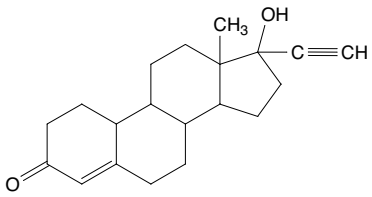
Norethisterone

CAS No. 68-22-4

Reasonably anticipated to be a human carcinogen

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

Also known as norethindrone



Carcinogenicity

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

Cancer Studies in Experimental Animals

Norethisterone caused tumors in two rodent species, at several different tissue sites, and by two different routes of exposure. Oral exposure to norethisterone caused benign liver tumors (hepatocellular neoplasia) in male mice and male rats, pituitary-gland tumors in female mice, and benign and malignant mammary-gland tumors in male rats. Subcutaneous implantation of pellets containing norethisterone caused ovarian tumors (granulosa-cell neoplasia) in female mice (IARC 1974, 1979). Norethisterone acetate administered orally caused benign liver tumors in male mice and female rats and uterine polyps in female rats (IARC 1982).

Cancer Studies in Humans

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

Studies on Mechanisms of Carcinogenesis

In female rats orally exposed first to the carcinogen *N*-2-acetylaminofluorene at a non-tumorigenic dose and then to norethisterone, benign and malignant liver tumors (neoplastic nodules and hepatocellular carcinoma) were observed (IARC 1982).

Joint dietary administration of norethisterone and synthetic estrogens to rodents caused tumors at the same tissue sites as observed for norethisterone alone. Pituitary-gland tumors were observed in mice of both sexes following administration of norethisterone plus mestranol or ethinylestradiol and also following administration of norethisterone acetate plus ethinylestradiol (an effect not seen in mice administered norethisterone acetate alone). In rats, administration of norethisterone plus mestranol caused malignant mammary-gland tumors in both sexes and benign liver tumors in males, and administration of norethisterone acetate plus ethinylestradiol caused benign mammary-gland and liver tumors in both sexes.

Properties

Norethisterone is a synthetic steroidal progestin that is a white crystalline powder at room temperature (IARC 1974, HSDB 2009). It is slightly soluble in 95% ethanol, pyridine, acetone, chloroform, dioxane, vegetable oil, and diethyl ether and sparingly soluble in alcohol. It is stable in air, but unstable in air in the presence of light (Akron 2009). When heated to decomposition, it emits acrid smoke and fumes. Physical and chemical properties of norethisterone are listed in the following table.

Property	Information
Molecular weight	298.4[a]
Density	1.2 g/cm^3[b]
Melting point	203°C to 204°C[a]
Log K_{ow}	2.97[a]
Water solubility	0.00704 g/L at 25°C[a]
Vapor pressure	7.31×10^{-9} mm Hg at 25°C[c]

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

Use

Norethisterone, an orally active progestin hormone, 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, and in hormone replacement therapies (IARC 1979, MedlinePlus 2009b). Since 1962, the most common use in the United States has been as the progestin in progestin-estrogen combination oral contraceptives. Norethisterone is also used as an intermediate in the commercial synthesis of norethisterone acetate and possibly in the synthesis of ethynodiol diacetate (IARC 1974). Norethisterone acetate has been used in the treatment of inoperable breast cancer or as an adjunct to surgery or radiotherapy (IARC 1979).

Production

Total annual U.S. sales of human medicine containing norethisterone before 1972 were estimated at less than 4,400 lb (IARC 1974). In 2009, norethisterone was produced by one manufacturer each in the United States, Europe, and India (SRI 2009) and was available from 22 suppliers, including 11 U.S. suppliers (ChemSources 2009). No data on U.S. imports of norethisterone were found.

Exposure

The routes of potential human exposure to norethisterone are ingestion, dermal contact, and inhalation (HSDB 2009). Norethisterone is a synthetic hormone and is administered most often as a contraceptive or hormone replacement in oral tablets or dermal patches (MedlinePlus 2009a). In 2009, 59 prescription products registered with the U.S. Food and Drug Administration contained norethindrone or norethindrone acetate as an active ingredient, of which 2 were dermal patches and 57 were oral tablets. Both dermal patches contained norethindrone acetate. When used as an oral contraceptive, norethisterone usually is given at a dose of 0.5 to 2.0 mg daily in combination with mestranol or ethinylestradiol (synthetic estrogen hormones) (IARC 1979). In the contraceptive "mini-pill," it is used continuously at a daily dose of 0.35 mg. Norethisterone acetate is also administered in several hormone replacement therapies (Medline Plus 2009b). For other medicinal uses, daily doses of norethisterone range from 10 to 30 mg (IARC 1979).

A study conducted to determine the presence of hormones in environmental water samples detected norethisterone in 12.8% of U.S. stream water samples, at a median concentration of 0.048 µg/L (Kolpin *et al.* 2002), but not in any sample collected in the Czech Republic (Morteani *et al.* 2006).

Potential occupational exposure to norethisterone may occur through inhalation or dermal contact by workers involved in its manufacture, formulation, packaging, or administration (HSDB 2009). In a study conducted in a factory that produced oral contraceptives, norethisterone was found in various sectors of the working environment at concentrations ranging from 0.30 to 59.56 µg/m^3 in airborne dust and from 0.019 to 14.7 µg/cm^2 in wipe samples (IARC 1979).

Regulations

Consumer Product Safety Commission (CPSC)

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

Food and Drug Administration (FDA)

Norethisterone is regulated as a prescription drug and is 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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