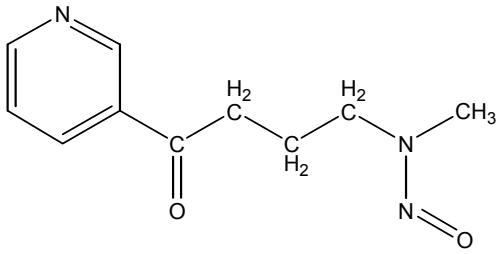
4-(*N*-NITROSOMETHYLAMINO)-1-(3-PYRIDYL)-1-BUTANONE
CAS No. 64091-91-4
First Listed in the *Sixth Annual Report on Carcinogens*



CARCINOGENICITY

4-(*N*-Nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK) is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity in experimental animals (IARC 1985, 1987). When administered by multiple subcutaneous injections, the compound induced neuroblastomas and rhabdomyosarcomas of the nasal cavity, adenocarcinoma and adenosquamous cell carcinomas of the lung, and hepatocellular carcinomas and hemangiosarcomas of the liver in rats of both sexes. In a similar study, NNK induced esthesioneuroepitheliomas, squamous cell carcinomas, anaplastic carcinomas, and spindle cell sarcomas of the nasal cavity; squamous cell carcinomas and adenocarcinomas of the lung; and benign and malignant tumors of the liver in rats of both sexes. An IARC Working Group interpreted the results as demonstrating dose-response relationships for induction of tumors of the nasal cavity, lung, and liver. In two studies in which NNK was administered by multiple subcutaneous injections and one study in which NNK was administered as a single subcutaneous injection, adenocarcinomas of the lung, pleomorphic carcinomas of the nasal cavity, and tumors of the trachea were induced in hamsters of both sexes. When administered by intraperitoneal injection, NNK induced adenomas and carcinomas of the lung in female mice.

No adequate data were available to evaluate the carcinogenicity of 4-(*N*-nitrosomethylamino)-1-(3-pyridyl)-1-butanone in humans (IARC 1985, 1987).

PROPERTIES

NNK is a light yellow crystalline solid with a melting point of 63°C to 65°C. It is slightly soluble in water and soluble in ethanol, acetone, methylene chloride, and other organic solvents of the mid-polarity range (NTP 2001). NNK occurs naturally in tobacco products or may be formed from the reaction of nicotine with sodium nitrate in aqueous solution. NNK occurs as a mixture of approximately 73% E-isomer and 27% Z-isomer. The abbreviation NNK was selected to emphasize the relationship of this compound to nicotine and stands for nicotine-derived nitrosamino ketone (IARC 1985). It is sensitive to prolonged exposure to air and light; however, solutions of NNK in water are stable for at least 24 hours. When heated to decomposition, it emits toxic fumes of carbon oxides and nitrogen oxides (NTP 2001).

USE

NNK has no known use other than as a laboratory chemical (IARC 1985).

PRODUCTION

NNK is not produced commercially, but is available from three U.S. suppliers in small quantities for laboratory research (IARC 1985, Chem Sources 2001). It is formed naturally by oxidation and nitrosation of nicotine during tobacco curing, ageing, processing, and smoking. Synthetic NNK is prepared by reacting sodium hydroxide and sodium nitrite with 4-(*N*-methyl)-1-(3-pyridyl)-1-butanone dihydrochloride or by reacting nicotine with sodium nitrite in aqueous solution (IARC 1985).

EXPOSURE

Potential exposure to NNK is widespread among tobacco product users and those exposed to sidestream smoke. It has been detected in tobacco at 0.1 to 35 mg/kg, in snuff products at 0.9 to 7 mg/kg, in mainstream cigarette or cigar smoke at 0.02 to 4.2 µg/cigarette, and in sidestream smoke at 0.2 to 15.7 ug/cigarette. One study showed that NNK concentrations decreased by 45% to 73% in filtered versus nonfiltered cigarettes. NNK may also form in the mouth during tobacco chewing or oral snuff use. Concentrations of NNK in the saliva from women who were snuff users ranged from 2.1 to 201 ng/g (IARC 1985).

REGULATIONS

OSHA regulates NNK under the Hazard Communication Standard and as a chemical hazard in laboratories. Regulations are summarized in Volume II, Table 131.

REFERENCES

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

IARC. International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Tobacco Habits Other than Smoking; Betel-Quid and Areca-Nut Chewing; Some Related Nitrosamines. Vol. 37. 291 pp. Lyon, France: IARC, 1985.

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.

NTP. National Toxicology Program. NTP Chemical Repository. 4-(N-Nitroso-N-methylamino)-1-(3-pyridyl)-1-butanone. Last updated August 13, 2001. (http://ntp-server.niehs.nih.gov and search 64091-91-4).