Estrogens, Steroidal*

Known to be a human carcinogen
First Listed in the *Tenth Report on Carcinogens* (2002)

Introduction

Steroidal estrogens are cholesterol derivatives comprising a group of structurally related, hormonally active molecules that control sex and growth characteristics. The National Toxicology Program previously evaluated some specific steroidal estrogens, including conjugated estrogens (listed in the *Fourth Annual Report on Carcinogens* in 1985 as *known to be human carcinogens*) and a number of individual steroidal estrogens (non-conjugated, including estradiol-17β, estrone, ethinylestradiol, and mestranol), which also were listed in the *Fourth Annual Report on Carcinogens* in 1985 as *reasonably anticipated to be human carcinogens*. The International Agency for Research on Cancer (IARC) also has identified steroidal estrogens as carcinogenic to humans, Group 1 (IARC 1987). In identifying steroidal estrogens as carcinogenic to humans, IARC noted that its evaluation applied to the group of chemicals as a whole and not necessarily to all individual chemicals within the group.

This listing of steroidal estrogens supersedes the previous listing of specific estrogens in the Report on Carcinogens and applies to all chemicals of this steroid class. The profile for steroidal estrogens includes information on carcinogenicity, properties, use, production, exposure, and regulations for steroidal estrogens as a class, as well as some specific information for individual estrogens.

Carcinogenicity

Steroidal estrogens are *known to be human carcinogens* based on sufficient evidence of carcinogenicity in humans, which indicates a causal relationship between exposure to steroidal estrogens and human cancer. Human epidemiology studies show that use of estrogen replacement therapy by postmenopausal women is associated with a consistent increase in the risk of uterine endometrial cancer and a less consistent increase in the risk of breast cancer. Some evidence suggests that oral contraceptive use also may increase the risk of breast cancer.

IARC (1999) evaluated the carcinogenic effects of estrogen replacement therapy used to relieve symptoms of menopause and reported that an increased risk of endometrial cancer was associated with increasing duration of estrogen therapy, as well as a small increased risk of breast cancer. Studies since the IARC (1999) review have supported these findings. Four studies (one cohort study and three large case-control studies) reported increased risk of endometrial cancer with estrogen replacement therapy (Cushing *et al.* 1998, Shapiro *et al.* 1998, Persson *et al.* 1999, Weiderpass *et al.* 1999); three of these studies reported strong positive associations between estrogen replacement therapy and risk of endometrial cancer with increased length of estrogen use. Three cohort studies of women taking either estrogen replacement therapy or hormone replacement therapy (estrogen-progestogen combined) have shown an association with breast cancer (Gapstur *et al.* 1999, Persson *et al.* 1999, Schairer *et al.* 2000). Two of four case-control studies found that estrogen-only replacement therapy was associated with an increased risk of breast cancer (Heinrich *et al.* 1998, Magnusson *et al.* 1999), whereas Brinton *et al.* (1998) reported a slight reduction in breast cancer risk among women receiving estrogen replacement therapy and Titus-Ernstoff *et al.* (1998) found no association of breast cancer risk with hormone replacement therapy. One study (Purdie *et al.* 1999) found that estrogen therapy was associated with ovarian cancer.

IARC (1999) also evaluated numerous case-control and cohort studies addressing the risks of various cancers associated with the use of oral contraceptives. Most of these studies have involved estrogen-progestogen combinations. In general, oral contraceptive use was associated with a small increased risk of breast cancer. Three case-control studies published after the IARC evaluation (Brinton *et al.* 1998, Titus-Ernstoff *et al.* 1998, Rohan and Miller 1999) did not find an increased risk of breast cancer with oral contraceptive use. Other studies indicate that oral contraceptive use may decrease the risk of ovarian and endometrial cancer (Salazar-Martinez *et al.* 1999), confirming the results of studies reviewed by IARC (1999).

The evidence for carcinogenicity of steroidal estrogens in humans is supported by experimental animal studies, which have shown that steroidal estrogens induce benign and malignant neoplasms, as well as preneoplastic lesions, in a variety of organs, including the mammary gland and female reproductive tract (IARC 1999). The strength of evidence in animals differs for different estrogenic compounds. Estrogen compounds generally cause endometrial, cervical, and mammary tumors in mice; mammary and pituitary tumors in rats; and kidney tumors in hamsters.

