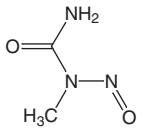
N-Nitroso-*N*-Methylurea
CAS No. 684-93-5

Reasonably anticipated to be a human carcinogen
First Listed in the *Second Annual Report on Carcinogens* (1981)



Carcinogenicity

N-Nitroso-*N*-methylurea is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity in experimental animals (IARC 1972, 1978, 1987). When administered in the diet, *N*-nitroso-*N*-methylurea induced squamous cell carcinomas of the forestomach, sarcomas and gliomas of the brain, and neurosarcomas in rats. When administered in the drinking water, *N*-nitroso-*N*-methylurea induced tumors of the brain (mainly gliomas), and one neurinoma of the spinal cord in rats; in guinea pigs, it induced carcinomas and sarcomas of the stomach, adenocarcinomas of the pancreas, malignant tumors of the ear duct, one neurinoma of the lumbar nerve, and leukemia. When administered intragastrically, *N*-nitroso-*N*-methylurea induced malignant tumors of the kidney, forestomach, small and large intestines, skin, and jaw in rats; odontogenic tumors and epidermoid carcinomas of the oral cavity, and adenocarcinomas of the small and large intestines in hamsters; and adenocarcinomas of the pancreas, stomach, and colon, lymphomas of the mesenteric lymph nodes, and one hepatocellular carcinoma in guinea pigs. When administered orally, the chemical induced malignant tumors of the stomach in pigs and squamous cell carcinomas of the oropharynx and/or esophagus in monkeys. When administered topically, *N*-nitroso-*N*-methylurea induced leukemia and malignant skin tumors (including papillomas) in mice; squamous and basal cell carcinomas of the skin in rats; and squamous cell carcinomas of the skin in hamsters. When administered by intratracheal instillations, *N*-nitroso-*N*-methylurea induced epidermoid carcinomas in the nasopharyngeal tube, pharynx, larynx, trachea, bronchi, esophagus, and forestomach, and large cell anaplastic carcinomas of the trachea in hamsters. When administered by subcutaneous injection, the chemical induced lymphomas, local sarcomas, lymphosarcomas involving the thymus, myocardium, lung, spleen, lymph nodes, liver, kidney, and bone marrow, leukemias, and pulmonary tumors in mice; nervous system tumors in rats; and local sarcomas, fibrosarcomas, carcinosarcomas, and epidermal carcinomas and papillomas of the forestomach in hamsters. When administered by intraperitoneal injection, *N*-nitroso-*N*-methylurea induced thymic lymphomas, pulmonary adenomas, lymphosarcomas, lung adenomas, hepatomas, and bronchial adenomas in mice; malignant tumors in the peritoneal cavity, lymphosarcomas, intestinal adenocarcinomas, and mammary tumors in rats; adenocarcinomas of the large and small intestines in hamsters; and adenocarcinomas of the pancreas, fibrosarcomas, angiosarcomas of the mesentery, one mesothelioma of the peritoneum, tumors of the small intestine, and one hemangiosarcoma of the liver in guinea pigs. Intravenous administration of *N*-nitroso-*N*-methylurea induced leukemia in mice and malignant tumors of the brain (gliomas, ependymomas, medulloblastomas, and intracranial sarcomas), spinal cord (spongioblastomas, medulloblastomas, and gliomas), peripheral nervous system neurinomas, mammary carcinomas, astrocytomas, oligodendrogliomas, anaplastic gliomas, gliosarcomas, and differentiated and anaplastic neurinomas in rats. Intravenous administration of *N*-nitroso-*N*-methylurea also induced adenocarcinomas of the small and large intestines, odontogenic tumors, epidermoid carcinomas of the oral cavity, sarcomas of the heart, and squamous cell carcinomas of the stomach in hamsters; carcinomas and papillomas of the oral cavity, and carcinomas and adenomas of the midventral sebaceous gland in gerbils; polymorphous gliomas and sarcomas, carcinomas and adenocarcinomas of the small intestine, vascular and central nervous system tumors, malignant hemangioendotheliomas of the lung, spleen, and heart, and anaplastic neurinomas in various organs in dogs. Prenatal exposure by injection of *N*-nitroso-*N*-methylurea induced pulmonary adenomas and hepatomas in the offspring of mice. When administered by urethral catheterization, *N*-nitroso-*N*-methylurea induced papillomas and transitional cell carcinomas of the bladder in female rats. Intrarectal administration of *N*-nitroso-*N*-methylurea induced adenomas and adenocarcinomas of the distal colon and rectum, squamous cell carcinomas of the anal canal, and lung adenomas and lymphomas in mice; large bowel adenomas, adenocarcinomas, and carcinomas in male rats; and large bowel adenocarcinomas in female guinea pigs. When administered by intracerebral injection, *N*-nitroso-*N*-methylurea induced kidney fibrosarcomas and one mammary gland carcinoma in rats and leukemia and pulmonary tumors in mice.

