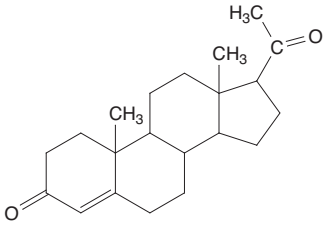
Progesterone

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 from studies in experimental animals.

Cancer Studies in Experimental Animals

Progesterone caused tumors of the mammary gland and female genital tract in several species of experimental animals. In female mice, progesterone administered by subcutaneous implantation increased the incidence of mammary-gland cancer (carcinoma) and caused its earlier onset, as well as causing tumors of the ovary (granulosa-cell tumors) and uterus (endometrial sarcoma). Administration of progesterone to newborn female mice by subcutaneous injection caused mammary-gland tumors and tumors of the genital tract, especially the vagina and cervix. In female dogs, long-term intramuscular injection of progesterone caused benign mammary-gland tumors (papilloma and adenoma) (IARC 1974b, 1979, 1982).

Progesterone administered in combination with other chemicals (known carcinogens) had similar effects. In female mice infected with mammary tumor virus, subcutaneous injection of progesterone increased the incidence of mammary-gland tumors induced by 3-methylcholanthrene; in uninfected mice, it caused earlier onset of tumors. In ovariectomized mice given 3-methylcholanthrene via intrauterine implantation, subcutaneous injection of progesterone promoted the development of uterine tumors (endometrial sarcoma). Subcutaneous implantation of progesterone together with local application of 3-methylcholanthrene caused vaginal and cervical cancer (squamous-cell carcinoma) in female mice. In rats, subcutaneous or intramuscular injection of progesterone following exposure to 7,12-dimethylbenz[*a*]anthracene or 3-methylcholanthrene resulted in increased incidence and/or earlier onset of mammary-gland tumors. In female rats administered 2-acetylaminofluorene in the diet, intramuscular injection of progesterone promoted the development of mammary-gland tumors (IARC 1974b, 1979, 1982).

Cancer Studies in Humans

At the time progesterone was listed in the *Fourth Annual Report on Carcinogens,* no epidemiological studies were available that evaluated the relationship between human cancer and exposure specifically to progesterone. Since that time, several additional epidemiological studies have been identified. These studies focused primarily on progesterone-only oral contraceptives or estrogen-progesterone combinations used as oral contraceptives or menopausal therapies. Relatively few studies have addressed the more limited use of progesterone as an injectable or implanted contraceptive or in treatment of other medical conditions (e.g., for amenorrhea, uterine bleeding or fibroma, or pregnancy complications or in certain infertility drugs).

The International Agency for Research on Cancer (IARC 1999) evaluated a number of cohort and case-control studies of cancer risk, principally of breast and endometrial cancer, associated with the use of progestogen-only contraceptives, and concluded that there was inadequate evidence of the carcinogenicity of progestogen-only contraceptives in humans. A subsequent review by La Vecchia and Franceschi (2002) supported these findings. However, a more recent case-control study reported an increased risk of breast cancer with prolonged use of progesterone contraceptives in premenopausal women over 40 years of age (Fabre *et al.* 2007). No other studies of progesterone-only contraceptives were identified.

Estrogens (steroidal) are listed in the Report on Carcinogens as *known human carcinogens;* it is difficult to distinguish the independent or interactive carcinogenic effects of progestogens and estrogens when they are used in combination. IARC evaluated the carcinogenicity of estrogen-progestogen combinations used as contraceptives and for menopausal therapy, concluding that (1) there was sufficient evidence of the carcinogenicity of oral contraceptives in humans based on increased risks of breast cancer among current and recent users only, of cancer of the cervix, and of liver cancer, and (2) sufficient evidence of the carcinogenicity of combined estrogen-progestogen menopausal therapy in humans based on increased risk of breast cancer (IARC 2007, Grosse *et al.* 2009). IARC concluded that the risk of endometrial cancer associated with menopausal therapy decreased with increasing duration of progestogen use.

One small case-control study of breast-cancer risk among women receiving infertility drugs, some of which contained progesterone, was identified; the study included 8 cases (Jensen *et al.* 2007). A significant threefold increase in risk associated with progesterone was found; however, all of these women had also received other drugs.

