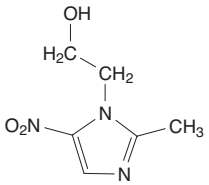
Metronidazole

CAS No. 443-48-1

Reasonably anticipated to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)



Carcinogenicity

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

Cancer Studies in Experimental Animals

Oral exposure to metronidazole caused tumors at several different tissue sites in mice and rats. Dietary administration of metronidazole caused benign and malignant lung tumors (adenoma, adenocarcinoma, and carcinoma) in mice of both sexes, lymphoma in female mice (Rustia and Shubik 1972, IARC 1977), liver cancer (hepatocellular carcinoma) and mammary-gland tumors (fibroadenoma) in female rats, and tumors of the pituitary gland (adenoma) and testes (Leydig-cell tumors) in male rats (IARC 1982).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to metronidazole. An excess of cancer of the uterine cervix was found in two epidemiological studies of women treated with metronidazole for vaginal trichomoniasis (Beard *et al.* 1979, Friedman and Ury 1980, IARC 1982); however, trichomoniasis is a risk factor for cervical cancer, and one of the studies (Beard *et al.* 1979) showed a greater excess of cancer among women with trichomoniasis who were not exposed to metronidazole. The study by Beard *et al.,* but not that by Friedman *et al.*, reported an excess of lung cancer, which may have been due to smoking.

Since metronidazole was listed in the *Fourth Annual Report on Carcinogens,* additional epidemiological studies have been identified. In a follow-up of the cohort study by Beard *et al.,* the incidence of lung cancer (bronchogenic carcinoma) was significantly increased in women exposed to metronidazole, and the excess remained after an attempt to adjust for smoking (Beard *et al*. 1988). In a study of over 12,000 people who had used metronidazole, no excess of cancer (all tissue sites combined) was found after two and a half years of follow-up (IARC 1987). A large cohort study of cancer in children prenatally exposed to metronidazole found no overall excess of cancer (all tissue sites combined); a twofold increase in the risk of neuroblastoma (cancer of the sympathetic nervous system) was not statistically significant (Thapa *et al.* 1998)

Properties

Metronidazole is a nitroamidazole compound that exists at room temperature as white to pale-yellow crystals with a slight odor (Akron 2009). It is soluble in water, ethanol, ether, chloroform, and dilute acids and sparingly soluble in dimethylformamide (IARC 1977). It is stable under normal temperatures and pressure, but may discolor upon exposure to light (Akron 2009). Physical and chemical properties of metronidazole are listed in the following table.

Property	Information
Molecular weight	171.2[a]
Melting point	158°C to 160°C[a]
Log K_{ow}	–0.02 at 25°C[a]
Water solubility	10 g/L at 25°C[b]
Vapor pressure	3.05×10^{-7} mm Hg at 25°C[c]

Sources: [a]HSDB 2009, [b]IARC 1977, [c]ChemIDplus 2009.

Use

Metronidazole is used primarily as a drug for the treatment of infections by the parasitic protozoans *Entamoeba histolytica, Trichomonas vaginalis,* and *Giardia lamblia* (IARC 1977). It has also been used to treat Vincent infection (trench mouth) and acne rosacea. It has been prescribed for invasive intestinal amoebiasis and amoebic hepatic abscess, antibiotic-associated colitis, infection by the protozoan *Balantidium coli,* dental infection, gastritis or ulcer due to *Heliobacter pylori*, and inflammatory bowel disease (MedlinePlus 2009). It is also used as a trichomonacidal agent in veterinary medicine (IARC 1977, MedlinePlus 2009). Metronidazole may be administered orally (in capsules or tablets), vaginally (in creams, gels, or tablets), topically (in gels, creams, or lotions), or by intravenous injection (MedlinePlus 2009).

Production

Commercial production of metronidazole in the United States was first reported in 1963 (IARC 1977). In 1974, only one U.S. company reported producing metronidazole. In 1977, annual U.S. sales of metronidazole for medical use were estimated to be less than 28,600 lb. In 2009, metronidazole was avaialble from 18 U.S. suppliers (Chem Sources 2009), and 42 drug products registered with the U.S. Food and Drug Administration contained metronidazole as an active ingredient (FDA 2009). No more recent data on U.S. production, imports, or exports were found.

Exposure

The primary routes of human exposure to metronidazole are ingestion, injection, or topical (including intravaginal) application for treatment of certain infectious diseases (MedlinePlus 2009). For treatment of bacterial infections, a recommended regimen is oral administration of 525 mg every 6 hours for seven days. As a systemic trichomonacidal agent, metronidazole typically is administered orally at a dosage of either 250 mg three times a day for seven days or 1 to 2 g twice on one day. When used to treat giardiasis, it is administered at 500 to 750 mg daily for five to ten days. For intravenous administration to treat bacterial infections, the typical regimen is 15 mg/kg of body weight initially, followed by 7.5 mg/kg every 6 hours for seven days. When administered prophylactically for colon surgery, metronidazole is injected 1 hour before surgery and at 6 and 12 hours after the first dose. When administered as a topical cream, it is usually applied twice a day for nine weeks. Metronidazole is also applied intravaginally either at 37.5 mg twice a day for five days for bacterial infections or 500 mg daily for 10 to 20 days for bacterial infections or trichomoniasis. In 2009, 149 clinical trials involving metronidazole were in progress or recently completed (ClinicalTrials 2009). Occupational exposure to metronidazole could occur through inhalation or dermal contact by workers involved in its manufacture, formulation, packaging, or administration.

Regulations

Consumer Product Safety Commission (CPSC)

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

Food and Drug Administration (FDA)

Metronidazole is 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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