Additional Information Relevant to Carcinogenicity

Although there is no evidence of genotoxic effects in nonmammalian systems, some steroidal estrogens can damage mammalian DNA and chromosomes (IARC 1999). The most frequently reported effects include DNA adduct formation, cytogenetic alterations (e.g., chromosome and chromatid breaks, micronuclei, sister chromatid exchange), and changes in chromosome number (aneuploidy). Most of these effects have been demonstrated in various tests using animal cells or cell-free systems. Studies with cultured human cell lines showed evidence of chromosomal aneuploidy, DNA strand breaks, micronucleus formation, and sister chromatid exchange. No data were found on genetic effects of steroidal estrogens in humans *in vivo*.

Among mammals, including humans, metabolism is essentially similar for estradiol, estrone, and estriol, which undergo similar phase I pathways (aromatic hydroxylation to catechol intermediates) and phase II pathways (glucuronidation, sulfonation, and *O*-methylation). The ratio of metabolic products depends on the target tissue, species, strain, sex, and experimental conditions. The available data suggest that the metabolism of conjugated estrogens derived from horses is similar (IARC 1999).

The evidence is strong that estrogen carcinogenesis is mediated through activation of the estrogen receptor. In addition, there is evidence that other mechanisms may play a role in the carcinogenic effects of estrogens in some tissues. Prolonged estrogen exposure induces cell proliferation in estrogen-dependent target cells, affects cellular differentiation, and alters gene expression. Although the molecular mechanisms responsible for estrogen carcinogenicity are not well understood, the evidence indicates that estrogen carcinogenesis is complex, involving proliferative effects and possibly direct and indirect genotoxic effects. The relative importance of each mechanism is likely a function of the specific estrogen and of the exposed tissue or cell type and its metabolic state (Yager and Liehr 1996).

Properties

Estrogens act as hormones in both females and males. Steroidal hormones are fat-soluble (lipophilic) molecules that are essential for the growth, differentiation, and function of many tissues in humans and other vertebrate animals. "Estrogen" is a collective term for the female hormones, the most powerful of which is estradiol. Estrogens control female secondary sexual characteristics, maintain the lining of the uterus, and prepare the body for pregnancy. Estrogens affect the growth, differentiation, and function of peripheral tissues of the reproductive system, including the breasts, uterus, vagina, and ovaries. Estrogens also play an important role in normal bone development and maintenance in both males and females. In the brain, estrogens affect many factors important to regulating procreation, including reproductive behavior, mood, and production and release of gonadotropin from the pituitary. Less well known are the important actions of estrogen in male tissues, such as the prostate, testis, and epididymis.

Both naturally occurring estrogens (e.g., estrone and estradiol-17β) and synthetic estrogens (e.g., mestranol and ethinylestradiol) are widely

used medicinal drugs. Conjugated estrogens are a noncrystalline mixture containing naturally occurring forms of mixed estrogens, principally sodium estrone sulfate and sodium equilin sulfate. Piperazine estrone sulfate is a synthetic conjugated estrogen. Conjugated estrogens generally occur as odorless, buff-colored powders that are soluble in water. Nonconjugated estrogens (both naturally occurring and synthetic) are practically insoluble in water but slightly soluble to soluble in organic solvents (e.g., ethanol, acetone, diethyl ether, and chloroform). Mestranol is a white crystalline powder with a molecular weight of 310.4 and a melting point of 150°C to 151°C. Ethinylestradiol occurs as an odorless, creamy or yellowish-white crystalline powder with a molecular weight of 296.4 and a melting point of 182°C to 184°C for the more stable form and 141°C to 146°C for the less stable form. Estrone is an odorless, white to creamy-white crystalline powder with a molecular weight of 270.4 and a melting point of 254.5°C to 256°C. Estradiol-17β occurs as an odorless, white or creamy-white crystalline powder with a molecular weight of 272.4 and a melting point of 173°C to 179°C (IARC 1979, 1999).

Use

Steroidal estrogens comprise a group of structurally related hormone molecules derived from the cholesterol molecule. Estradiol-17β is the most active naturally occurring estrogenic hormone. Estradiol-17β and its metabolite estrone are secreted by the ovaries in women with normal menstrual cycles and by the placenta in pregnant women. They both are essential for the growth and normal maintenance of the lining of the uterus, for the development of the accessory and secondary female sex characteristics, and for pregnancy (Prosser 1973).

Conjugated estrogens, estradiol, and synthetic esters of estradiol, especially ethinylestradiol and estradiol valerate, are most commonly used for estrogen replacement therapy or in combination with a progestogen for hormone replacement therapy. Unopposed estrogens, as commonly prescribed in the 1960s and 1970s were shown to cause endometrial cancer; however, addition of a progestogen greatly diminished that risk (Loose-Michael and Stancel 2001). These replacement therapies are used to treat symptoms of menopause, including menopause surgically induced by removing the ovaries. Estrogens are used to prevent the sweating episodes called "hot flashes" and the shrinking and irritation that sometimes occur in the vulva, vagina, and urinary organs during menopause. Estrogens can be used to prevent common postmenopausal conditions such as osteoporosis and ischemic heart disease. They also have been used to treat low estrogen levels (hypoestrogenism) in males and females caused by hypogonadism, castration, or primary ovarian failure (FDA 1999, IARC 1999, HSDB 2003).

