# MORPHOLINE

Data were last evaluated in IARC (1989).

## 1. Exposure Data

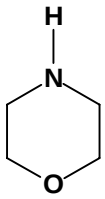
### 1.1 Chemical and physical data

1.1.1 *Nomenclature*

*Chem. Abstr. Serv. Reg. No.*: 110-91-8

*Chem. Abstr. Name*: Morpholine

1.1.2 *Structural and molecular formulae and relative molecular mass*




$C_4H_9NO$ Relative molecular mass: 87.12

1.1.3 *Physical properties* (for details, see IARC, 1989)

(*a*) *Boiling-point*: 128.3°C; 24.8°C at 1.3 kPa

(*b*) *Melting-point*: –4.7°C; –4.9°C

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

### 1.2 Production, use and human exposure

Morpholine is a synthetic organic liquid used mainly as an intermediate in the production of rubber chemicals and optical brighteners, as a corrosion inhibitor in steam condensate systems, as an ingredient in waxes and polishes and as a component of protective coatings on fresh fruits and vegetables. Occupational exposure may occur during the production of morpholine and in its various uses, but data on exposure levels are sparse. It has been detected in samples of foodstuffs and beverages (IARC, 1989).

## 2. Studies of Cancer in Humans

No data were available to the Working Group.

## 3. Studies of Cancer in Experimental Animals

Morpholine was tested for carcinogenicity by oral administration in two strains of mice, one strain of rats and one strain of hamsters. The studies in one of the strains of mice and in hamsters were considered inadequate for evaluation. In the other strain of mice, no significant increase in the incidence of tumours was seen in treated animals. In the study in rats, a few tumours of the liver and lung occurred in treated animals. Morpholine was also tested by inhalation exposure in rats; it did not increase the incidence of tumours over that found in controls (IARC, 1989).

## 4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

### 4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

No data were available to the Working Group.

4.1.2 *Experimental systems*

Morpholine is absorbed after oral, dermal and inhalation administration. In rats it was distributed to all organs and eliminated rapidly. In rabbits, mice, rats and hamsters, almost all morpholine was excreted unchanged in the urine following its administration by any route, whereas guinea-pigs excreted 20% of the dose as *N*-methylmorpholine-*N*-oxide. *N*-Nitrosomorpholine was formed in rodents following concomitant administration with nitrite or nitrous oxide and *in vitro* when added to human saliva (IARC, 1989).

### 4.2 Toxic effects

4.2.1 *Humans*

Rhinitis, lower airway irritation and corneal oedema have been reported in workers exposed to morpholine (IARC, 1989).

4.2.2 *Experimental systems*

Diluted morpholine is a skin and eye irritant in rabbits and guinea-pigs. Its inhalation is irritant in rats and damages the airways in rabbits. Skin application in rabbits, oral administration and skin application in guinea-pigs or inhalation in rats caused necrosis of kidney tubules and liver. Oral administration induced stomach and small intestine haemorrhages in guinea-pigs and rats, liver degeneration in rats and renal insufficiency in mice (IARC, 1989).

### 4.3 Reproductive and developmental effects

No data were available to the Working Group.

### 4.4 Genetic and related effects

4.4.1 *Humans*

Peripheral blood lymphocytes were analysed for chromosomal aberrations in 24 workers (16 men and 8 women) occupationally exposed to morpholine for 3–10 years. The average atmospheric concentration of morpholine was 0.53–0.93 mg/m$^3$, reaching maxima of 0.74–2.14 mg/m$^3$. The percentages of cells with any aberrations were: controls, 1.61 ± 0.2%; exposed, 2.08 ± 0.2%; and the percentages of cells with deletions were: controls, 0.69 ± 0.2%; exposed, 0.86 ± 0.2%. According to the database of the Institute of Medical Genetics (Moscow, Russia), the expected percentage of cells with aberrations is 1.19 (437 individuals analysed) (Katosova *et al.*, 1991). [The Working Group noted the lack of information regarding other exposures, the characteristics of the control group and the types of aberration recorded.]

4.4.2 *Experimental systems*

Morpholine did not induce mutations in bacteria, unscheduled DNA synthesis in primary cultures of rat hepatocytes or chromosomal aberrations in Chinese hamster lung fibroblasts. According to an abstract, it induced a small increase in *tk* locus mutations of mouse lymphoma cells and increased the frequency of morphologically transformed BALB/c 3T3 cells. In a transplacental exposure study with Syrian hamsters, it did not induce micronuclei, chromosomal aberrations or mutations in embryo cells (IARC, 1989).

## 5. Evaluation

No epidemiological data relevant to the carcinogenicity of morpholine were available.

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

**Overall evaluation**

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

## 6. References

IARC (1989) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 47, *Some Organic Solvents, Resin Monomers and Related Compounds, Pigments and Occupational Exposures in Paint Manufacture and Painting*, Lyon, pp. 199–213

Katosova, L.D., Fomenko V.N. & Davydenko, L.N. (1991) Results of cytogenetic examination of workers exposed to morpholine. *Gig. Tr. prof. Zabol.*, **6**, 35–36 (in Russian)