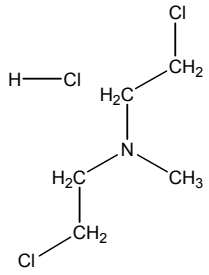
NITROGEN MUSTARD HYDROCHLORIDE
CAS No. 55-86-7
First Listed in the *Fourth Annual Report on Carcinogens*



CARCINOGENICITY

Nitrogen mustard hydrochloride is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity in experimental animals (IARC 1975, 1982, 1987). The generic name nitrogen mustard is used interchangeably with nitrogen mustard hydrochloride, and since only nitrogen mustard hydrochloride is produced, it was assumed to be nitrogen mustard hydrochloride under study. When administered topically, nitrogen mustard hydrochloride induced local papillomas and squamous cell carcinomas in female mice. When administered by intravenous injection, it induced tumors in different organs in rats. When administered by subcutaneous, intravenous, or intraperitoneal injection, the compound induced lung tumors and lymphomas in mice.

An IARC Working Group reported that there was limited evidence for the carcinogenicity of nitrogen mustard hydrochloride in humans (IARC 1987). Case reports and epidemiological studies of humans exposed to nitrogen mustard hydrochloride alone were not available to IARC Working Groups, except for one study involving the treatment of mycosis fungoides. In this study, squamous cell carcinomas occurred after long-term topical therapy with nitrogen mustard hydrochloride for mycosis fungoides. Treatment with the compound in combination with other cytotoxic drugs and/or radiation resulted in many cases of leukemia and various malignant tumors in patients with Hodgkin's disease and other solid tumors (IARC 1982).

PROPERTIES

Nitrogen mustard, in its pure form, occurs as a colorless liquid with a faint fishy odor. It decomposes slowly on standing, turning yellow to amber, and forms polymeric quaternary ammonium salts. It is slightly soluble in water, but is miscible with carbon disulfide, carbon tetrachloride, and many other organic solvents. Nitrogen mustard hydrochloride, which is the commercial form, is composed of large white, hygroscopic crystals that are soluble in water and methanol. When heated to decomposition, nitrogen mustard hydrochloride emits very toxic fumes of hydrochloric acid and other chlorinated compounds as well as nitrogen oxides. Dry crystals are stable up to 40°C. Aqueous solutions of nitrogen mustard hydrochloride are not stable. Solutions in DMSO, 95% ethanol or acetone are stable for 24 hours under normal laboratory conditions. The initial pH of a 2% aqueous solution is 3.0 to 4.0 (IARC 1975, HSDB 2001, NTP 2001).

USE

Currently, 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, and bronchogenic carcinoma. 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 rheumatoid arthritis, in tissue transplantation studies, and a variety of other nonmalignant diseases. 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, HSDB 2001).

PRODUCTION

Nitrogen mustard is not manufactured in commercial quantities in the U.S. and is not imported. Nitrogen mustard hydrochloride was produced by one U.S. company between 1950 and the mid 1970s; however, only 1.5 kg (3.3 lb) were manufactured and sold in the U.S. in 1974 (IARC 1975). The substance was not listed in the TSCA (1979) Inventory, nor were any environmental release data reported to the Toxic Chemical Release Inventory (TRI99 2001). Chem Sources (2001) reports one current U.S. supplier.

EXPOSURE

The primary routes of potential human exposure to nitrogen mustard hydrochloride are injection, inhalation, and dermal contact. Patients may receive the chemical as a chemotherapeutic agent by intravenous injection or as a topical ointment. Intravenous injections may be administered as a single total dose of 0.4 mg/kg body weight or in 2 or 4 daily doses of 0.1 to 0.2 mg/kg body weight (IARC 1975). Topical treatment consists of applying the ointment or solution to the entire skin surface area once a day for several months until the condition improves. Subsequent treatments may be reduced to several times per week (MEDLINEplus 2001).

The National Occupational Exposure Survey (1981-1983) indicated that 4,564 total workers, including 2,038 women, potentially were exposed to the compound in the workplace (HSDB 2001). Potential occupational exposure may occur for health professionals (e.g., pharmacists, nurses, and physicians) during drug preparation, administration, or cleanup. Potential occupational exposure also may occur during the production of nitrogen mustard, and the manufacture, formulation, and packaging of nitrogen mustard hydrochloride pharmaceuticals. Nitrogen mustard hydrochloride is not known to occur in nature (IARC 1975).

REGULATIONS

EPA regulates nitrogen mustard under the Superfund Amendments and Reauthorization Act (SARA), subjecting it to reporting requirements. EPA has proposed regulating nitrogen mustard as a hazardous constituent of waste under the Resource Conservation and Recovery Act (RCRA). Nitrogen mustard hydrochloride is regulated under the Emergency Planning and Community Right-To-Know Act (EPCRA) with a threshold planning quantity of 10 lb.

FDA regulates nitrogen mustard hydrochloride under the Food, Drug, and Cosmetic Act (FD&CA) as a prescription drug approved for human use. Under FD&CA, nitrogen mustard hydrochloride must have warning labels regarding potential carcinogenicity, mutagenicity, teratogenicity, and/or impairment of fertility.

OSHA regulates nitrogen mustard under the Hazard Communication Standard and as a chemical hazard in laboratories. Regulations are summarized in Volume II, Table 123.

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. Mechlorethamine. Profile Last updated August 9, 2001. Last review date, May 16, 1996.

IARC. International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Some Aziridines, N-, S- and O-Mustards and Selenium. Vol. 9. 286 pp. Lyon, France: IARC, 1975.

IARC. International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Chemicals, Industrial Processes and Industries Associated with Cancer in Humans. Supplement 4. 292 pp. Lyon, France: IARC, 1982.

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.

MEDLINEplus. Drug Information: Mechlorethamine. http://www.nlm.nih.gov/medlineplus/druginformation.html, 2001.

NTP. National Toxicology Program. NTP Chemical Repository. Nitrogen Mustard Hydrochloride. Last updated August 13, 2001. (http://ntp-server.niehs.nih.gov and search 55-86-7).

TRI99. Toxic Chemicals Release Inventory 1999. Data contained in the Toxic Chemical Release Inventory (TRI). Available from the U.S. Environmental Protection Agency Office of Environmental Information, http://www.epa.gov/triexplorer/reports.htm, 2001.

TSCA. Toxic Substances Control Act, Chemical Substance Inventory, 1979: public record.