Estrogens have been used in oral contraceptives since the early 1960s. Steroidal estrogens, most commonly ethinylestradiol, are also used with various progestogens in combined oral contraceptive formulations. Currently, many of the oral contraceptives used in the United States contain either 30 or 35 μg of ethinylestradiol because this dose has contraceptive efficacy, is well tolerated, and has a low risk of side effects (e.g., such adverse events as breakthrough bleeding) (Schwend and Lippman 1996). Mestranol is available only in combination with progestogens and is used in typical estrogen therapies, particularly in some oral contraceptive formulations. Combined oral contraceptives typically are administered as a pill taken daily for 20 to 22 days, followed by a seven-day pill-free interval during which withdrawal bleeding is expected to occur (IARC 1999, HSDB 2003).

Steroidal estrogens are used to relieve certain symptoms of breast cancer in some women and men with metastatic disease and are used in the treatment of prostate cancer (androgen-dependent carcinoma). Steroidal estrogens, often in combination with progestogens or androgens, also are used to treat amenorrhea, endometriosis, and postpartum breast engorgement. Some estrogens, such as conjugated estrogens and estrone, have been used in cosmetics products (IARC 1979). Estrogens (such as estradiol-17β and ethinylestradiol) also are used in a variety of veterinary treatments. Steroidal estrogens also are used for biochemical research (FDA 1999, HSDB 2003).

Production

In the United States, commercial production of some steroidal estrogens was first reported in the late 1930s through the 1960s (estradiol-17β in 1939, estrone in 1941, ethinylestradiol in 1945, and conjugated estrogens in 1968) (IARC 1979). Steroidal estrogens are isolated from the urine of pregnant horses or are synthesized. The principal estrogen present in conjugated estrogens is sodium estrone sulfate (between 52.5% and 61.5%). The estrogenic potency of conjugated estrogens is expressed by the equivalent quantity of sodium estrone sulfate. Conjugated estrogens also contain sodium equilin sulfate (between 22.5% and 30.5%) (IARC 1999).

Ethinylestradiol, mestranol, estradiol, estradiol benzoate, and estradiol valerate are produced or formulated in the United States, but no production figures have been reported (IARC 1999). In the early 1970s, annual U.S. sales of ethinylestradiol, mestranol, estradiol-17β, and estrone were estimated to be less than 50 kg (110 lb), 100 kg (220 lb), 100 kg (220 lb), and 2,000 kg (4,400 lb), respectively (IARC 1974). In 1975, U.S. production of 13 estrogenic and progestogenic substances, including conjugated estrogens, amounted to approximately 10,500 kg (23,100 lb) (IARC 1979). No recent data on production volumes are available. According to ChemSources (2003), the number of current U.S. suppliers of selected steroidal estrogens are as follows: estradiol-17β, 23; estrone, 17; ethinylestradiol, 10; mestranol, 10; sodium estrone sulfate, 3; piperazine estrone sulfate, 2; and sodium equilin sulfate, 1.

The U.S. does import and export steroidal estrogens. The International Trade Association (ITA 2003) reported that the United States imported 6,765 kg (14,914 lb) of "estrogens of animal or vegetable origin" in 2000 and 5,937 kg (13,089 lb) in 2002. Other import categories included "estradiol cyclopentylpropionate (estradiol cypionate); estradiol benzoate" (1,406 kg (3,100 lb) in 2000 and 112 kg (247 lb) in 2002) and "estrogens not derived from animal or vegetable materials" (8,766 kg (19,325 lb) in 2000 and 52,420 kg (115,552 lb) in 2002). U.S. exports of "estrogens and progestins" were 128,152 kg (282,522 lb) in 2000 and 56,361 kg (124,253 lb) in 2002.

Exposure

Under normal conditions, the ovaries produce estrogens in response to pituitary hormones. Estradiol is the main naturally occurring estrogen. Estradiol is substantially more potent than its metabolites estrone and estriol at the receptor level. In a woman with a normal menstrual cycle, the ovary releases 70 to 500 μg of estradiol per day, depending on the phase of the menstrual cycle. This estradiol is converted mainly to estrone and also to small amounts of estriol. After menopause, most estrogen naturally occurring in a woman's body comes from peripheral tissues that produce estrone from androstenedione, a hormone released by the adrenal cortex. Estrone and its sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women (IARC 1999).