No adequate human studies of the relationship between exposure to *N*-nitroso-*N*-methylurea and human cancer have been reported (IARC 1978).

Properties

N-Nitroso-*N*-methylurea exists as pale yellow crystals. It is soluble in water and polar organic solvents and insoluble in nonpolar organic solvents. The compound is highly reactive and is sensitive to humidity and light. Its stability in aqueous solutions is pH-dependent with reported half-lives ranging from 125 hours (pH 4) to about 2 minutes (pH 9). It decomposes to diazomethane (a highly toxic and explosive gas) in alkaline solutions (IARC 1978). Explosive decomposition may occur following prolonged storage at room temperature. When heated to decomposition, it emits toxic fumes of nitrogen oxides (HSDB 2001).

Use

N-Nitroso-*N*-methylurea was once widely used to synthesize diazomethane in the laboratory; however, this use was replaced by other reagents. It has been studied as a chemotherapeutic agent in cancer treatment, either alone or in combination with cyclophosphamide. Small quantities are used in research to study its mutagenic effects on plants (IARC 1972, 1978; HSDB 2001).

Production

N-Nitroso-*N*-methylurea is available in small quantities for research purposes, but has never been produced in commercial quantities in the United States (IARC 1978, HSDB 2001). The 1979 TSCA Inventory identified one producer of *N*-nitroso-*N*-methylurea in 1977 with a reported production of 500 lb (TSCA 1979). No current production data were located. Chem Sources (2001) listed nine U.S. suppliers.

Exposure

The potential for human exposure is limited because *N*-nitroso-*N*-methylurea is not produced or used in large quantities in the United States According to the Toxic Chemicals Release Inventory (TRI), a total of 170 lb were released to the environment from two industrial facilities in 1999. Approximately 96% of the total was released from one facility. No environmental releases were reported in prior years (TRI99 2001).

Occupational exposure may occur through inhalation or dermal contact at facilities where this chemical is used in research. In air, it exists solely as vapor where it is degraded (estimated half-life of 10 days) by reaction with photochemically-produced hydroxyl radicals. It

hydrolyzes in water (half-life of 1.2 hours at pH 7 at 20°C). A limited number of research laboratory workers may also be possibly exposed; several accidents have been reported in which laboratory personnel were exposed when the compound exploded at room temperature (HSDB 2001). The potential for direct exposure exists when injecting cancer patients with *N*-nitroso-*N*-methylurea in conjunction with cyclophosphamide, as a chemotherapeutic agent; however, no data were found for the frequency or extent of this use (IARC 1978). Health professionals such as pharmacists, physicians, and nurses are potentially exposed to the compound during the preparation and administration of the pharmaceuticals or during clean-up.

Regulations

EPA

Clean Air Act

NESHAP: Listed as a Hazardous Air Pollutant (HAP)

Clean Water Act

Effluent Guidelines: Listed as a Toxic Pollutant (nitrosamines)

Water Quality Criteria: Based on fish/shellfish and water consumption = 0.0008 µg/L (nitrosamines); based on fish/shellfish consumption only = 1.24 µg/L (nitrosamines)

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable Quantity (RQ) = 1 lb

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste codes in which listing is based wholly or partly on substance - U177

Listed as a Hazardous Constituent of Waste

FDA

Action level for *N*-nitrosamines in rubber baby bottle nipples is 10 ppb

References

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