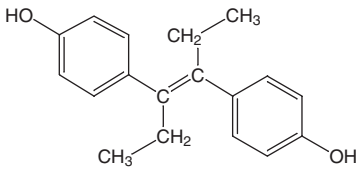
Diethylstilbestrol
CAS No. 56-53-1

Known to be a human carcinogen
First Listed in the *First Annual Report on Carcinogens* (1980)



Carcinogenicity

Diethylstilbestrol is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity in humans. The strongest evidence comes from epidemiological studies of women exposed to diethylstilbestrol *in utero* ("diethylstilbestrol daughters"), which found that diethylstilbestrol caused clear-cell adenocarcinoma of the vagina and cervix. This type of cancer, which typically develops in elderly women, developed in diethylstilbestrol daughters between the ages of 10 and 30 years. Most (though not all) case-control studies found that *in utero* exposure to diethylstilbestrol increased the risk of testicular cancer in males ("diethylstilbestrol sons"). Several follow-up studies (including cohort studies and randomized clinical trials) found that women who took diethylstilbestrol at high doses during pregnancy were at increased risk for breast cancer. Some studies suggest that diethylstilbestrol-induced breast cancer may have a long latency period (15 to 20 years), but the evidence is inconclusive. As has been found for other estrogens, diethylstilbestrol taken to relieve the symptoms of menopause increases the risk of endometrial cancer (IARC 1974, 1979, 1987). Since diethylstilbestrol was reviewed for listing in the *First Annual Report on Carcinogens* and by the International Agency for Research on Cancer (IARC), additional studies on diethylstilbestrol daughters and sons have been published. A study of a large cohort of diethylstilbestrol daughters first identified in the mid 1970s confirmed a 40-fold increase in the risk of clear-cell adenocarcinoma of the vagina or cervix and estimated a cumulative incidence rate of 1.5 per 1,000 exposed women (Hatch *et al.* 1998). The evidence for increased risk of breast cancer in diethylstilbestrol daughters is inconclusive because of the young age of the cohort (Hatch *et al.* 1998, Palmer *et al.* 2002). Another cohort study reported an increased risk of testicular cancer among diethylstilbestrol sons, supporting the findings from earlier case-control studies; however, this result was not statistically significant (Strohsnitter *et al.* 2001).

The findings in humans are supported by studies in experimental animals showing that administration of diethylstilbestrol by various routes causes cancer in multiple species (mice, rats, hamsters, frogs, dogs, and monkeys) and at multiple tissue sites (primarily estrogen-sensitive organs and tissues). As in humans, prenatal exposure to diethylstilbestrol caused cervical and vaginal tumors in female mice and hamsters and testicular tumors in male hamsters. Prenatal exposure also caused uterine tumors in mice and hamsters and ovarian, mammary-gland, and lung tumors in mice. Tumors of the genital tract were observed in rats exposed to diethylstilbestrol (administered by injection) *in utero* or three weeks postpartum. Mice developed cervical and vaginal tumors after receiving a single subcutaneous (s.c.) injection of diethylstilbestrol on the first day of life, and male rats developed reproductive-tract tumors after receiving daily s.c. injections for the first month of life. Diethylstilbestrol also caused cancer in animals exposed as adults. When administered orally, diethylstilbestrol caused mammary-gland, cervical, vaginal, endometrial, uterine, and bone tumors in mice and pituitary-gland, liver, and mammary-gland tumors in rats. Subcutaneous injections or implants of diethylstilbestrol increased the incidences of leukemia and testicular, lymphoid, and mammary-gland tumors in mice, mammary-gland tumors in rats, kidney tumors in hamsters, ovarian tumors in mice and dogs, and uterine tumors in squirrel monkeys. Diethylstilbestrol dipropionate caused tumors of the liver and the hematopoietic system (organs and tissues involved in production of blood) in male and female frogs and pituitary-gland tumors in rats (IARC 1974, 1979, 1987).

Since diethylstilbestrol was reviewed for listing in the *First Annual Report on Carcinogens* and by IARC, multigenerational studies in mice and additional prenatal-exposure studies in rats have been published. In the multigenerational studies, mice were exposed to diethylstilbestrol *in utero*, either during the period of major organogenesis or just before birth, or on the first five days of life. Female mice from each exposure regimen (the F_1 generation) were raised to maturity and bred with unexposed male mice. Both male and female offspring of these mice (the F_2 generation) had increased incidences of reproductive-tract tumors, including uterine adenocarcinoma and other tumors in females and seminal-vesicle tumors and other tumors and lesions in males (Newbold *et al.* 1998, 2000). As in hamsters and mice, prenatal exposure to diethylstilbestrol caused uterine tumors in Donryu rats (a carcinogen-sensitive strain with an increased estrogen-to-progesterone ratio) (Kitamura *et al.* 1999).

