classified as acutely hazardous to the aquatic environment, since the lowest acute effect value is >> 1 mg/L (72-h ErC50 for marine algae: 9 mg/L).
Chronic data are available for two trophic levels, Daphnids and algae; therefore, the classification is based on the available chronic and acute toxicity data.

- *Chronic toxicity data:*

Chronic data are available aquatic invertebrates (21-d EC10: 8.134 mg/L) and for freshwater algae (96-h NOErC = 10 mg/L), indicating that the substance does not present a long-term hazard according to the categories outlined in Table 4.1.0(b) (ii) (Commission Regulation (EU) No 286/2011 amending Regulation (EC) No 1272/2008) for rapidly degradable substances.

- *Acute toxicity data:*

Fish is the trophic level not covered by chronic data. Therefore, the asessment is based on the respective available acute toxicity data. Acute toxicity to fish is >>1 mg/L (96h LC50 for fish: 180 mg/L). The substance is rapidly biodegradable (freshwater); the measured BCF is < 500. According to the criteria outlined in Table 4.1.0(b) (iii) (Commission Regulation (EU) No 286/2011 amending Regulation (EC) No 1272/2008) the substance is not to be classified as chronically hazardous to the aquatic environment.

- Conclusion: The substance is not to be classified as chronically hazardous to the aquatic environment.

Atmospheric compartment

The test substance is not in Annex I of Regulation (EC) 2037/2000 on substances that deplete the ozone layer.

The test substance does not belong to the greenhouse gases listed in P Forster, PV Ramaswamy et al. Changes in Atmospheric Constituents and in Radiative Forcing. In: Climate Change 2007: The Physical Basis. Contribution of Working Group I to the Fourth Assessment Report of the Intergovernmental Panel on Climate Change.

Short-term toxicity to fish:

In freshwater as well as saltwater, with high probability not harmful to fish.
Freshwater: LC_{50} (96 h): 180 mg/L (Oncorhynchus mykiss, static conditions, analytically verified concentrations)
Saltwater: LC_{50} (96 h): 179 mg/L (Vala muli engeli, static, nominal, no analytical verification)

Long-term toxicity to fish:

No experimental data available.

Short-term toxicity to aquatic invertebrates:

Morpholine is acutely harmful to aquatic invertebrates.
EC_{50} (48 h): 45 mg/L (Daphnia magna, OECD 202, static)

Long-term toxicity to aquatic invertebrates:
EC_{50} (21 d): 8.134 mg/L (Daphnia magna, OECD 211, semi-static)

Growth inihibition to aquatic algae:
Morpholine is acutely toxic to aquatic algae (based on marine data).
Freshwater data:
ErC_{50} (96 h): 28 mg/L (Pseudokirchneriella subcapitata, EPA guideline, effect on growth, static, analytically verified concentrations)
NOErC (96 h): 10 mg/L (Pseudokirchneriella subcapitata, EPA guideline, effect on growth, static, analytically verified concentrations)

Saltwater data:
ErC50 (72 h): 9 mg/L (Skeletonema costatum, ISO 10253, effect on growth, static, nominal, no analytical verification)

Toxicity to microorganisms:
The inhibition of the degradation activity of activated sludge is not anticipated when introduced to biological treatment plants in appropriate low concentrations.
EC_{20} (30 min): > 1000 mg/L (OECD 209; one test with domestic activated sludge and two tests with industrial activated sludge)
EC_3 (16 h): 310 mg/L (Pseudomonas putida)

Persistence and degradability

Phototransformation
After evaporation or exposure to the air, the product will be rapidly degraded by photochemical processes.
No direct photolysis is to be expected in the hydrosphere, since the substance does not adsorb light in the UV spectrum > 260 nm.

Hydrolysis
The substance is readily biodegradable (according to OECD criteria). In addition, hydrolysis is not expected under environmental conditions, due to the structural properties of the substance.

Biodegradation
The substance is readily biodegradable (according to OECD criteria).

Bioaccumulation
Significant accumulation in organisms is not to be expected.

Transport and distribution:
Adsorption / desorption
Adsorption of the substance to the solid soil phase is not expected under environmentally relevant conditions.

Henry's Law constant
From the water surface, the substance will not evaporate into the atmosphere.

Distribution modelling
Over time, the substance will preferentially distribute into the compartments water (97.1%) and air (2.9%). However, since the substance will be ionized under environmentally relevant conditions, the distribution into water may still be underestimated.

Biodegradation
Biodegradation in water: screening tests
Readily biodegradable according to OECD criteria.

Biodegradation in water: simulation tests
Readily biodegradable in a wastewater treatment plant after adaptation.

Biodegradation in soil
In accordance with column II of Annex IX, the study does not need to be conducted, if the substance is readily biodegradable. Morpholine proved to be readily biodegradable according to OECD criteria.

