

## Estrogens, Steroidal

CAS No.: none assigned

Known to be human carcinogens

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 nonconjugated steroidal estrogens, including estradiol-17 $\beta$ , estrone, ethinylestradiol, and mestranol (which also were listed in the *Fourth Annual Report on Carcinogens* in 1985 as *reasonably anticipated to be human carcinogens*). In identifying steroidal estrogens as carcinogenic to humans, the International Agency for Research on Cancer noted that its evaluation applied to the group of chemicals as a whole and not necessarily to all individual chemicals within the group (IARC 1987).

This listing of steroidal estrogens supersedes the previous listings of steroidal estrogens and conjugated 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.

#### Cancer Studies in Humans

Human epidemiological studies have shown that the 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 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), and three of these studies reported strong positive associations between risk of endometrial cancer and duration of estrogen use. Three cohort studies of women taking either estrogen replacement therapy or hormone replacement therapy (estrogen and progestogen combined) found 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 a third study reported a slight reduction in breast-cancer risk among women receiving estrogen replacement therapy (Brinton *et al.* 1998), and a fourth found no association of breast-cancer risk with hormone replacement therapy (Titus-Ernstoff *et al.* 1998).

One study found that estrogen therapy was associated with ovarian cancer (Purdie *et al.* 1999).

IARC (1999) also evaluated cancer risks associated with the use of oral contraceptives. Most of these studies 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 did not find an increased risk of breast cancer with oral contraceptive use (Brinton *et al.* 1998, Titus-Ernstoff *et al.* 1998, Rohan and Miller 1999). Other studies indicated that oral contraceptive use might decrease the risk of ovarian and endometrial cancer (Salazar-Martinez *et al.* 1999), confirming the results of studies reviewed by IARC.

Since steroidal estrogens were listed in the *Tenth Report on Carcinogens*, additional epidemiological studies have been identified. These studies reported an increased risk of endometrial cancer among women using estrogen-only therapy, supporting the findings of earlier studies (Epstein *et al.* 2009), and less consistent findings for breast cancer in case-control studies of estrogen-only menopausal therapy (Prentice *et al.* 2008a, 2009, Calle *et al.* 2009, Jick *et al.* 2009). In 2009, IARC concluded there was sufficient evidence of the carcinogenicity of estrogen-only therapy in humans based on increased risks of endometrial cancer and ovarian cancer and limited evidence based on increased risk of breast cancer (Grosse *et al.* 2009). The findings for ovarian cancer were based on two meta-analyses (Greiser 2007, Zhou 2008). Since then, another meta-analysis has estimated a significant overall increase in ovarian cancer risk related to duration of use of estrogen-only therapy (Pearce *et al.* 2009).

Since estrogen-only oral contraceptives were phased out starting in the mid 1970s, most of the studies of oral contraceptive use have involved estrogen-progestogen combinations. In subsequent reviews, IARC concluded that there was sufficient evidence of the carcinogenicity of combination oral contraceptives in humans based on increased risks of breast, cervical, and liver cancer (IARC 2007) and sufficient evidence for the carcinogenicity of combined estrogen-progestogen menopausal therapy in humans based on increased risk of breast cancer (Grosse *et al.* 2009). The results of studies published since the 2007 review were consistent with the conclusions of the IARC review, finding increased risk of breast cancer associated with both oral contraceptive use (Rosenberg *et al.* 2009) and estrogen-progestogen menopausal therapy (Prentice *et al.* 2008b, 2009, Calle *et al.* 2009, Chlebowski *et al.* 2009, Jick *et al.* 2009, Lyytinen *et al.* 2009). In both reviews, IARC also noted that a lower risk of endometrial cancer was associated with oral contraceptive use. The 2009 IARC review concluded that the risk of endometrial cancer associated with menopausal therapy decreased with increasing duration of progestogen use. In two large studies of endometrial cancer, combination therapy reduced the increase in risk of endometrial cancer associated with estrogen-only therapy in women with higher body mass index (McCullough *et al.* 2008, Epstein *et al.* 2009). A reanalysis of cervical-cancer cases from over 20 studies found an increased risk among current oral contraceptive users (Appleby *et al.* 2007), supporting the results of the IARC review. The IARC reviews and a reanalysis of 45 epidemiological studies (Beral *et al.* 2008) found that oral contraceptive use was associated with a decreased risk of ovarian cancer.

