Social Europe

Recommendation from the Scientific Expert Group on Occupational Exposure Limits for piperazine

SEG/SUM/78

July 1997

European Commission

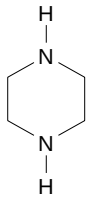
Table of Contents

Recommendation from the Scientific Expert Group on Occupational Exposure Limits for Piperazine

8 hour TWA	:	0.1 mg/m^3
STEL (15 mins)	:	0.3 mg/m^3
Additional classification	:	-

Substance:

Piperazine



Synonyms : 1,4-diazacyclohexane; 1,4-diethylenediamine; hexahydropyrazine; hexahydro-1,4-diazine
EINECS N° : 203-808-3
EEC N° : 612-057-00-4 Classification : C; R34-42/43-52/53
CAS N° : 110-85-0
MWt : 86.14
Conversion factor (20°C, 101 kPa) : 3.58 mg/m^3 = 1 ppm

1. Occurrence/use

Piperazine is a white or transparent crystalline compound. It has a MPt of 106 °C, a BPt of 146 °C and a vapour pressure of 0.023 kPa at 20°C. It is very hygroscopic and alkaline. Its physical state in the atmosphere cannot be asssumed to be confined to vapour, and it is therefore appropriate to express exposure levels in mg/m^3 rather than ppm

Piperazine (as hexahydrate or salts like adipate, phosphate, citrate) is mainly used as an anthelmintic drug in animals, and in some countries also in humans. Piperazine ring containing compounds are also used as a basis for several other pharmaceuticals. Other uses are as accelerators in the rubber industry, in antioxidants, corrosion inhibitors, surfactants, fibres, resins, insecticides, textile dyes and in analytical chemistry. The production rate in the EU is in excess of 1000 tonnes per annum.

2. Health Significance

Piperazine is readily absorbed from the gastrointestinal tract, and to a lesser extent via the lungs (Bellander *et al*., 1988).

Piperazine (anhydrate/hexahydrate) is irritating to the skin and mucous membranes. Piperazine solutions and salts are less and not irritating, respectively. Occupational skin contact can result in allergic eczema.

On inhalation or oral administration, the acute toxicity is low. Data on the toxicity in experimental animals are limited. No data are available on reproductive toxicology or carcinogenicity.

Few mutagenicity studies are available for piperazine. Negative results were reported with the Ames test, two host-mediated assays and the detection of DNA strand-breaks in liver cells after i.p. application to rats (Haworth *et al*., 1983; Braun *et al*., 1977; Arriaga Alba *et al*., 1989; Stewart and Farber, 1973). A meeting summary, without any details given, reports a positive result in the mouse lymphoma thymidine kinase assay and a negative result in the BALB/3T3 transformation assay (Conaway *et al*., 1982).

In man, an investigation of workers handling amines in the period 1942-1979 demonstrated an association between piperazine exposure and development of symptoms of asthma and chronic bronchitis (Hagmar *et al*., 1984). No new cases of asthma were noted when exposure levels were ≤ 0.3 mg/m^3, but exposure to 0.4 mg/m^3 provoked attacks of dyspnea in sensitised subjects and exposure to 0.7 mg/m^3 resulted in a case of asthma (Hagmar, 1986). Examination in a small group of workers exposed to average levels below 0.1 mg/m^3 showed no difference in small airway function when compared with unexposed controls (Hagmar *et al*., 1987). Data from a study using the radioallergent sorbent test (RAST) and RAST inhibition techniques suggested that piperazine may cause asthmatic symptoms by either type I allergy or by nonspecific bronchial irritation (Hagmar and Welinder, 1986).

An investigation on the effects of nitrosable drug exposure during pregnancy showed an increased relative risk of major malformations and of tumours in offspring (Olshan and Faustman, 1989). Transient neurological disorders have been noted after oral therapeutic treatment with piperazine, primarily in patients with renal insufficiency or a history of CNS disease.

It is possible for piperazine to undergo nitrosation to generate a nitrosamine that is potentially carcinogenic. In workers occupationally exposed to 0.3 mg/m^3 piperazine, small amounts of N-mononitrosopiperazine were found in the urine (Bellander *et al*., 1988). No significant difference in chromosomal aberrations or micronuclei was found in workers in a chemical factory exposed to a number of chemicals including piperazine (Hagmar *et* al., 1988), whereas Hogstedt *et* al., (1988) reported an increase in size and frequency of micronuclei in exposed workers at a chemical plant where exposure to piperazine vapour and/or dust occurred. No association was found between exposure to piperazine and increased cancer morbidity among workers in a chemical factory (Hagmar *et al*., 1986).

