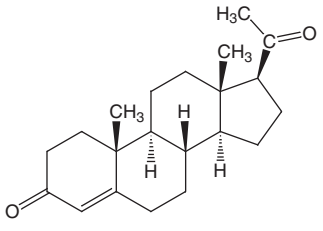
Progesterone
CAS No. 57-83-0

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



Carcinogenicity

Progesterone is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity in experimental animals (IARC 1982). When progesterone was implanted subcutaneously, mammary carcinomas were induced at a significantly earlier age and at a higher incidence in female mice. Long-term subcutaneous implants induced ovarian granulosa cell tumors or endometrial stromal sarcomas in female mice (IARC 1974, 1979). Subcutaneous injections of progesterone induced increased incidences of mammary tumors in adult female mice and lesions of the vaginal or cervical epithelia and genital tract lesions in newborn female mice. Hyperplastic alveolar-like nodules and other dysplasias were also induced in female neonatal mice (IARC 1979). Long-term subcutaneous injections in female dogs induced endometrial hyperplasia, inhibition of ovarian development, marked mammary hyperplasia, and some fibroadenomatous nodules of the mammary gland (IARC 1979, 1982).

Female mice injected subcutaneously with progesterone showed decreased latent periods for the induction of mammary tumors by 3-methylcholanthrene. Ovariectomized female mice receiving injections of progesterone developed sarcomas of the uterine horn when given an intrauterine implant of 3-methylcholanthrene and developed increased incidences of squamous cell carcinomas of the cervix or vagina when treated intravaginally with 7,12-dimethylbenz[*a*]anthracene (IARC 1974, 1979). Local applications of 3-methylcholanthrene and subcutaneous implantations of progesterone induced increased incidences of vaginal-cervical invasive squamous cell carcinomas in female mice (IARC 1979). Rats receiving subcutaneous or intramuscular injections of progesterone had decreased latent periods and/or increased incidences of mammary tumors induced by oral administration of 3-methylcholanthrene or 7,12-dimethylbenz[*a*]anthracene, but only when the known carcinogens were administered first. An increased incidence of mammary tumors was induced in female rats fed 2-acetylaminofluorene in the diet and injected intramuscularly with progesterone. Newborn female rats receiving a subcutaneous injection of progesterone and a subsequent intragastric instillation of 7,12-dimethylbenz[*a*]anthracene developed increased incidences of mammary adenocarcinomas (IARC 1979).

No adequate human studies of the relationship between exposure to progesterone and human cancer have been reported (IARC 1974, 1979, 1982).

Properties

Progesterone is a white crystalline powder that occurs in two forms that are readily interconvertible: orthorhombic prisms and orthorhombic needles. Its molecular weight is 314.5, its melting point is 127°C to 131°C, and it has a specific gravity of 1.166 at 23°C. It is insoluble in water, sparingly soluble in vegetable oils, and soluble in ethanol, acetone, dioxane, and concentrated sulfuric acid. It is sensitive to light (HSDB 2001).

Use

Progesterone is a naturally occurring steroidal hormone found in a wide variety of tissues and biological fluids. It is secreted by the ovary in normal adult cycling females, by the placenta in pregnant females, and by the adrenal cortex. It is essential for the normal functioning of the uterine lining, for the development of mammary glands, and support of pregnancy through parturition (Prosser 1973). Progesterone is used in medicine to treat secondary amenorrhea and dysfunctional uterine bleeding. It has also been used to treat female hypogonadism, dysmenorrhea and premenstrual tension, habitual and threatened abortion, preeclampsia and toxemia of pregnancy, mastodynia, uterine fibroma, and neoplasms of the breast and endometrium (PDR 2002). Progesterone embedded in an intrauterine device is used for contraception (Mosby 2001). In veterinary medicine, progesterone is used to control habitual abortion and to delay estrus and ovulation in cattle, swine, and dogs (IARC 1979).

Production

Progesterone is a naturally occurring steroid hormone produced endogenously by all mammalian species. The production rate in humans ranges from 0.15 mg/24 hr in prepubescent boys to 19.58 mg/24 hr in normal adult cycling females (Tagatz & Gurpide 1973). The USITC identified one producer of progesterone for 1988, but no production data were reported (USITC 1989). Chem Sources (2001) identified 18 current U.S. suppliers of progesterone. The 1979 TSCA Inventory identified one importer of progesterone in 1977, but data on the amount of U.S. imports and exports of progesterone were not available (TSCA 1979). U.S. imports of progesterone of animal or vegetable origin were reported to be 11,700 lb in 2000 (ITA 2001). In 1975, U.S. production of 13 estrogen and progestin substances, including progesterone, amounted to 23,100 lb. Before U.S. governmental restrictions in 1973, total U.S. sales of progesterone for use in human medicine were estimated to have been <110 lb annually (IARC 1974).

Exposure

The primary routes of potential exogenous human exposure to progesterone are ingestion, injection of medications containing the compound, implantation, dermal contact, and inhalation. Injection dosages range from 2 to 50 mg, either in single or multiple administrations. Progesterone embedded in an intrauterine contraceptive device is a potential route of exposure to a limited population. Embedded systems release progesterone from the system *in situ* at an average rate of 65 µg/day for one year by a membrane-controlled diffusion (Mosby's GenRx 2000). Prescribed progesterone capsules come in doses of 100 and 200 mg micronized progesterone. Prescribed vaginal gel applicators deliver 45 mg (4% gel) or 90 mg (8% gel) progesterone (PDR 2002). Human placental extracts, of which progesterone is believed to be the main constituent, have been used in preparations for cosmetic use (at levels of 0.1% to 1.0%), hair conditioners, shampoos, and grooming aid tonics (<0.1%) (IARC 1979). Potential consumer exposure through dermal contact could occur from use of these cosmetics. FDA reported that progesterone has been detected in cow's milk at concentrations of 1 to 30 ng/mL and in milk products at up to 300 µg/kg (in butter). It has also been found to occur naturally in certain plant species (IARC 1979). Animal meat may contain an average of 0.33 mg progesterone/kg if the animal was treated with a progesterone implant. Consumers could potentially be exposed to progesterone by ingesting these food products. Potential occupational exposure to progesterone may occur through inhalation and dermal contact during its production or formulation into pharmaceuticals. A joint investigation

of an oral contraceptive plant, conducted by NIOSH and CDC, found evidence of hyperestrogenism in both male and female workers and wide variations in air sample concentrations of estrogen and progesterone (DCI 1977). The National Occupational Exposure Survey (1981-1983) indicated that 287 workers, including 54 women, potentially were exposed to progesterone (NIOSH 1984). This estimate was derived from observations of the actual use of the compound. The National Occupational Hazard Survey, conducted by NIOSH from 1972 to 1974, estimated that 22,963 workers were potentially exposed to progesterone in the workplace in 1970 (NIOSH 1976).

Regulations

FDA

Acceptable incremental levels of progesterone in edible tissues above the concentrations of progesterone naturally present in untreated animals range from 3-15 ppb

Conditions for use for progesterone in animal drugs are specified

Progesterone in topically applied hormone-containing drugs for over the counter use is no longer considered generally recognized as safe (GRAS) and effective

Progesterone is a prescription drug subject to labeling and other requirements

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