Properties

Diethylstilbestrol is a synthetic nonsteroidal estrogen (female sex hormone). It has a molecular weight of 268.4 and occurs as small white plates from benzene or as a white crystalline powder. It has a melting point of 169°C to 172°C and a log octanol-water partition coefficient of 5.07. Diethylstilbestrol is practically insoluble in water and soluble in ethanol, chloroform, diethyl ether, acetone, dioxane, ethyl acetate, methyl alcohol, vegetable oils, and aqueous solutions of alkaline hydroxides. It emits acrid smoke and fumes when heated to decomposition (HSDB 2003). Diethylstilbestrol dipropionate has a molecular weight of 380.4 and occurs as odorless, tasteless, colorless crystals or a white crystalline powder. It has a melting point of 105°C to 107°C. Diethylstilbestrol dipropionate is soluble in 90% ethanol, diethyl ether, olive oil, fixed oils, acetone, and chloroform, but it is very slightly soluble in water and insoluble in solutions of alkaline hydroxides. Diethylstilbestrol dipropionate differs from diethylstilbestrol in solubility and rate of absorption, but once absorbed into the body diethylstilbestrol dipropionate is converted to diethylstilbestrol.

Use

Diethylstilbestrol was the first synthetic estrogen. It was synthesized in 1938 and was widely prescribed in the United States from the early 1940s until 1971, primarily as a treatment to prevent miscarriages or premature deliveries. The U.S. Food and Drug Administration (FDA) issued a drug bulletin in 1971 advising physicians to stop prescribing diethylstilbestrol to pregnant women because of its link to a rare vaginal cancer (clear-cell adenocarcinoma) in diethylstilbestrol daughters (CDC 2003). Other uses in human medicine continued at least through the 1970s and in some cases into the early 1980s. These uses included hormone replacement therapy, control of menstrual disorders, relief or prevention of postpartum breast engorgement, palliative therapy for cancer of the prostate in men and breast cancer in postmenopausal women, and as a postcoital contraceptive. In 1978, the FDA withdrew approval of any estrogen-containing drug product (including diethylstilbestrol) for the suppression of postpartum breast engorgement (FDA 1998). Diethylstilbestrol sometimes was given in combination with androgens, vitamins, and antibiotics (IARC 1974, 1979). Its use in the treatment of advanced prostate cancer fell out of

favor because of its cardiovascular toxicity, the emergence of safer agents, and manufacturers' economic considerations (Malkowicz 2001). Nevertheless, diethylstilbestrol continues to be used in clinical trials for treatment of prostate and breast cancer (Smith *et al.* 1998, Peethambaram *et al.* 1999) and in biochemical research.

Diethylstilbestrol also has been used in veterinary medicine and as a growth promoter (as a feed supplement or subcutaneous implant) in cattle, sheep, and poultry (IARC 1979). Its use as a growth promoter was banned in 1979 (Raun and Preston 2002).

Production

U.S. production of diethylstilbestrol was first reported in 1941, as 227 kg (500 lb), and last reported in 1952, as 1,800 kg (3,970 lb) (IARC 1974). In 1972, 454 kg (1,000 lb) of diethylstilbestrol diphosphate (an ester form) were produced (HSDB 2003). Between the early 1940s and early 1970s, there were three to five U.S. producers of diethylstilbestrol, and in 1976, there was one U.S. producer (IARC 1974, 1979). Diethylstilbestrol is no longer manufactured by pharmaceutical companies in the United States (CDC 2004). Annual U.S. imports ranged from about 3,000 to 7,800 kg (6,700 to 17,000 lb) in the 1970s, but had dropped to 130 kg (290 lb) by 1982 (IARC 1974, 1979; HSDB 2003). No export data were found. In 2003, 13 U.S. suppliers of diethylstilbestrol were identified (ChemSources 2003).

Exposure

Most current exposure to diethylstilbestrol is through its oral administration as a drug used in clinical trials for the treatment of prostate and breast cancer. Exposure also occurred through the past use of diethylstilbestrol to prevent miscarriages, as hormone replacement therapy, to treat prostate cancer, and in other medical therapies. It has been estimated that between 5 and 10 million Americans received diethylstilbestrol during pregnancy or were exposed to the drug *in utero* (NIH 1999). In one large cohort of diethylstilbestrol daughters, the median total doses administered to their mothers at five study sites ranged from 1,625 to 10,424 mg (Giusti *et al.* 1995). Many different forms of diethylstilbestrol, including oral tablets (0.1, 0.25, 0.5, 1, and 5 mg), injectable solutions (0.2, 0.5, 1, and 5 mg/mL), and a vaginal suppository (0.1 and 0.5 mg) were approved by the FDA prior to withdrawal of diethylstilbestrol (FDA 2003). Diethylstilbestrol diphosphate also was available as oral tablets (50 mg) and an injectable solution (250 mg/50 mL).

Diethylstilbestrol residues were detected in beef and sheep livers in 1972 and 1973. When diethylstilbestrol was used as a growth promoter for sheep and cattle, people could have been exposed to it at concentrations of up to 10 ppb in beef and mutton (IARC 1979). The National Occupational Exposure Survey (1981–1983) estimated that 1,492 workers, including 934 women, potentially were exposed to diethylstilbestrol during its manufacture or during product formulation (NIOSH 1984). The concentration of diethylstilbestrol in ambient air-samples from plants that manufactured diethylstilbestrol ranged from 0.02 to 24 $\mu g/m^3$ (IARC 1979).

Regulations

CPSC

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

EPA

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable Quantity (RQ) = 1 lb

Resource Conservation and Recovery Act

Listed as a Hazardous Constituent of Waste

Listed Hazardous Waste: Waste codes in which listing is based wholly or partly on substance - U089

FDA

All oral and parenteral drug products containing greater than 25 mg per unit dose diethylstilbestrol are removed from the market because they were found to be unsafe or not effective and they may not be compounded

Diethylstilbestrol is prohibited from extralabel use in food-producing animals

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