#### Cancer Studies in Experimental Animals

In rodents, steroidal estrogens caused benign and malignant tumors, as well as pre-cancerous lesions, in a variety of organs, including the mammary gland and female reproductive tract (IARC 1999). The strength of evidence in experimental animals differed among various estrogenic compounds. Estrogenic compounds generally caused en-

ometrial, cervical, and mammary-gland tumors in mice, mammary- and pituitary-gland tumors in rats, and kidney tumors in hamsters.

### Studies on Mechanisms of Carcinogenesis

Although there is no evidence of genotoxic effects in nonmammalian test systems, some steroidal estrogens can damage mammalian DNA and chromosomes (IARC 1999). The most frequently reported effects included DNA adduct formation, cytogenetic alterations (e.g., chromosome and chromatid breaks, micronucleus formation, and sister chromatid exchange), and aneuploidy. Most of these effects were demonstrated in various tests using animal cells or cell-free systems. Studies with cultured human cell lines showed evidence of 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 three naturally occurring unconjugated estrogens: estradiol, estrone, and estriol are metabolized via similar phase I pathways (aromatic hydroxylation to catechol intermediates) and phase II pathways (glucuronidation, sulfonation, and O-methylation). The distribution of metabolic products depends on the target tissue, species, strain, sex, and experimental conditions (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. For example, prolonged estrogen exposure causes cell proliferation in estrogen-dependent target cells, affects cellular differentiation, and alters gene expression. Although the molecular mechanisms responsible for estrogen carcinogenicity are not 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

Steroidal estrogens comprise a group of structurally related hormone molecules derived from the cholesterol molecule (IARC 1979a). Estrogens are found in males and females, and are the primary sex hormones in females. Steroidal estrogens are fat-soluble (lipophilic) molecules that are essential for the growth, differentiation, and function of tissues in humans and other vertebrate animals. "Estrogen" is a collective term for the naturally occurring female hormones estradiol, estriol, and estrone. In females, estrogen is important in the development of secondary sexual characteristics, in the regulation of the menstrual cycle, and in pregnancy. In males, estrogen is important in the maturation of sperm. Estrogen also plays an important role in normal bone development and maintenance in both males and females. In the brain, estrogen affects factors regulating procreation, including reproductive behavior, mood, and production and release of gonadotropins from the pituitary.

Both naturally occurring estrogens (e.g., estrone and estradiol-17 $\beta$ ) and synthetic estrogens (e.g., mestranol and ethinylestradiol) are widely used medicinal drugs. Estradiol-17 $\beta$  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 1979b, 1999). 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. Estriol exists as very small, monoclinic crystals with a molecular weight of 288.4 and a melting point of 282°C.

Conjugated estrogens are a noncrystalline mixture containing naturally occurring forms of mixed estrogens, principally sodium es-

trone 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.

### Use

Estradiol-17 $\beta$  is the predominant estrogen in non-pregnant women, and estriol is the primary estrogen produced during pregnancy. Estradiol-17 $\beta$  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 growth and normal maintenance of the lining of the uterus, for 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 tract during menopause. Estrogens can be used to prevent common postmenopausal conditions such as osteoporosis and ischemic heart disease and have been shown to decrease the rate of colorectal cancer. They also have been used to treat low estrogen levels (hypoestrogenism) in males and females caused by hypogonadism, castration, or primary ovarian failure (IARC 1999, HSDB 2009).

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  $\mu$ g 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 2009).

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, are also used to treat amenorrhea, endometriosis, and postpartum breast engorgement. Some estrogens, such as conjugated estrogens and estrone, have been used in cosmetic products (IARC 1979b). Estrogens (such as estradiol-17 $\beta$  and ethinylestradiol) are also used in a variety of veterinary treatments. Steroidal estrogens are also used in biochemical research (HSDB 2009).