Recommendation

The studies of Hagmar *et al*. (1984, 1986, 1987), demonstrating that no new cases of asthma were reported in workers exposed at levels below 0.3 mg/m^3, were considered to be the best available basis for proposing occupational exposure limits. Since the number of workers investigated in these studies is too small to generalise this observation, the recommended 8-hour TWA is 0.1 mg/m^3. The recommended 8-hour TWA is 0.1 mg/m^3. A STEL (15 mins) of 0.3 mg/m^3 was proposed to limit peaks in exposure which could result in respiratory sensitisation.

Workers sensitised to piperazine with existing asthmatic symptoms may not be protected by the proposed limits.

No "skin" notation was considered to be necessary.

The methods of Skarping *et al.* (1986), using an aqueous impinger and selective nitrogen detector, are appropriate at both the TWA and STEL levels, though for the STEL further validation will be required. Other equivalent methods (suitably validated) may be used, but both vapour and particulate should be included.

Key Bibliography

Arriaga Alba, M., Espinosa Aguirre, J., Ramirez, J. and Cortinas de Nava, C. (1989) Mutagenicity of urine from mice exposed orally to nitrite and various aminated antiparasitic drugs. Environm. Molec. Mutag. 14, 13-19.

Bellander, T., Österdahl, B.-G., Hagmar, L. and Skerving, S. (1988). Excretion of N-mononitrosopiperazine in urine in workers manufacturing piperazine. Int. Arch. Occup. Environ. Health 60, 25-29.

Braun, R., Schöneich, J. and Ziebarth, D. (1977) In vivo formation of N-nitroso compounds and detection of their mutagenic activity in the host-mediated assay. Cancer Res. 37, 4572-4579.

Conaway, C.C., Myhr, B.C., Rundell, J.O. and Brusick, D.J. (1982) Evaluation of morpholine, piperazine and analogues in the L5178Y mouse lymphoma assay and BALB/3T3 transformation assay. Environm. Mutag. 4, 390.

DECOS (1991). Health-based recommended occupational exposure limit for piperazine. RA 7/91. The Hague, The Netherlands: Directorate-General of Labour, Ministry of Social Affairs and Employment.

Hagmar, L. (1986). Occupational respiratory disease caused by piperazine. Thesis. University of Lund, Sweden (Dept of Occupational Medicine).

Hagmar, L. and Welinder, H. (1986). Prevalence of specific IgE antibodies against piperazine in employees of a chemical plant. Int. Arch. Allergy Appl. Immun. 81, 12-16.

Hagmar, L., Arborelius Jr., M., Bellander, T., and Skerfving, S. (1987). Small airway function in workers exposed to piperazine. Int. Arch. Occup. Environ. Health. 59, 521-528.

Hagmar, L., Bellander, T., Englander, V., Ranstam, J. Attewell, R. and Skerfving, S. (1986). Mortality and cancer morbidity among workers in a chemical factory. J. Work Environ. Health. 12, 545-551.

Hagmar, L., Bellander, T., Hogstedt, B., Hallberg, T., Attewell, R. Raihle, G., Au, W. W., Legator, M. S., Mitelman, F. and Skerfving, S. (1988). Biological effects in a chemical factory with mutagenic exposure. I. Cytogenetic and haematological parameters. Int Arch. Occ. Environ. Health. 60, 437-444.

Hagmar, L., Bellander, T., Ranstam, J. and Skerfving, S. (1984). Piperazine-induced airway symptoms: exposure-response relationships and selection in an occupational setting. Am. J. Ind. Med. 6, 347-357.

Haworth, S., Lawlor, T., Mortelmans, K., Speck, W. and Zeiger, E. (1983) Salmonella mutagenicity test results for 250 chemicals. Environm. Mutag., Suppl. 1, 3-142.

Hogstedt, B., Bratt, I., Holmen, A., Hagmar, L. and Skerfving, S. (1988). Frequency and size distribution of micronuclei in lymphocytes stimulated with phytohemagglutinin and pokeweed mitogen in workers exposed to piperazine. Hereditas 109, 139-142.

Olshan, A. F. and Faustman, E. M. (1989). Nitrosable drug exposure during pregnancy and adverse pregnancy outcome. Int. J. Epidemiol. 18, 8991-899.

Skarping, G., Bellander T. and Mathiasson, L. (1986) Determination of piperazine in working atmosphere and in human urine using derivitization and capillary gas chromatography with nitrogen and mass selective detection. J. Chromatogr. 370, 245-258.

Stewart, B.W. and Farber, E. (1973) Strand breakage in rat liver DNA and its repair following administration of cyclic nitrosamines. Cancer Res. 33, 3209-3215.