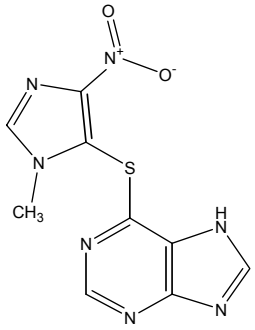
AZATHIOPRINE
CAS No. 446-86-6
First Listed in the *Fourth Annual Report on Carcinogens*



CARCINOGENICITY

Azathioprine is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity in humans (IARC 1982, 1987). Two large prospective epidemiological studies have shown that renal transplant patients, who usually receive azathioprine as an immunosuppressant, become at high risk for non-Hodgkin's lymphoma, squamous cell cancers of the skin, hepatobiliary carcinomas, and mesenchymal tumors. Although this is true for each of the various etiological entities resulting in the need for a transplant, a commonality among these is heavy exposure to foreign antigens. Other patients who have received azathioprine as an immunosuppressant, including those with rheumatoid arthritis, systemic lupus and other "collagen" disorders, inflammatory bowel disease, and certain skin and renal diseases, have also been studied; the same array of malignancies was found to be in excess, although to a lesser extent. For these patients, however, the picture is still not completely clear, because patients with rheumatoid arthritis constituted the largest category in the latter study, and some, but not all studies, have found that this disease conveys a risk for non-Hodgkin's lymphoma in the absence of treatment.

An IARC Working Group reported that there is limited evidence of carcinogenicity of azathioprine in experimental animals (IARC 1981, 1982, 1987). Suggestive evidence was obtained that lymphomas were induced in mice after intraperitoneal, subcutaneous, or intramuscular injection of azathioprine and that thymic lymphomas and squamous cell carcinomas of the ear duct were induced in rats after oral administration, but there were limitations in the design and reporting of these studies.

PROPERTIES

Azathioprine occurs as an odorless, pale yellow powder or crystals. It is insoluble in water and very slightly soluble in ethanol and chloroform. It is sensitive to oxidation and decomposes in strong alkali solutions. When heated to decomposition, it emits toxic fumes of nitrogen oxides and sulfur oxides (IARC 1981).

USE

Azathioprine is an immunosuppressive agent, generally used in combination with a corticosteroid to prevent rejection following renal homotransplantation. It is also used following transplantation of other organs. Other uses of azathioprine include the treatment of a variety of presumed autoimmune diseases, including rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, dermatomyositis, periarteritis nodosa, scleroderma, refractory thrombocytopenic purpura, autoimmune hemolytic anemia, chronic active liver disease, regional enteritis, ulcerative colitis, various autoimmune diseases of the eye, acute and chronic glomerulonephritis, the nephrotic syndrome, Wegener's granulomatosis, and multiple sclerosis (IARC 1981, IPCS INCHEM 1996).

PRODUCTION

Azathioprine was manufactured by one U.S. company from 1980 to 1994, but the amounts were undisclosed (USITC 1981-1991, 1993-1995). No import or export data were located. Five current U.S. suppliers of azathioprine were identified (Chem Sources 2001).

EXPOSURE

The primary routes of potential human exposure to azathioprine are ingestion, inhalation, and dermal contact. Since the 1970s, it has been used orally as a pharmaceutical to prevent rejection following organ transplantation and to treat a variety of autoimmune diseases. Azathioprine is readily absorbed from the gut and is known to cross the human placenta. Potential occupational exposure to azathioprine may occur during its manufacture, formulation, packaging, or administration (IARC 1981). In a study of workers involved in the production of azathioprine at a pharmaceutical plant in South Africa, results of the industrial hygiene monitoring, which showed that the air inside the airhoods worn when the dry product was handled was in fact contaminated, suggest that the workers are at risk of developing adverse health effects. The highest median 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 1,394 total workers, including 650 women, were potentially occupationally exposed to azathioprine (NIOSH 1984).

REGULATIONS

Because azathioprine is used as a pharmaceutical and is in low quantities relative to other chemicals, it is not regulated by EPA. However, there may be a small pollution problem relative to hospital wastes.

FDA regulates azathioprine under the Food, Drug, and Cosmetic Act (FD&CA) as a prescription drug approved for human use. FDA also regulates the labeling of all human prescription drugs containing azathioprine.

OSHA regulates azathioprine under the Hazard Communication Standard and as a chemical hazard in laboratories. It is listed as a medication that a physician and employer may wish to review. Regulations are summarized in Volume II, Table 18.

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