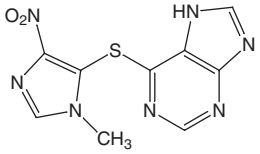
Azathioprine
CAS No. 446-86-6

Known to be a human carcinogen
First Listed in the *Fourth Annual Report on Carcinogens* (1985)



Carcinogenicity

Azathioprine is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity in humans. Two large prospective epidemiological studies reported a high incidence of non-Hodgkin's lymphoma, squamous cell cancers of the skin, hepatobiliary carcinomas, and mesenchymal tumors in renal transplant patients, who are treated almost routinely with azathioprine and prednisone. Non-transplant patients (for example, patients with rheumatoid arthritis, systemic lupus and other collagen disorders, inflammatory bowel disease, and certain skin and renal diseases) treated with azathioprine also had an increased, although lower, risk of the same cancers as the transplant patients. Rheumatoid arthritis also is a risk factor for non-Hodgkin's lymphoma (IARC 1981, 1982, 1987).

There is limited evidence of carcinogenicity of azathioprine in experimental animals. Squamous-cell carcinomas of the ear duct were observed in rats after oral administration, and lymphomas were observed in mice after intraperitoneal, subcutaneous, or intramuscular injection of azathioprine. The International Agency for Research on Cancer (IARC) (1981, 1982, 1987) considered these results to be inconclusive because of limitations in the study design and inadequate reporting.

Properties

Azathioprine is a purine analog and antimetabolite (inhibits purine synthesis). It has a molecular weight of 277.3 and occurs as an odorless, pale yellow powder or crystals. It is insoluble in water and very slightly soluble in ethanol and chloroform; however, its sodium salt is soluble in water. The log octanol-water partition coefficient is 0.10. It is sensitive to oxidation and decomposes in strong alkali solutions. The melting point is 243°C to 244°C. When heated to decomposition, it emits toxic fumes of nitrogen oxides and sulfur oxides (IARC 1981, HSDB 2003).

Use

Azathioprine is an immunosuppressive agent, generally used in combination with a corticosteroid to prevent rejection following allogeneic (from a genetically different donor) kidney transplants and to manage severe cases of rheumatoid arthritis in adults when other treatments have failed. It also may be used following transplant surgery for other organs and as a second-line treatment for a variety of immunological diseases such as systemic lupus erythematosus, autoimmune hemolytic anemia, chronic active hepatitis, ulcerative colitis, Crohn's disease, myasthenia gravis, and others (IARC 1981, IPCS 1996, HSDB 2003).

Production

Azathioprine was first produced commercially in the United States in 1970 and was manufactured by one U.S. company (IARC 1981). Although no current U.S. producers were identified in 2003 (SRI 2003), there were at least three U.S. suppliers (ChemSources 2003). Five U.S. pharmaceutical companies with drug products approved by the U.S. Food and Drug Administration (FDA) containing azathioprine as the active ingredient were identified (FDA 2003). No import or export data were located.

Exposure

The routes of exposure to azathioprine during medical treatment are ingestion and intravenous injection. Kidney transplant patients and adults with severe cases of rheumatoid arthritis or other immunological diseases may be treated with azathioprine (IARC 1981). It is available in 25-, 50-, 75-, and 100-mg tablets. The injectable form is available as the sodium salt in 100-mg vials (FDA 2003). The usual dose is 3 to 5 mg/kg body weight (b.w.) daily for kidney transplant patients, which may be reduced to 1 to 3 mg/kg for maintenance. For rheumatoid arthritis, the initial dose is 1 mg/kg b.w. per day and may be increased up to 2.5 mg/kg b.w. per day (RxList 2003). In 2002, sales of generic forms of azathioprine totaled $68 million for approximately 1 million prescriptions (DrugTopics 2003a,b).

Potential occupational exposure to azathioprine may occur via inhalation of dust during its manufacture, formulation, and packaging. A study conducted at a pharmaceutical plant in South Africa reported that the highest median concentration of azathioprine dust measured in the breathing zone was 0.26 mg/m^3 and in personal samples was 0.07 mg/m^3 (Jeebhay *et al.* 1993). The National Occupational Exposure Survey (1981-1983) estimated that 1,849 total workers, including 880 women, were potentially occupationally exposed to azathioprine (NIOSH 1984).

Regulations

CPSC

Any orally-administered, prescription drug for human use requires child-resistant packaging

FDA

Azathioprine is a prescription drug subject to labeling and other requirements

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