

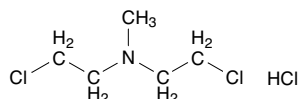
Nitrogen Mustard Hydrochloride

CAS No. 55-86-7

Reasonably anticipated to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)

Also known as nitrogen mustard, mechlorethamine, or mechlorethamine hydrochloride



Carcinogenicity

Nitrogen mustard hydrochloride is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals. In the literature, the names “nitrogen mustard” and “nitrogen mustard hydrochloride” are used interchangeably. Only nitrogen mustard hydrochloride is produced commercially, so it is assumed that nitrogen mustard hydrochloride was used in all cancer studies in animals reported below.

Cancer Studies in Experimental Animals

Nitrogen mustard hydrochloride caused tumors in two rodent species, at several different tissue sites, and by several different routes of administration. Subcutaneous, intravenous, or intraperitoneal injection of nitrogen mustard hydrochloride caused lung tumors in mice. Exposure by intravenous injection also caused thymic lymphoma in mice and tumors at various tissue sites in male rats. Dermal exposure to nitrogen mustard hydrochloride caused benign and malignant skin tumors (squamous-cell papilloma and carcinoma) in female mice (IARC 1975, 1982).

Cancer Studies in Humans

When used as an antineoplastic agent, nitrogen mustard hydrochloride usually is used in combination with other antineoplastic drugs; however, it has been used alone to treat mycosis fungoides (IARC 1975, 1982). Squamous-cell carcinoma has occurred following repeated application of nitrogen mustard hydrochloride to the skin of patients with mycosis fungoides. Cases have also been reported in which leukemia and other cancers have developed in Hodgkin's disease patients treated with drug combinations that included nitrogen mustard hydrochloride with or without radiation therapy.

Since nitrogen mustard hydrochloride was listed in the *Fourth Annual Report on Carcinogens*, additional cancer studies in humans have been identified. The International Agency for Research on Cancer reported that there was limited evidence for the carcinogenicity of nitrogen mustard hydrochloride in humans (IARC 1987). IARC noted that although there were numerous case reports of cancer following treatment with nitrogen mustard hydrochloride, the patients had also been treated with radiation or other drugs. No epidemiological studies of nitrogen mustard hydrochloride as a single agent have been published since the last IARC review. A large case-control study of lung cancer following treatment for Hodgkin's lymphoma found that lung-cancer risk increased significantly with increasing cumulative dose of mechlorethamine (nitrogen mustard hydrochloride) among patients treated with a combination of mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) (*P* for trend < 0.001 for mechlorethamine evaluated separately) (Travis *et al.* 2002). The other available studies did not evaluate independent effects of nitrogen mustard hydrochloride (Franklin *et al.* 2005), did not adjust for

exposure to other drugs, or were based on small numbers of exposed cases (Zaridze *et al.* 1993).

Properties

Nitrogen mustard hydrochloride is a compound analogous to mustard gas, with sulfur replaced by nitrogen. It exists at room temperature as white to off-white crystals or powder with a fishy odor. It is soluble in water and ethanol. The dry crystals are stable at room temperature, but unstable in aqueous solution (IARC 1975). Physical and chemical properties of nitrogen mustard hydrochloride are listed in the following table.

Property	Information
Molecular weight	192.5 ^a
Specific gravity	1.118 g/cm ³ at 25°C ^b
Melting point	109°C to 111°C ^a
Boiling point	87°C at 18 mm Hg ^b
Log <i>K_{ow}</i>	-1.24 ^a
Water solubility	10g/L ^a
Dissociation constant (p <i>K_a</i>)	6.43 at 25°C ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

The only known commercial use of nitrogen mustard is as a chemical intermediate in the production of its hydrochloride. Nitrogen mustard hydrochloride is used in limited quantities as an antineoplastic agent, either alone or in combination with other chemotherapeutic agents, to treat neoplastic diseases, including Hodgkin's disease, leukemia, generalized lymphosarcoma, mycosis fungoides, polycythemia vera, and bronchogenic carcinoma. It may also be used to treat non-Hodgkin's lymphoma, malignant melanoma, breast cancer, kidney cancer (renal-cell carcinoma), and cancer of the gastrointestinal tract (MedlinePlus 2009). It is also used to control pleural, peritoneal, and pericardial effusions caused by metastatic tumors. Clinical investigations were performed to evaluate its use in treatment of a variety of nonmalignant diseases, including rheumatoid arthritis, and in tissue transplantation. Research was conducted to investigate its use as a chemosterilant and as a cross-linking agent for the manufacture of ion-exchange fibers. Formerly, the pure form of nitrogen mustard was produced as a potential chemical warfare agent; however, it was never used in combat (IARC 1975).

Production

Nitrogen mustard hydrochloride was produced by one U.S. company from 1950 to the mid 1970s; however, only 1.5 kg (3.3 lb) was manufactured and sold in the United States in 1974 (IARC 1975). Neither nitrogen mustard nor its hydrochloride is now manufactured in commercial quantities in the United States or elsewhere; however, nitrogen mustard hydrochloride is available from eight U.S. suppliers (ChemSources 2009). It is registered by the U.S. Food and Drug Administration for use by one pharmaceutical firm in one product (FDA 2009).

Exposure

The primary routes of potential human exposure to nitrogen mustard hydrochloride are injection, inhalation, and dermal contact. Patients may receive nitrogen mustard hydrochloride as a chemotherapeutic agent by intravenous injection. Intravenous injections may be administered as a single total dose of 0.4 mg/kg of body weight or in two or four daily doses of 0.1 to 0.2 mg/kg (IARC 1975). The one pharmaceutical product containing nitrogen mustard hydrochloride currently registered for use in the United States is intended for intravenous administration. In 2010, 312 clinical trials evaluating the

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use of nitrogen mustard hydrochloride were in progress or recently completed (ClinicalTrials 2010). The use of a topical cream containing nitrogen mustard hydrochloride to treat mycosis fungoides has been studied. The treatment consisted of applying the ointment or solution to the entire skin surface area once a day for several months until the condition improved; subsequent treatments could be reduced to several times per week (MedlinePlus 2009). As of 2009, no topical creams containing nitrogen mustard hydrochloride were approved by the FDA (FDA 2009).

Nitrogen mustard hydrochloride is not known to occur in nature (IARC 1975), and no environmental releases have been reported to the U.S. Environmental Protection Agency's Toxics Release Inventory. Health professionals potentially may be exposed during preparation, administration, or cleanup of the pharmaceutical product. Potential occupational exposure may also occur during the production of nitrogen mustard hydrochloride and the manufacture, formulation, and packaging of nitrogen mustard hydrochloride pharmaceutical products (IARC 1975). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 4,618 workers, including 2,398 women, potentially were exposed to nitrogen mustard hydrochloride (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Nitrogen mustard is a listed substance subject to reporting requirements.

Reportable quantity (RQ) = 10 lb for nitrogen mustard.

Threshold planning quantity (TPQ) = 10 lb for nitrogen mustard.

Resource Conservation and Recovery Act

Nitrogen mustard hydrochloride salt is listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

Nitrogen mustard hydrochloride is a prescription drug subject to labeling and other requirements.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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