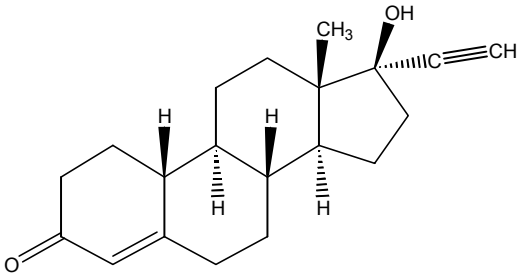
NORETHISTERONE
CAS No. 68-22-4
First Listed in the *Fourth Annual Report on Carcinogens*



CARCINOGENICITY

Norethisterone is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity in experimental animals (IARC 1974, 1979, 1982). When administered in the diet, norethisterone increased the incidence of benign liver cell tumors in male mice and male rats and pituitary tumors in female mice; further, dietary administration induced benign and malignant mammary tumors in male rats. When administered subcutaneously, the compound induced granulosa cell tumors in ovaries of mice.

No adequate human studies of the relationship between exposure to norethisterone and human cancer have been reported (IARC 1982).

PROPERTIES

Norethisterone occurs as a white, odorless, crystalline powder with a slightly bitter taste. It is practically insoluble in water, slightly soluble in diethyl ether and vegetable oil, and soluble in ethanol, acetone, chloroform, dioxane, and pyridine. It is unstable in the presence of air and light. When heated to decomposition, it emits acrid smoke and fumes. Norethisterone is available in the United States as a grade containing 97% to 102% active ingredient on an anhydrous basis (HSDB 2002).

USE

Norethisterone, an orally active progestin, has been used in small amounts in human medicine since 1957 to treat conditions such as amenorrhea, dysfunctional uterine bleeding, endometriosis, premenstrual tension, and dysmenorrhea. Since 1962, the most common use in the United States has been as the progestin in progestin-estrogen combination oral contraceptives. Norethisterone has been used in the treatment of inoperable malignant neoplasms of the breast or as an adjunct to surgery or radiotherapy (IARC 1979). Norethisterone is also used as an intermediate in the commercial synthesis of norethisterone acetate and possibly in the synthesis of ethynodiol diacetate (IARC 1974).

PRODUCTION

Chem Sources (2001) identified 12 U.S. suppliers for norethisterone. Norethisterone is not produced in the United States. Data on imports were not available. Prior to 1972, total U.S. sales for human medicine containing norethisterone were estimated to have been <4,400 lb/year (IARC 1974).

EXPOSURE

The primary routes of potential human exposure to norethisterone are ingestion, dermal contact, and inhalation. When used as an oral contraceptive, it is usually given in a dose of 0.5 to 2.0 mg daily in combination with mestranol or ethinylestradiol. It is also used continuously at a daily dose of 0.35 mg in the so-called contraceptive "mini-pill". In its other medicinal uses, norethisterone is given in daily doses ranging from 10 to 30 mg (IARC 1979). Potential occupational exposure may occur through inhalation or dermal contact for workers involved in the manufacture, formulation, packaging, or administration of norethisterone. In a study conducted in a factory producing oral contraceptives, norethisterone was found in various sectors of the working environment at concentrations ranging from 0.30 to 59.56 $\mu g/m^3$ and in wipe samples from 0.019 to 14.7 $\mu g/cm^2$ (IARC 1979, HSDB 2002).

REGULATIONS

Because this chemical is used as a pharmaceutical and 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 norethisterone under the Food, Drug, and Cosmetic Act (FD&CA) as a prescription drug approved for human use. FDA has ruled that oral contraceptives for general use must carry patient and physician warning labels concerning use, risks, and contraindications.

OSHA regulates norethisterone under the Hazard Communication Standard and as a chemical hazard in laboratories. Regulations are summarized in Volume II, Table 139.

REFERENCES

Chem Sources. Chemical Sources International, Inc. http://www.chemsources.com, 2001.

HSDB. Hazardous Substances Data Bank. Online database produced by the National Library of Medicine. Norethindrone. Profile last updated January 14, 2002. Last review date, September 14, 1995.

IARC. International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Sex Hormones. Vol. 6. 243 pp. Lyon, France: IARC, 1974.

IARC. International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Sex Hormones (II). Vol. 21. 583 pp. Lyon, France: IARC, 1979.

IARC. International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Chemicals, Industrial Processes and Industries Associated with Cancer in Humans. Supplement 4. 292 pp. Lyon, France: IARC, 1982.