Estrone is found in the urine of pregnant women and mares, in bulls and stallions, in ovarian fluids of many animals, in human placentas, and in palm kernel oil. Conjugated estrogens are naturally occurring substances found in the urine of pregnant mares (IARC 1979).

Steroidal estrogens also occur naturally in plants. Currently, more than 360 plants have been identified that have estrogenic activity. A few plants contain the principal estrogens found in mammals, estradiol and estrone (Setchell 1985). Meat and milk also may contain estrogens (Collins and Musey 1985). Veterinary use of steroidal estrogens (to promote growth and treat illnesses) can increase estrogens in tissues of food-producing animals to above their normal levels.

Conjugated estrogens used in combined oral contraceptives are available as tablets, and those used for postmenopausal estrogen therapy

are available in tablets, transdermal patches and gels, vaginal inserts and creams, subcutaneous implants, and injectable formulations. Oral contraceptive use in the United States began in 1960, but before this time, estrogen preparations were used to treat menstrual disorders. Oral contraceptive use increased rapidly into the mid 1970s, but declined in the late 1970s because of increased awareness that oral contraceptives increased the risk of heart disease. Pills with lower doses of estrogens were developed in the 1970s and 1980s, and those containing more than 50 µg of estrogen were slowly eliminated. The percentage of women born in the United States between 1945 and 1949 who have ever used oral contraceptives is 85%, compared with 60% of women born a decade earlier and less than 30% of women born before 1930 (IARC 1999).

The use of postmenopausal estrogen therapy also became common in the United States in the 1960s. Between 1962 and 1967, the number of women using this therapy increased by 240%. By 1967, approximately 13% of the women in the United States 45 to 64 years old used this type of therapy. The number of prescriptions for estrogens, not counting those used for oral contraceptives, increased from approximately 15 million in 1966 to more than 25 million in 1976. Prescriptions declined to approximately 15 million by 1982 because of concerns about endometrial cancer but again increased rapidly to approximately 40 million by 1992 (IARC 1999).

In 2002, more than 100 million prescriptions were filled for brand-name and generic products containing estrogens (either conjugated or esterified) as an active ingredient (DrugTopics 2003b). The retail value of estrogen-containing products sold in that year exceeded $3 billion (DrugTopics 2003a).

The first combined oral contraceptive pills contained more than three times the amount of estrogen and progestogen used in current formulations. The standard dose is approximately 30 to 35 µg of estrogen, with lower doses available. Doses used in postmenopausal estrogen therapy vary with the particular indication and method of administration. Typical daily doses used to treat menopausal symptoms are 0.625 to 1.25 mg of conjugated equine estrogens or 0.5 to 4.0 mg of estradiol. Minimal daily doses used to prevent osteoporosis are 0.625 mg of conjugated equine estrogens (pills), 2 mg of estradiol (pills), or 0.05 mg of estradiol (skin patch). Transdermal implants may contain 50 to 100 mg of estradiol and last for six to nine months (IARC 1999).

Estrone also has been used in hormonal skin preparations for cosmetic use at concentrations of less than 0.1%. Unspecified estrogen and estrogenic hormones, which are believed to consist primarily of estrone, have been used in hormonal skin preparations (less than 0.1% to 5%), moisturizing lotions (1% to 5%), wrinkle-smoothing creams, hair conditioners, hair straighteners, shampoos, and grooming aid tonics (less than 0.1%) (IARC 1979).

Potential exposure to steroidal estrogens in the workplace may occur through inhalation and dermal contact during production, processing, and packaging. In a facility producing oral contraceptives, mestranol was found in various sectors of the working environment at levels ranging from 0.06 to 8.61 µg/m^3 and on samples wiped from surfaces at levels of 0.003 to 2.05 µg/cm^2 (IARC 1979). The National Occupational Hazard Survey, conducted by the National Institute of Occupational Safety and Health (NIOSH) from 1972 to 1974, estimated that in 1970, 2,770 people potentially were exposed to specific steroidal estrogens (ethinylestradiol, estrone, estradiol-17β) in the workplace (NIOSH 1976). The National Occupational Exposure Survey (1981 to 1983) included the estimated number of workers exposed to estradiol-17β (9,083), estrone (4,444), and ethinylestradiol (853), (NIOSH 1984). No other occupational exposure estimates were located.

Regulations

FDA

Estrogens are prescription drugs subject to labeling, patient package inserts, and other requirements.

*No separate CAS registry number assigned to estrogens, steroidal.

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