Bioaccumulative potential

According to a MITI study (corresponding to OECD 305C), morpholine does not significantly accumulate in aquatic organisms (BCF < 2.8) [CITI, 1992].

No data are available concerning accumulation in terrestrial organisms.

Mobility in soil

Adsorption
Adsorption to solid soil phase is not expected.

Henry's Law Constant
From the water surface, the substance will not evaporate into the atmosphere.

Distribution
Over time, the substance will preferentially distribute into the compartments water (97.1%) and air (2.9%).
However, since the substance will be ionized under environmentally relevant conditions, the distribution into water may still be underestimated.

Other adverse effects

No additional data.

13 Disposal considerations

Disposal methods

Dispose of waste and container in accordance with local and/or national regulations. Hazardous waste shall not be mixed together with other waste. Different types of hazardous waste shall not be mixed together if this may entail a risk of pollution or create problems for the further management of the waste. Hazardous waste shall be managed responsibly. All entities that store, transport or handle hazardous waste shall take the necessary measures to prevent risks of pollution or damage to people or animals. Recycle/reuse. Remove for physico-chemical/biological treatment. **DO NOT** discharge into drains or the environment.

The most favorable course of action is to use an alternative chemical product with less inherent propensity for occupational harm/injury/toxicity or environmental contamination. Recycle any unused portion of the material for its approved use or return it to the manufacturer or supplier. Ultimate disposal of the chemical must consider: the material's impact on air quality; potential migration in soil or water; effects on animal and plant life; and conformance with environmental and public health regulations.

Package lots
Distill for reuse or package and label for disposal by burning.

Small quantities
Wear eye protection, laboratory coat, and rubber gloves. Dissolve the morpholine (1 mL) in 50 mL of 3 M sulfuric acid (prepared by slowly adding 8 mL of concentrated sulfuric acid to 21 mL or water). Weigh 10 g of potassium permanganate and stir small portions of the solid into the morpholine solution over a period of about 1 hr. Stir the mixture at room temperature for 48 hr, and then neutralize the solution by adding solid sodium carbonate or a 10% solution of sodium hydroxide. Add solid sodium bisulfite until solution is colorless. Decant the clear liquid into the drain and discard any brown solid with regular refuse.

Incineration is acceptable and the preferred method of disposal; however, nitrogen oxide emission controls may be required to meet environmental regulations. Morpholine is also broken down by activated sludge and this is a possible method of disposal under controlled conditions.

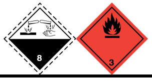
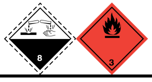
Place in a nonhalogenated solvent disposal container for disposal by burning. The compound should be burned in furnace equipped with afterburner and scrubber.

Morpholine may be disposed of by atomizing in a suitable combustion chamber equipped with an appropriate effluent gas cleaning device.

1. Dissolve in such combustible solvent as alcohols, benzene, etc. Spray the solution into a furnace with afterburner and scrubber.
2. Pour into a mixture of sand and soda ash (9:1). After mixing, put into a paper carton stuffed full with packing paper to serve as fuel. Burn in a furnace and stand or position oneself on upwind side.

14 Transport information

UN Number

TRANSPORTATION CLASSIFICATION	ADR/RID	ADN(R)	IMDG	ICAO/IATA
Identification Number	2054	2054	2054	2054
Proper Shipping Name	MORPHOLINE	MORPHOLINE	MORPHOLINE	MORPHOLINE
Transport Hazard Class(es)	8(3) 	8(3) 	8(3) 	8(3) 
Packing Group	I	I	I	I
Environmental Hazards	NO	NO	NO	NO
Emergency Response	ERG: 132	-	EMS: F-E, S-C	-
Exempt/Limited Quantities	Exempt Quantity Road 5Kg F: 200 Quantity Limitations 0.5L - Passenger Rail	-	-	Quantity Limitations 0.5L - Passenger 2.5 L - Cargo

UN Proper Shipping Name

Refer above section 14.1

Transport hazard class(es)

Refer above section 14.1

Packing group, if applicable

Refer above section 14.1

Environmental hazards

Refer above section 14.1

Special precautions for user

DO NOT load with Class 1, 2.3 & 6.2.
Keep aluminium gas cylinders apart from caustic bases.
May be loaded with Class 5.1, 5.2 & 8A if kept at least 1 metre apart.
Can be loaded with all other classes.
Goods of different classes **must** be segregated by an air space of at least 100mm or by an approved segregation device or non-dangerous goods.

P, B, L and O provisions as per SANS 10231:2006

O2 Closed vehicles that carry liquids with a flash point of not more than 60,5 °C or flammable substances or articles of class 2, shall not be entered by persons who carry lighting apparatus other than portable lamps so designed and constructed that they cannot ignite any flammable vapours or gases which may have penetrated into the interior of the vehicle. In the case of vehicles of type F (see SANS 1518), a good electrical connection from the vehicle chassis to earth shall be established before tanks are filled or emptied. In addition, the rate of filling shall be limited.