## Production

In the United States, commercial production of some steroidal estrogens was first reported in the late 1930s through the 1960s (estradiol-17 $\beta$  in 1939, estrone in 1941, ethinylestradiol in 1945, and conjugated estrogens in 1968) (IARC 1979b). Steroidal estrogens are isolated from the urine of pregnant horses or are synthesized. The available data suggest that the metabolism of estrogens in horses is similar to that in humans (IARC 1999). 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 were estimated to be less than 50 kg (110 lb) for ethinylestradiol, 100 kg (220 lb) for mestranol, 100 kg (220 lb) for estradiol-17 $\beta$ , and 2,000 kg (4,400 lb) for estrone (IARC 1974). In 1975, U.S. production of 13 estrogenic and progestogenic substances, including conjugated estrogens, amounted to about 10,500 kg (23,100 lb) (IARC 1979b). No recent data on production volumes were found. Numbers of U.S. suppliers of selected steroidal estrogens in 2010 were 18 for estradiol-17 $\beta$ , 15 for estrone, 14 for ethinylestradiol, 13 for mestranol, 1 for sodium estrone sulfate, 3 for piperazine estrone sulfate, and 1 for sodium equilin sulfate. (Chem-Sources 2010). U.S. imports of "estrogens of animal or vegetable origin" were 6,765 kg (14,914 lb) in 2000 and 5,689 kg (12,516 lb) in 2009. Other import categories included "estradiol cyclopentylpropionate (estradiol cypionate); estradiol benzoate," with imports of 1,406 kg (3,100 lb) in 2000 and 653 kg (1,437 lb) in 2009, and "estrogens not derived from animal or vegetable materials," with imports of 8,766 kg (19,325 lb) in 2000 and 1,002 kg (2,204 lb) in 2002. U.S. exports of "estrogens and progestins" were 128,152 kg (282,522 lb) in 2000 and 29,028 kg (63,861 lb) in 2009 (USITC 2010).

## 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 at the receptor level than its metabolites estrone and estriol. In a woman with a normal menstrual cycle, the ovary releases 70 to 500  $\mu$ g of estradiol per day, depending on the phase of the 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 1979b). Over 360 plants have been identified that have estrogenic activity, and 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 ther-

apy are available in tablets, transdermal patches and gels, vaginal inserts and creams, subcutaneous implants, and injectable formulations. In 2009, over 84 million prescriptions were filled for brand-name and generic products containing estrogens (either conjugated or esterified) as an active ingredient (DrugTopics 2009a). The retail value of estrogen-containing products sold in that year exceeded \$2.6 billion (DrugTopics 2009b).

Oral contraceptive use in the United States began in 1960, but before then, 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. 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. Pills with lower doses of estrogen were developed in the 1970s and 1980s, and those containing more than 50  $\mu$ g of estrogen were slowly eliminated. 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 30 to 35  $\mu$ g of estrogen, with lower doses available (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 15 million in 1966 to over 25 million in 1976. Prescriptions had declined to 15 million by 1982 because of concerns about endometrial cancer but again increased rapidly to 40 million by 1992. Doses used in postmenopausal estrogen therapy vary with the indication and the method of administration. Typical daily doses for treatment of 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 has also 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 1979b).

Potential exposure to steroidal estrogens in the workplace may occur through inhalation or dermal contact during production, processing, or packaging. In a facility producing oral contraceptives, mestranol was found in various sectors of the work environment at air concentrations ranging from 0.06 to 8.61  $\mu$ g/m<sup>3</sup> and on samples wiped from surfaces at levels of 0.003 to 2.05  $\mu$ g/cm<sup>2</sup> (IARC 1979b). The National Occupational Hazard Survey (conducted from 1972 to 1974) estimated that in 1970, 2,770 workers potentially were exposed to specific steroidal estrogens (ethinylestradiol, estrone, estradiol-17 $\beta$ ) (NIOSH 1976). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 9,083 workers potentially were exposed to estradiol-17 $\beta$  and 4,444 to estrone (NIOSH 1990).



## Regulations

### Consumer Products Safety Commission (CPSC)

Any orally administered prescription drug for human use requires child-resistant packaging; however, conjugated estrogen tablets dispensed in mnemonic packages containing no more than 32 mg do not require child-resistant packaging.

### Food and Drug Administration (FDA)

Estrogens are prescription drugs subject to labeling and other requirements. Estradiol residue limits in animal tissues for human consumption are prescribed in 21 CFR 556.

## 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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