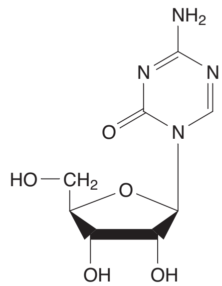
Azacitidine

CAS No. 320-67-2

Reasonably anticipated to be a human carcinogen

First listed in the *Eighth Report on Carcinogens* (1998)

Also known as 5-azacytidine, 5-azaC, or Vidaza (a registered trademark of Celgene Corporation)



Carcinogenicity

Azacitidine *is reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Exposure to azacitidine by injection caused tumors at several different tissue sites in mice and rats. Intraperitoneal injection of azacitidine caused cancer of the hematopoietic system (lymphocytic or histiocytic lymphoma or granulocytic leukemia or sarcoma) in female mice and skin and lung tumors in mice of both sexes. Prenatal exposure of mice to azacitidine caused leukemia, lymphoma, and tumors of the lung and liver (NCI 1978, Luz and Murray 1988, IARC 1990). In male rats, intraperitoneal injection of azacitidine caused skin cancer (squamous-cell carcinoma) and tumors of the testis (interstitial-cell neoplasia) (IARC 1990).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to azacitidine.

Studies on Mechanisms of Carcinogenesis

In an initiation-promotion study, partially hepatectomized male rats were administered *N*-nitrosodiethylamine followed by chronic administration of azacitidine by intraperitoneal injection. The incidence of liver tumors and the combined incidence of skin and lung tumors were increased; all surviving rats developed hyperplastic liver nodules (Carr *et al.* 1988, IARC 1990).

Azacitidine in the absence of mammalian metabolic activation is genotoxic in a wide variety of prokaryotic, lower eukaryotic, and mammalian *in vitro* test systems. It caused DNA damage and base-pair substitution mutations (but not frame-shift mutations) in prokaryotic systems and mitotic recombination, gene conversion, chromosomal aberrations, and gene mutations in somatic and germ cells of lower eukaryotes (yeast, fruit flies, and plants). In cultured rodent cells, azacitidine inhibited DNA synthesis and caused sister chromatid exchange, chromosomal aberrations, gene mutations (in some but not all studies), and morphological cell transformation. In cultured human cells, azacitidine caused DNA damage and gene mutations; studies on sister chromatid exchange and chromosomal aberrations gave conflicting results. Azacitidine did not cause dominant lethal mutations in male mice exposed *in vivo* (IARC 1990).

The carcinogenic or tumor-enhancing activity of azacitidine has been postulated to result directly or indirectly from its ability to inhibit DNA methylation (Harrison *et al.* 1983, Riggs and Jones 1983, Kerbel *et al.* 1984, 1986, Takenaga 1986, Glover and Leyland-Jones 1987, Glover *et al.* 1987, IARC 1990, 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), and hypomethylation is associated with the expression of genes that are normally silent or downregulated. DNA hypomethylation is somatically heritable, causing alterations in gene expression that are maintained in daughter cells as the affected cells proliferate (Holliday 2006). In pBOR-Il-3 mice, which are transgenic for the interleukin-3 (IL-3) gene (expression of which is driven by a long-terminal repeat), injection of azacitidine increased the incidence of thymic lymphoma over that observed in nontransgenic controls. The authors concluded that increased expression of IL-3, resulting from demethylation of the transgene long-terminal repeat by azacitidine, was responsible for the increased incidence of lymphoma (Saavedra *et al.* 1996). There is no evidence to suggest that the mechanisms by which azacitidine causes tumors in experimental animals would not also operate in humans.

Properties

Azacitidine is a pyrimidine analogue of cytidine that exists at room temperature as a white crystalline powder (IARC 1990). It is soluble in warm and cold water, 0.1 N hydrochloric acid, 0.1 N sodium hydroxide, 35% ethanol, and dimethyl sulfoxide, and slightly soluble in acetone, chloroform, and hexane. Azacitidine is stable under normal temperatures and pressures (Akron 2009), but is very unstable in aqueous solution, breaking down to complex products within hours (IARC 1990). Its stability in aqueous solutions depends on pH; in neutral and alkaline solutions, it has a half-life of 4 hours, but in Ringer's solution (pH 6.2), its half-life is 65 hours (Glover and Leyland-Jones 1987). Physical and chemical properties of azacitidine are listed in the following table.

Property	Information
Molecular weight	244.2[a]
Melting point	228°C to 230°C (decomposes)[a]
Log K_{ow}	–3.83[b]
Water solubility	89 g/L at 25°C[b]
Vapor pressure	4.1×10^{-12} mm Hg at 25°C[b]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

Azacitidine is a cytostatic anticancer drug that has been used in the United States since 1970. (NCI 1978). One product containing azacitidine as the active ingredient has been approved by the U.S. Food and Drug Administration; it is available in 100-mg vials for subcutaneous injection (FDA 2009). Azacitidine is approved to treat chronic myelomonocytic leukemia and myelodysplastic syndromes. It is also used to treat acute myeloblastic leukemia, breast cancer, colon cancer, melanoma, and ovarian cancer (IARC 1990, Santini *et al.* 2001, Celgene 2010). Azacitidine is also used in clinical trials in combination with other antineoplastic agents, such as vincristine, prednisone, vinblastine, cytarabine, or amsacrine (IARC 1990).

Production

Azacitidine may be produced synthetically or isolated from the bacterium *Streptoverticillium ladakanus* (IARC 1990). In 2009, azacitidine was available from 22 suppliers worldwide, including 15 U.S.

suppliers (ChemSources 2009). No data on U.S. imports or exports of azacitidine were found.

Exposure

The primary route of human exposure to azacitidine is intravenous or intramuscular injection in patients receiving anticancer therapy. Daily doses are 40 to 750 mg/m^2 of body surface. The typical treatment regimen starts with a dose of 75 mg/m^2 daily for one week of every four-week period (IARC 1990, Riley and DeRuiter 2005); the dose may be increased to 100 mg/m^2 as needed and if side effects are tolerable. In 2009, 80 clinical trials using azacitidine (alone or in combination with other drugs) for treatment of several types of cancer were in progress or recently completed (ClinicalTrials 2009). Occupational exposure could occur among health professionals and support staff (including custodians) by dermal contact, inhalation, or accidental ingestion during drug preparation or administration or cleanup of medical waste, including disposal of excretions from treated patients (Zimmerman *et al.* 1981, NIOSH 2004). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 1,069 health-services workers, including 698 women, potentially were exposed to azacitidine (NIOSH 1990).

Regulations

Food and Drug Administration (FDA)

Azicitidine is regulated as a prescription drug subject to labeling and other requirements.

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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