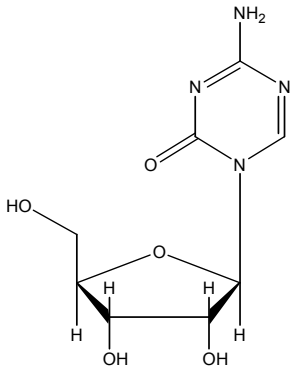
AZACITIDINE
CAS No. 320-67-2
First Listed in the *Eighth Report on Carcinogens*



CARCINOGENICITY

Azacitidine (5-Azacytidine; 5-AzaC) is *reasonably anticipated to be a human carcinogen* based on evidence of malignant tumor formation at multiple tissue sites in multiple species of experimental animals (NCI 1978, Luz and Murray 1988, IARC 1990).

5-AzaC, when administered by intraperitoneal (i.p.) injection, induced lymphoreticular neoplasms and skin and lung tumors in male and/or female mice (NCI 1978, Luz and Murray 1988, IARC 1990), and leukemia, lymphoma, and tumors of the liver and lung in offspring of treated pregnant dams (IARC 1990). In male rats, 5-AzaC administered i.p. induced squamous cell carcinoma of the skin and interstitial-cell tumors of the testes, and appeared to increase the incidence of non-testis tumors in male offspring of treated dams (IARC 1990).

No data were available to evaluate the carcinogenicity of 5-AzaC in humans (IARC 1990).

ADDITIONAL INFORMATION RELEVANT TO CARCINOGENESIS OR POSSIBLE MECHANISMS OF CARCINOGENESIS

Using an initiation-promotion experimental design, chronic i.p. treatment of male rats, previously acutely administered *N*-nitrosodiethylamine (DEN) and partially hepatectomized, with 5-AzaC resulted in a synergistic increase in the frequency of liver, lung, and skin tumors (Carr *et al*. 1988, IARC 1990).

The carcinogenic/enhancement activity of 5-AzaC has been postulated to result directly or indirectly from its ability to inhibit DNA methylation (Harrison *et al*. 1983, Kerbel *et al*. 1984, Kerbel *et al*. 1986, Takenaga 1986, Glover *et al*. 1987, Glover and Leyland-Jones 1987, Jones and Buckley 1990, Haaf 1995). Altered levels of DNA methylation can affect gene expression (Cedar 1988, IARC 1990, Fajkus *et al*. 1992, Velge *et al*. 1995), with hypomethylation being associated with the expression of genes that are normally silent or downregulated (Jones *et al*. 1983, Nyce *et al.* 1983, Riggs and Jones 1983, Collard *et al*. 1989, Jones and Buckley 1990, Pascale *et al*. 1993). In addition, 5-AzaC in the absence of metabolic activation is positive in a wide variety of prokaryotic, lower eukaryotic, and mammalian *in vitro* test systems, inducing

DNA damage, mutations (base-pair substitution mutations only) in prokaryote systems; mitotic recombination, gene conversion, and gene mutations in somatic and germ cells of lower eukaryotes (yeast, *Drosophila*, plants), and DNA damage, chromosomal aberrations, mutations (but not point), and morphological transformation in cultured mammalian cells. Studies to evaluate the genetic activity of 5-AzaC in somatic cells of mammals have not been reported; however, it was reported as negative for dominant lethal mutations in mice (IARC 1990).

No data were available to suggest that the mechanisms thought to account for tumor induction by 5-AzaC in experimental animals would not also operate in humans.

PROPERTIES

5-AzaC is a white crystalline powder with a melting point of 228 to 230°C. It is soluble in water, ethanol, acetone, chloroform, hexane, and dimethyl sulfoxide. 5-AzaC is very unstable in aqueous media, with rapid degradation to complex products occurring within hours of dissolution in intravenous solutions at room temperature. The chemical may discolor upon exposure to light and is probably combustible (NTP 2001).

USE

5-AzaC is an antineoplastic agent that has been used as an investigational drug since the l970s for the treatment of patients with acute myeloblastic anemia, acute lymphoblastic leukemia, and myelodysplastic syndromes (IARC 1990, NTP 2001, Santini *et al*. 2001, Pharmion 2001). 5-AzaC has been used clinically in cancer treatment trial protocols in combination with other antineoplastic agents such as vincristine, prednisone, vinblastine, cytarabine, or amsacrine (IARC 1990). 5-AzaC (alone or in combination with phenylbutyrate or amifostine) is currently being tested in at least seven clinical trials for the following conditions: beta thalassemia, acute myeloid leukemia, myelodysplastic syndrome, advanced or metastatic solid tumors, non-Hodgkins lymphoma, multiple myeloma, non-small cell lung cancer, and prostate cancer (ClinicalTrials.gov 2001).

PRODUCTION

5-AzaC is synthesized in Germany. It can be prepared by synthetic methods or can be isolated from a culture of the bacterium *Streptoverticillium ladakanus* (IARC 1990). No data on imports or exports of 5-AzaC were available. Chem Sources (2001) listed 11 U.S. suppliers of 5-AzaC.

EXPOSURE

The primary routes of potential human exposure to 5-AzaC are intravenous and intramuscular injection and intravenous infusion at daily doses of 40 to 750 mg/m^2 (IARC 1990). Occupational exposure may occur for workers formulating or packaging the solutions and for health care professionals administering the drug. The National Occupational Exposure Survey (1981-1983) indicated that 1,069 workers, including 699 women, potentially were exposed to 5-AzaC (NIOSH 1990). This estimate was derived from total observations of the use of the actual compound (48%) and trade name products (52%).

REGULATIONS

According to a monograph in the 1996 *Handbook on Injectable Drugs (HID)* entitled "Azacitidine Investigational" (Trissel 1996), azacitidine is still an investigational drug. Its investigational number is NSC-102816. No new information regarding drug status was found.

OSHA regulates azacitidine under the Hazard Communication Standard and as a chemical hazard in laboratories. Regulations are summarized in Volume II, Table 17.

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