Properties

Progesterone is a steroid hormone that is an odorless white crystalline powder at room temperature. It is practically insoluble in water, sparingly soluble in vegetable oils, and soluble in acetone, alcohol, dioxane, and concentrated sulfuric acid. It is sensitive to light, but stable in air (IARC 1979). Physical and chemical properties of progesterone are listed in the following table.

Property	Information
Molecular weight	314.5[a]
Specific gravity	1.166 at 23°C[a]
Melting point	127°C to 131°C[a]
Log K_{ow}	3.87[a]
Water solubility	0.00881 g/L at 25°C[a]
Vapor pressure	1.3×10^{-6} mm Hg at 25°C[b]

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

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 female mammals, 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 for support of pregnancy through childbirth (Prosser 1973). Progesterone is used in medicine to treat secondary amenorrhea and abnormal uterine bleeding and in combination hormone-replacement therapies (MedlinePlus 2009). It has also been used to treat female hypogonadism, dysmenorrhea and premenstrual tension, habitual and threatened abortion, preeclampsia, mastodynia, uterine fibroma, and neoplasms of the breast and endometrium (IARC 1979, HSDB 2009). Progesterone embedded in an intrauterine device is used for contraception (FDA 2009). In veterinary medicine, progesterone has

been used to control habitual abortion and to delay estrus and ovulation in cattle, swine, and dogs. It is also used to improve weight gain and feed efficiency in animals (IARC 1979).

Production

Progesterone is a naturally occurring steroid hormone produced endogenously by all mammalian species. Daily production in humans ranges from 0.8 mg in men to 26 mg in adult women with normal menstrual cycles (IARC 1974a). Before the U.S. government imposed restrictions in 1973, estimated total annual U.S. sales of progesterone for use in human medicine were less than 110 lb (IARC 1974b). In 1975, U.S. production of 13 estrogen and progestin substances, including progesterone, amounted to 23,100 lb (IARC 1979). One U.S. commercial producer of progesterone was identified in 2009 (SRI 2009), and progesterone was available from 36 U.S. suppliers in 2010 (Chem Sources 2010). U.S. imports of progesterone of animal or vegetable origin were 26,400 lb in 2001, the last year these products were imported (USITC 2009).

Exposure

The primary routes of potential exogenous human exposure to progesterone are ingestion, injection of medications containing progesterone, implantation, dermal contact, and inhalation. The U.S. Food and Drug Administration has approved 26 products containing progesterone as an active ingredient for use in the United States (FDA 2009). These medications are available as tablets (12), injectables (9), capsules (2), vaginal gels (2), or vaginal inserts (1). A limited segment of the population is exposed to progesterone embedded in intrauterine contraceptive devices. Embedded systems release progesterone at an average daily rate of 65 µg for one year, via membrane-controlled diffusion (Mosby 2001). Progesterone capsules come in doses of 100 and 200 mg of micronized progesterone. Vaginal gel applicators deliver 45 mg (4% gel) or 90 mg (8% gel) of progesterone (FDA 2009). Human placental extracts, of which progesterone is believed to be the main constituent, have been used in preparations for cosmetic use (at concentrations of 0.1% to 1.0%), hair conditioners, shampoos, and grooming-aid tonics (at < 0.1%) (IARC 1979). Consumers could be dermally exposed to progesterone through use of these products.

In 1977, the FDA reported that progesterone was found 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 was also detected as a natural constituent in certain plant species. The meat from animals treated with progesterone implants may contain progesterone at an average concentration of 0.33 mg/kg. Consumers could potentially be exposed to progesterone by ingesting these food products (IARC 1979).

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 manufacturing facility conducted by the National Institute for Occupational Safety and Health and the Centers for Disease Control and Prevention found evidence of hyperestrogenism in both male and female workers and wide variations in air-sample concentrations of estrogen and progesterone (Mills *et al.* 1984). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 287 workers, including 55 women, potentially were exposed to progesterone (NIOSH 1990).

Regulations

Consumer Product Safety Commission (CPSC)

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

Food and Drug Administration (FDA, an HHS agency)

Progesterone is a prescription drug subject to labeling and other requirements.

Maximum levels of progesterone in edible animal tissues are prescribed in 21 CFR 556.540.

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

Guidelines

National Institute for Occupational Safety and Health (NIOSH, CDC, HHS)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA, Dept. of Labor)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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