O15 The provisions in 5.3.4 concerning the supervision of vehicles shall apply to class 4 whatever the mass and to

substances of class 3 when the total mass of these substances in the vehicle exceeds 100 kg.
O20 The provisions in 5.3.4 concerning the supervision of vehicles shall apply when the total mass of these substances in the vehicle exceeds 10 000 kg.

5.3.4 A vehicle that carries dangerous goods shall be under constant supervision while stopped or parked if one or both of the following applies:

a) the dangerous goods carried have an exempt quantity of 10 kg or 10 L, or less; or

b) any one or more of special provisions O14 to O20 (inclusive) in C.5 applies.

Excerpt from ERG Guide 132 [Substances - Flammable Liquids - Corrosive]

Public Safety

CALL Emergency Response Telephone Number on Shipping Paper first. If Shipping Paper not available or no answer, refer to appropriate telephone number listed on the inside back cover. As an immediate precautionary measure, isolate spill or leak area for at least 50 meters (150 feet) in all directions. Keep unauthorized personnel away. Stay upwind, uphill and/or upstream. Ventilate closed spaces before entering.

Protective Clothing

Wear positive pressure self-contained breathing apparatus (SCBA). Wear chemical protective clothing that is specifically recommended by the manufacturer. It may provide little or no thermal protection. Structural firefighters' protective clothing provides limited protection in fire situations ONLY; it is not effective in spill situations where direct contact with the substance is possible.

Evacuation

Spill - See Table 1 - Initial Isolation and Protective Action Distances for highlighted materials. For non-highlighted materials, increase, in the downwind direction, as necessary, the isolation distance shown under "PUBLIC SAFETY".
Fire - If tank, rail car or tank truck is involved in a fire, ISOLATE for 800 meters (1/2 mile) in all directions; also, consider initial evacuation for 800 meters (1/2 mile) in all directions.

Emergency Response

Fire

Some of these materials may react violently with water.

Small Fire

Dry chemical, CO2, water spray or alcohol-resistant foam.

Large Fire

Water spray, fog or alcohol-resistant foam. Move containers from fire area if you can do it without risk. Dike fire-control water for later disposal; do not scatter the material. **DO NOT** get water inside containers.

Fire involving Tanks or Car/Trailer Loads

Fight fire from maximum distance or use unmanned hose holders or monitor nozzles. Cool containers with flooding quantities of water until well after fire is out. Withdraw immediately in case of rising sound from venting safety devices or discoloration of tank. **ALWAYS** stay away from tanks engulfed in fire. For massive fire, use unmanned hose holders or monitor nozzles; if this is impossible, withdraw from area and let fire burn.

SPILL OR LEAK

Fully encapsulating, vapor-protective clothing should be worn for spills and leaks with no fire. ELIMINATE all ignition sources (no smoking, flares, sparks or flames in immediate area). All equipment used when handling the product must be grounded. **DO NOT** touch or walk through spilled material. Stop leak if you can do it without risk. Prevent entry into waterways, sewers, basements or confined areas. A vapor-suppressing foam may be used to reduce vapors. Absorb with earth, sand or other non-combustible material and transfer to containers (except for Hydrazine). Use clean, non-sparking tools to collect absorbed material.

Large Spill

Dike far ahead of liquid spill for later disposal. Water spray may reduce vapor, but may not prevent ignition in closed spaces.

First Aid

Ensure that medical personnel are aware of the material(s) involved and take precautions to protect themselves. Move victim to fresh air. Call 911 or emergency medical service. Give artificial respiration if victim is not breathing. **DO NOT** use mouth-to-mouth method if victim ingested or inhaled the substance; give artificial respiration with the aid of a pocket mask equipped with a one-way valve or other proper respiratory medical device. Administer oxygen if breathing is difficult. Remove and isolate contaminated clothing and shoes. In case of contact with substance, immediately flush skin or eyes with running water for at least 20 minutes. In case of burns, immediately cool affected skin for as long as possible with cold water. **DO NOT** remove clothing if adhering to skin. Keep victim calm and warm. Effects of exposure (inhalation, ingestion or skin contact) to substance may be delayed.

Transport in bulk according to Annex II of MARPOL 73/78 and the IBC Code

Not applicable.

15 Regulatory information

Safety, health and environmental regulations specific for the product in question

SA NATIONAL LEGISLATION
Hazardous Substances Act 15 of 1973 and Regulations.
Occupational Health and Safety Act 85 of 1993 and Regulations.

