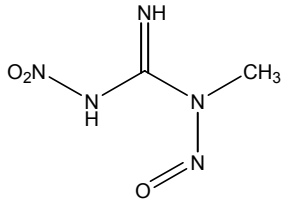
N-METHYL-*N*′-NITRO-*N*-NITROSOGUANIDINE

CAS No. 70-25-7

First Listed in the *Sixth Annual Report on Carcinogens*



CARCINOGENICITY

N-Methyl-*N*′-nitro-*N*-nitrosoguanidine (MNNG) is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity in experimental animals (IARC 1974, 1987). MNNG is carcinogenic in all species tested: mouse, rat, hamster, rabbit, and dog. When administered in the drinking water, MNNG induced adenomas, adenocarcinomas, a few leiomyosarcomas, and signet-ring cell carcinomas of the glandular stomach in rats. Additional malignant tumors were observed, especially at high concentrations, in the duodenum, jejunum and mesentery, together with papillomas in the forestomach and liver tumors. When administered in the drinking water, MNNG induced leiomyosarcomas in the walls of gastric cysts, neonatally grafted into the subcutaneous tissues of mice, adenocarcinomas and sarcomas of the glandular stomach in male hamsters, and adenocarcinomas in the stomachs of dogs. When administered by gavage, a single dose of MNNG induced three squamous cell carcinomas and one papilloma of the stomach in three of six male mice; the spontaneous occurrence of gastrointestinal tumors is considered extremely rare in the species used in this study. When administered by gavage as a single high dose, the compound induced malignant tumors in the glandular and forestomach of rats. When administered as a series of gavage treatments at irregular intervals, the compound induced squamous papillomas and squamous cell carcinomas of the forestomach and tumors in the glandular stomach, liver, and peritoneum in rats of both sexes. When administered by subcutaneous injection, the compound induced fibrosarcomas and polymorphic sarcomas at the injection site in adult rats. In a similar study, fibrosarcomas and rhabdomyosarcomas were induced at the injection site in male rats. Newborn rats that received a single subcutaneous injection of MNNG developed adenocarcinomas, fibrosarcomas, and myosarcomas of the small intestine. A single subcutaneous injection of MNNG induced lung and liver tumors and hemangioendotheliomas in mice. When administered by intraperitoneal injection, MNNG induced benign and malignant tumors of the cecum, ileum, and jejunum in male mice. When administered by a single intraperitoneal injection, the compound induced tumors of the stomach, jejunum, and cecum in male rats, and carcinomas and sarcomas of the stomach and small intestine in suckling rats. When administered by intrarectal instillation, the compound induced one or more adenomatous polyps and polypoid carcinomas in the colon and rectum of seven of nine rats. In additional studies not reviewed by IARC, when administered topically, MNNG induced skin papillomas and carcinomas in male and female mice (O'Connell *et al*. 1987, Mitchell *et al*. 1988).

There is inadequate evidence for the carcinogenicity of MNNG in humans. Three cases of brain tumors (gliomas) and one of colon cancer have been reported for workers in a genetics laboratory over a 13-year period. All the subjects had probably been exposed to the compound for 6 to 15 years prior to death, but other carcinogens had also been used in the laboratory (IARC 1974, 1987).

PROPERTIES

MNNG occurs as a pale yellow to pink crystalline powder that may become green or orange when exposed to light. MNNG is only slightly soluble in water and is soluble in polar organic solvents; however, it often decomposes in solution. MNNG will react with various nucleophiles, especially with amines and thiols and at acid pH; the chemical slowly releases nitrous acid. Contact of MNNG with alkali hydroxide produces the very toxic gas, diazomethane. When heated to decomposition, it emits very toxic fumes of nitrogen oxides. MNNG will explode under high impact, and it is sensitive to heat, light and moisture (IARC 1974, HSDB 2001, NTP 2001).

USE

MNNG currently has no known commercial use. It is used in small quantities as a research chemical. In the past, MNNG was used to prepare diazomethane (IARC 1974, HSDB 2001).

PRODUCTION

Although MNNG is not produced commercially in the United States, six current U.S. suppliers were listed for MNNG (Chem Sources 2001). No import or export data were reported (HSDB 2001).

EXPOSURE

The extent of exposure of the general population to MNNG is unknown, but exposure is probably limited to scientists using it as a research chemical (IARC 1974, HSDB 2001). The total worker exposure estimated by the National Occupational Exposure Survey (1981-1983) was 522 workers (NIOSH 1984).

REGULATIONS

EPA regulates MNNG under the Clean Water Act (CWA), Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), and Resource Conservation and Recovery Act (RCRA). EPA has established effluent guidelines, rules for regulating hazardous spills, general threshold amounts, and requirements for handling and disposal of MNNG wastes. A reportable quantity (RQ) of 10 lb has been established for MNNG under CERCLA.

OSHA regulates MNNG under the Hazard Communication Standard and as a chemical hazard in laboratories. Regulations are summarized in Volume II, Table 111.

REFERENCES

Chem Sources. Chemical Sources International, Inc. http://www.chemsources.com, 2001.

HSDB. Hazardous Substances Data Bank. Online database produced by the National Library of Medicine. N-Methyl-N'-Nitro-N-Nitrosoguanidine. Profile last updated August 9, 2001. Last review date, January 31, 1998.

IARC. International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Some Aromatic Amines, Hydrazine and Related Substances, *N*-Nitroso Compounds and Miscellaneous Alkylating Agents. Vol. 4. 286 pp. Lyon, France: IARC, 1974.

IARC. International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Overall Evaluations of Carcinogenicity. Supplement 7. 440 pp. Lyon, France: IARC, 1987.

Mitchell, R.E.J., D.P. Morrison, and N.J. Gragtmans. The Influence of a Hyperthermia Treatment on Chemically Induced Tumor Initiation and Progression in Mouse Skin. Carcinogenesis Vol. 9, No. 3, 1988, pp. 379-385.

NIOSH. National Institute for Occupational Safety and Health. National Occupational Exposure Survey (1981-83). Cincinnati, OH: Department of Health and Human Services, 1984.

NTP. National Toxicology Program. NTP Chemical Repository. N-Methyl-Nitro-N'-Nitrosoguanidine. Last updated August 13, 2001. (http://ntp-server.niehs.nih.gov and search 70-25-7).

O'Connell, J., S. Nesnow, and T.J. Slaga. Initiation, Promotion and Complete Carcinogenesis by *N*-Methyl-*N*′-nitro-*N*-nitrosoguanidine or Ethylnitrosourea in the SENCAR Mouse Skin Tumorigenesis Model. Cancer Lett. Vol. 37, No. 3, 1987, pp. 301-310.