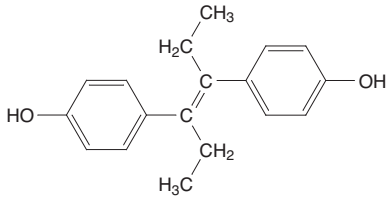
Diethylstilbestrol

CAS No. 56-53-1

Known to be a human carcinogen

First listed in the *First Annual Report on Carcinogens* (1980)

Also known as DES, diethylstilboestrol, or stilboestrol



Carcinogenicity

Diethylstilbestrol is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

The strongest evidence for carcinogenicity comes from epidemiological studies of women exposed to diethylstilbestrol *in utero* ("diethylstilbestrol daughters"), which found that diethylstilbestrol caused clear-cell adenocarcinoma, a rare cancer 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 also 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, 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).

Cancer Studies in Experimental Animals

Diethylstilbestrol caused tumors in several animal species, by several different routes of exposure, and at several different tissue sites (primarily estrogen-sensitive organs and tissues). Diethylstilbestrol has been tested by oral administration (mice and rats), local application (mice), subcutaneous implantation or injection (frogs, mice, rats, hamsters, dogs, and monkeys), prenatal exposure (mice, hamsters, and monkeys), and neonatal exposure (mice and rats).

Prenatal exposure to diethylstilbestrol caused benign cervical and vaginal tumors (epidermoid tumors) in female mice, benign and malignant cervical and vaginal tumors (polyps, squamous-cell papilloma, and myosarcoma) in female hamsters, and benign and malignant testicular tumors (granuloma, adenoma, and leiomyosarcoma) in male hamsters. Prenatal exposure also caused uterine cancer (adenocarcinoma) in female mice and hamsters, benign ovarian tumors (cystadenoma and granulosa-cell tumors) in female mice, and benign lung tumors (papillary adenoma) in mice of both sexes. Prenatal exposure did not cause tumors in monkeys observed for up to six years after birth. Mice developed cervical and vaginal tumors after receiving a single subcutaneous injection of diethylstilbestrol on the first day of life, and male rats developed cancer of the reproductive tract (squamous-cell carcinoma) after receiving daily subcutaneous injections for the first month of life.

Diethylstilbestrol also caused cancer in experimental animals exposed as adults. When administered orally, diethylstilbestrol caused cancer of the mammary gland (carcinoma and adenocarcinoma) in mice of both sexes and benign mammary-gland tumors (fibroadenoma) in rats of both sexes. In addition, cancer of the cervix and uterus (adenocarcinoma), vagina (squamous-cell carcinoma), and bone (osteosarcoma) occurred in mice, and benign and malignant pituitary-gland and liver tumors (hepatocellular tumors and hemangioendothelioma) occurred in rats. Intravaginal application of diethylstilbestrol to mice caused cancer of the vagina and cervix (epidermoid carcinoma). Subcutaneous injections or implants of diethylstilbestrol in mice increased the incidences of leukemia and benign or malignant tumors of the testis (interstitial-cell tumors), lymphoid tissue, mammary gland (carcinoma), cervix, vagina, and ovary (cystadenoma). Subcutaneous administration to rats increased the incidences of benign or malignant tumors of the mammary gland (fibroadenoma, carcinoma, or adenocarcinoma), bladder (carcinoma), and adrenal gland. Subcutaneously administered diethylstilbestrol also increased the incidences of kidney cancer (carcinoma) in male hamsters, benign or maliganant ovarian tumors (papillary adenoma or carcinoma) in dogs, and uterine tumors (mesothelioma) in squirrel monkeys. Subcutaneous injection of 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 benign pituitary-gland tumors in rats (IARC 1974, 1979).

Since diethylstilbestrol was listed in the *First Annual Report on Carcinogens,* multigenerational studies in mice and several 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. Offspring of these mice (the F_2 generation) had increased incidences of reproductive-tract tumors. Females developed uterine cancer (adenocarcinoma), and males developed cancer of the rete testis (the network of sperm-carrying tubules) and benign and malignant seminal-vesicle tumors (papilloma, carcinosarcoma, and sarcoma) (Newbold *et al.* 1998, 2000). Prenatal exposure to diethylstilbestrol also caused uterine cancer (adenocarcinoma) 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 that is an odorless white crystalline powder at room temperature. It is practically insoluble in water and soluble in alcohol, ether, chloroform, fatty oils, dilute hydroxides, acetone, dioxane, ethyl acetate, methanol, and vegetable oils. The *trans*-isomer is used for commercial purposes and is stable in the environment. The *cis*-isomer is not stable and tends

to convert to the *trans* form (IARC 1979). Diethylstilbestrol dipropionate is an ester of diethylstilbestrol with propionic acid that is soluble in organic solvents and vegetable oils (O'Neil *et al.* 2006). Physical and chemical properties of diethylstilbestrol are listed in the following table.

Property	Information
Molecular weight	268.4
Melting point	169°C to 172°C
Log K_{ow}	5.07
Water solubility	0.012 g/L at 25°C

Source: HSDB 2009.

Use

Diethylstilbestrol was the first synthetic estrogen, originally synthesized in 1938. It 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 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 has also 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) was produced (HSDB 2009). From the early 1940s to the early 1970s, three to five U.S. companies produced diethylstilbestrol; by 1976, there was one U.S. producer (IARC 1974, 1979). Diethylstilbestrol is no longer manufactured by U.S. pharmaceutical companies (CDC 2004), but 17 U.S. suppliers of diethylstilbestrol were identified in 2009 (ChemSources 2009). Annual U.S. imports of diethylstilbestrol 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 2009). No data on U.S. exports of diethylstilbestrol were found.

Exposure

Most current exposure to diethylstilbestrol is through its oral administration as a drug in clinical trials for the treatment of prostate and breast cancer. Exposure also occurred in the past through the 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 million 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 (FDA 2009). Diethylstilbestrol diphosphate also was available as oral tablets (50 mg) and as 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.

The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 1,492 workers, including 934 women, potentially were exposed to diethylstilbestrol during its manufacture or during product formulation (NIOSH 1990). The concentration of diethylstilbestrol in ambient-air samples from plants that manufactured diethylstilbestrol ranged from 0.02 to 24 μg/m^3 (IARC 1979).

Regulations

Environmental Protection Agency (EPA)

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of diethylstilbestrol = U089.

Listed as a hazardous constituent of waste.

Food and Drug Administration (FDA, an HHS agency)

All oral and parenteral drug products containing greater than 25 mg per unit dose of diethylstilbestrol were 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.

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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