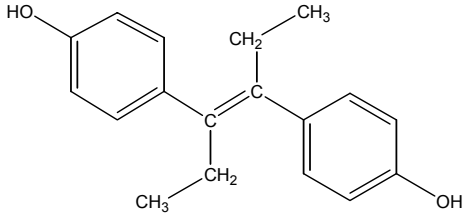
DIETHYLSTILBESTROL
CAS No. 56-53-1
First Listed in the *First Annual Report on Carcinogens*



CARCINOGENICITY

Diethylstilbestrol is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity in humans (IARC 1974, 1979, 1982, 1987). Diethylstilbestrol taken during pregnancy has been shown to increase the incidence of clear cell adenocarcinomas of the vagina or cervix and vaginal adenosis in daughters exposed *in utero*. The evidence for an association with other human cancers is either limited (endometrium) or inadequate (breast, ovary).

An IARC Working Group reported that there is sufficient evidence of carcinogenicity of diethylstilbestrol in experimental animals (IARC 1974, 1979, 1982, 1987). When administered orally (by gavage or in the diet), diethylstilbestrol induced mammary carcinomas and adenocarcinomas in mice of both sexes. One study reported adenocarcinomas of the cervix, endometrium, and uterine horns in female mice given diethylstilbestrol in the diet. Male and female rats fed diets containing diethylstilbestrol developed pituitary tumors, and male rats developed mammary tumors (mostly fibroadenomas). Subcutaneous injection resulted in increased incidences of leukemia and breast tumors in male mice; breast tumors in male mice suckled by diethylstilbestrol-injected females; ovarian cystadenomas in adult female mice; and cancers of the cervix and vagina in newborn female mice. Castrated newborn male rats developed invasive squamous cell carcinomas of the coagulatory gland or ejaculatory duct when injected subcutaneously. Diethylstilbestrol by subcutaneous injection induced increased incidences of renal carcinomas in male hamsters and ovarian papillary carcinomas in female dogs. Subcutaneous implants of diethylstilbestrol-containing pellets induced interstitial cell tumors of the testis, mammary tumors, or lymphoid tumors in male mice and mammary carcinomas and lymphoid tumors in female mice. Subcutaneous implants in rats induced mammary carcinomas and urinary bladder carcinomas in conjunction with calculi in both sexes. Subcutaneous implants induced malignant adenomatous renal tumors, with many metastases, in male hamsters and malignant uterine mesotheliomas in female squirrel monkeys. Prenatal exposure to diethylstilbestrol induced adenocarcinomas of the uterine endometrium, epidermoid tumors of the cervix and vagina, and cystadenomas and granulosa cell tumors of the ovary in female mice and lung papillary adenomas in mice of both sexes. Prenatal exposure to diethylstilbestrol induced high incidences of metaplastic, dysplastic, and neoplastic lesions of the genital tract, including cervical polyps and squamous cell papillomas of the cervix and vagina in female hamsters, and granulomas in the epididymis and testis and epididymal cystic formations in male hamsters.

PROPERTIES

Diethylstilbestrol occurs as white platelets from benzene or as white crystalline powder. It is practically insoluble in water, but it is soluble in ethanol, chloroform, diethyl ether, acetone, dioxane, ethyl acetate, methyl alcohol, vegetable oils, and aqueous solutions of alkaline hydroxides. The commercial product is available as USP grade (HSDB 2000).

USE

Diethylstilbestrol is a synthetic hormone. It is used as a treatment for symptoms associated with menopause, menstrual disorders, postpartum breast engorgement, primary ovarian failure, and chemotherapy of advanced breast cancer and advanced prostate cancers. Diethylstilbestrol was used from 1940 to 1971 as a treatment to prevent spontaneous abortions in humans. It was extensively utilized as a growth promoter for cattle and sheep and as a treatment for estrogen-deficiency disorders in veterinary medicine and, more recently, for postcoital contraception (IARC 1974, 1979, NIH 1984). This compound is also used in biochemical research (NTP 2001).

PRODUCTION

Chem Sources (2001) identified eight U.S. suppliers of diethylstilbestrol. The USITC (1982-1991, 1993-1995) does not presently identify any companies producing diethylstilbestrol; one company, however, was listed as a producer until 1981 (USITC 1982). In 1983, approximately 343 lb were imported into the United States (USITC 1984b). The 1979 TSCA Inventory identified one importer of diethylstilbestrol in 1977, but no volume was reported (TSCA 1979). In 1976, the United States imported 13,000 lb, but domestic production data have not been reported since 1952, when 3,970 lb of diethylstilbestrol were produced. U.S. production of diethylstilbestrol was first reported in 1941 (IARC 1974).

EXPOSURE

The primary routes of potential human exposure to diethylstilbestrol are ingestion, inhalation, and dermal contact. Most exposure to diethylstilbestrol occurs as a result of its oral administration as a drug. An estimated 500,000 patients each year are treated with diethylstilbestrol, mainly males who are treated for neoplastic disease. During its previous use in pregnant women, children were exposed *in utero*. While there are no specific data, a NIH Task Force estimated that up to 4 to 6 million Americans (i.e., mothers, daughters, sons) may have been exposed between 1940 and 1971 to diethylstilbestrol during the mothers' pregnancies (NIH 1984). Dosages for its current medical uses range from 0.1 to 0.5 mg/day in a cyclic regimen for treatment of symptoms during the climacteric and following ovariectomy, up to 15 mg/day for chemotherapy of advanced breast carcinoma (IARC 1979).

The National Occupational Exposure Survey (1981-1983) indicated that 1,478 total workers, including 920 women, potentially were exposed to diethylstilbestrol during its manufacture or product formulation (NIOSH 1984). Air samples collected inside the plastic suits of full-time workers in a plant manufacturing diethylstilbestrol contained concentrations of 0.4 to 1.8 $\mu g/m^3$. Two sets of air samples collected in areas outside the main workroom contained 0.2 and 12.8 $\mu g/m^3$. An air sample taken in a finishing room contained 24 $\mu g/m^3$. Air samples taken in the ambient air of three plants where diethylstilbestrol was mixed with animal feed contained

0.02 to 1.03 μg/m^3 (IARC 1979). Health professionals involved in preparing diethylstilbestrol and administering it to patients could possibly be exposed through dermal contact.

Diethylstilbestrol residues have been detected in beef and sheep livers assayed in 1972 and 1973. When diethylstilbestrol was used as a growth promoter for sheep and cattle, most of the population could have been potentially exposed to levels of <10 ppb in beef and mutton (IARC 1979). Diethylstilbestrol has also been found in certain drinking water samples at concentrations of 0.11 to 0.26 ng/L (IARC 1979).

REGULATIONS

EPA established a reportable quantity (RQ) of 1 lb for diethylstilbestrol under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). The EPA Carcinogen Assessment Group includes diethylstilbestrol on its list of potential carcinogens. As a result of this listing, EPA regulates diethylstilbestrol under the hazardous waste disposal rule of the Resource Conservation and Recovery Act (RCRA). Under the Toxic Substances Control Act (TSCA), EPA has determined that there are significant new uses of diethylstilbestrol and specifies procedures for manufacturers, importers, and processors to report on their significant new uses.

FDA, under the Food, Drug and Cosmetic Act (FD&CA), requires product labeling to inform patients of the risks involved in taking diethylstilbestrol. FDA also has suspended certain diethylstilbestrol and diethylstilbestrol-containing drug products.

OSHA regulates diethylstilbestrol as a chemical hazard in laboratories under the Hazard Communication Standard. Regulations are summarized in Volume II, Table 71.

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