SA NATIONAL STANDARDS
SANS 10228 : 2006 : Identification and Classification of Dangerous Goods for Transport by Road and Rail.
SANS 10231 : 2018 : Transport of dangerous goods - Operational requirements for road vehicles.
SANS 10234 : 2008 : Globally Harmonized System of classification and labelling of chemicals (GHS).
SANS 11014 : 2010 : Safety Data Sheets for chemical Products.

REACH Regulation (EC) No 1907/2006
This product contains only components that have been either pre-registered, registered, are exempt from registration, are regarded as registered or are not subject to registration according to Regulation (EC) No. 1907/2006 (REACH)., The aforementioned indications of the REACH registration status are provided in good faith and believed to be accurate as of the effective date shown above. However, no warranty, express or implied, is given. It is the buyer´s/user´s responsibility to ensure that his/her understanding of the regulatory status of this product is correct.

Seveso III: Directive 2012/18/EU
Listed in Regulation: Not applicable

Atmospheric Standards
This action promulgates standards of performance for equipment leaks of Volatile Organic Compounds (VOC) in the Synthetic Organic Chemical Manufacturing Industry (SOCMI). The intended effect of these standards is to require all newly constructed, modified, and reconstructed SOCMI process units to use the best demonstrated system of continuous emission reduction for equipment leaks of VOC, considering costs, non air quality health and environmental impact and energy requirements. Morpholine is produced, as an intermediate or a final product, by process units covered under this subpart.

FDA Requirements

1. Morpholine is a food additive permitted for direct addition to food for human consumption, as long as 1) the quantity of the substance added to food does not exceed the amount reasonably required to accomplish its intended physical, nutritive, or other technical effect in food, and
2. 2) any substance intended for use in or on food is of appropriate food grade and is prepared and handled as a food ingredient.

Morpholine is an indirect food additive for use only as a component of adhesives.

Chemical safety assessment
Performed for substance: Yes

16 Other information

Other information

Full text of H-Statements referred to under section 2
Hazard statements

H226	Flammable liquid and vapour.
H302	Harmful if swallowed.
H311	Toxic in contact with skin.
H314	Causes severe skin burns and eye damage.

H331	Toxic if inhaled.

Precautionary statements

P210+P233	Keep away from heat/sparks/open flames/hot surfaces. — No smoking. Keep container tightly closed.
P240+P241+P242	Ground/bond container and receiving equipment. Use explosion-proof electrical/ventilating/lighting equipment. Use only non-sparking tools.
P243	Take precautionary measures against static discharge.
P260	Do not breathe dust/fume/gas/mist/vapours/spray.
P264	Wash thoroughly after handling.
P270	Do not eat, drink or smoke when using this product.
P271	Use only outdoors or in a well-ventilated area.
P280	Wear protective gloves/protective clothing/eye protection/face protection.
P301+P312	IF SWALLOWED: call a POISON CENTER or doctor/physician IF you feel unwell.
P301+P330+P331	IF SWALLOWED: Rinse mouth. Do NOT induce vomiting.
P302+P352	IF ON SKIN: Wash with plenty of soap and water.
P303+P361+P353	IF ON SKIN (or hair): Remove/Take off Immediately all contaminated clothing. Rinse SKIN with water/shower.
P304+P340	IF INHALED: Remove victim to fresh air and Keep at rest in a position comfortable for breathing.
P305+P351+P338	IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
P310	Immediately call a POISON CENTER or doctor/physician.
P321	Specific treatment (see P330+P351+P352 on this label).
P362+P364	Take off contaminated clothing and wash it before reuse.
P363	Wash contaminated clothing before reuse.
P370+P378	In case of fire: Use water spray, dry powder, foam, carbon dioxide to extinguish.
P403+P233+P235	Store in a well-ventilated place. Keep container tightly closed. Keep cool.
P405	Store locked up.
P501	Dispose of contents and container in accordance with local, regional, national, international regulations.

Labelling REGULATION (EC) No 1272/2008

Signal Word

Danger

Pictograms Hazard to Human

GHS02	Flammable hazard
GHS05	Corrosive hazard
GHS06	Toxic hazard

Pictogram Hazard during Transport

Class 3	Flammable substance
Class 8	Corrosive substance

Training advice

Provide adequate information, instruction and training for operators.

Information sources

1. ECHA - European Chemicals Agency https://echa.europa.eu/de/registration-dossier/-/registered-dossier/13364/1
2. National Center for Biotechnology Information. PubChem Database. Morpholine, CID=8083, https://pubchem.ncbi.nlm.nih.gov/compound/8083 (accessed on Apr. 30, 2019)

Compiled by Aquatrade Water Treatment Chemicals (Pty) Ltd R. van Rooyen, SHEQ Co-ordinator and E. Le Sar, Director.

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Revision History

Revision	Date	Change
1.0	2019/05/02	Preparation of the safety data sheet according to SANS 11014:2010