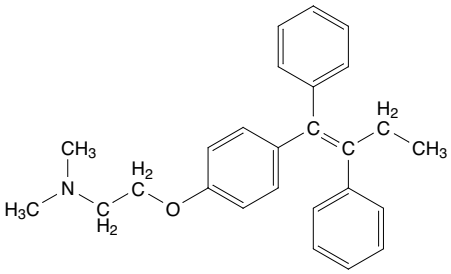
Tamoxifen

CAS No. 10540-29-1

Known to be a human carcinogen

First listed in the *Ninth Report on Carcinogens* (2000)

Also known as (*Z*)-2-[4-(1,2-diphenylbut-1-enyl)phenoxy]-*N*,*N*-dimethyl-ethanamine



Carcinogenicity

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

Cancer Studies in Humans

Data from epidemiological studies and clinical trials indicate a causal relationship between exposure to tamoxifen and cancer of the uterus (endometrial type). However, there also is conclusive evidence that tamoxifen therapy reduces the risk of contralateral breast cancer in women with a previous diagnosis of breast cancer and may prevent or delay the occurrence of breast cancer in women at increased risk for this disease (IARC 1996). By the mid 1990s, the potential effect of tamoxifen in increasing the risk of endometrial cancer had been reported in one adequate cohort study, four adequate case-control studies, and fourteen randomized clinical trials.

The cohort study (Curtis *et al.* 1996) examined the effect of tamoxifen on the risk of endometrial cancer in 87,323 women with breast cancer reported to the National Cancer Institute's Surveillance, Epidemiology, and End Results program and found a significant excess of endometrial cancer among women who had received tamoxifen therapy. Two of the four case-control studies (van Leeuwen *et al.* 1994, Sasco *et al.* 1996) found statistically nonsignificant increases in the risk of endometrial cancer; however, among women treated with tamoxifen, risk increased significantly with increasing duration of therapy and cumulative dose in one of these studies (van Leeuwen *et al.* 1994). The third case-control study, conducted in the United States, found no increased risk; however, the duration of tamoxifen use was shorter than in the other studies (Cook *et al.* 1995). The fourth case-control study found an increased risk of endometrial cancer with tamoxifen use; however, the effects of potentially confounding factors could not be ruled out (Hardell 1988).

The two largest randomized clinical trials found a strong, significant association between risk of endometrial cancer and use of tamoxifen (Fisher *et al.* 1994, Rutqvist *et al.* 1995). In the 12 smaller trials, the incidence of endometrial cancer was not significantly increased; however, when the results of these 12 studies were combined, 29 cases of endometrial cancer were reported in tamoxifen-treated individuals, compared with 14 in the control group (IARC 1996). In 32 case studies, 102 cases of endometrial cancer were reported in women who had received tamoxifen for breast cancer. One case series reported significantly more high-grade endometrial tumors in tamoxifen-treated breast-cancer patients than in patients who had not received tamoxifen (Magriples *et al.* 1993); this difference, however, was not observed in six other studies (IARC 1996).

In a review, MacMahon (1997) concluded that the published results suggested a causal association between tamoxifen use and endometrial cancer but were not conclusive, because of confounding factors such as prior hysterectomy or hormone replacement therapy. The International Agency for Research on Cancer examined the same potentially confounding factors but considered them unlikely to have had a major effect on the reported relative risks; IARC therefore concluded that several of the studies cited supported a positive association between tamoxifen use and endometrial cancer (IARC 1996).

Cancer Studies in Experimental Animals

Uterine abnormalities, including endometrial cancer (carcinoma), have been reported in experimental animals exposed to tamoxifen. Rats receiving tamoxifen daily by stomach tube for 20 to 52 weeks developed squamous-cell metaplasia, dysplasia, and carcinoma of the uterus; no comparable lesions were observed in controls (Mantyla *et al.* 1996). In newborn mice of both sexes, exposure to tamoxifen on days 1 to 5 of life significantly increased the incidence of reproductive-tract abnormalities, including uterine cancer and seminal-vesicle tumors (Newbold *et al.* 1996, 1997). Tamoxifen administered orally to mice for three months caused benign ovarian and testicular tumors. In eight studies in rats with various exposure durations, tamoxifen caused precancerous liver lesions and benign or malignant liver tumors. One study in rats reported a decreased incidence of tumors in hormone-dependent tissues; however, reduced weight gain may have been a contributing factor. In intact and ovariectomized mice given tamoxifen by subcutaneous injection, development of mammary-gland tumors was inhibited (IARC 1996).

Studies on Mechanisms of Carcinogenesis

Several studies found that women receiving estrogen-replacement therapy unopposed by progesterone had highly elevated risks of endometrial cancer (IARC 1979, 1999). For this reason, conjugated estrogens are classified as *known to be human carcinogens* (see Estrogens, Steroidal). Tamoxifen acts as an anti-estrogen in the breast (and is therefore used to treat breast cancer), but acts as an estrogen agonist in the uterus. Therefore, tamoxifen will likely affect the uterus in the same way as conjugated estrogens. The available data strongly indicate that endometrial cancer following exposure to estrogen is caused by estrogen-receptor-mediated responses.

In experimental animals and *in vitro,* tamoxifen readily forms DNA adducts in several tissues and types of cells. Either these adducts or the estrogenic activity of tamoxifen could be responsible for liver cancer observed in rats exposed to tamoxifen. DNA adducts generally have not been detected in human tissue samples; however, low levels of DNA adducts were observed in leukocytes and endometrial tissue from breast-cancer patients receiving tamoxifen (Hemminki *et al.* 1996, 1997). Although tamoxifen did not cause mutations in bacteria, it induced micronucleus formation in human cells *in vitro* (Otto *et al.* 1996). *In vivo*, it increased aneuploidy and chromosomal aberrations in the livers of female Sprague-Dawley rats (Sargent *et al.* 1996). The available data indicate that the carcinogenicity of tamoxifen in humans is due to estrognen-receptor-mediated mechanisms. Genotoxic mechanisms may also be involved in human cancer, but the available data suggest that genotoxic effects are smaller in humans than in rodents.

Tamoxifen has been tested in tumor initiation-promotion studies (IARC 1996). In rats, it promoted the development of *N*-nitrosodiethylamine–induced liver tumors in several studies and kidney tumors in one study. In several other studies in rats, tamoxifen inhibited the development of 7,12-dimethyl[*a*]benzanthracene-induced mammary-gland tumors. In mice, tamoxifen inhibited the

development of 3-methylcholanthrene–induced cervical cancer and virus-induced leukemia. In two studies in hamsters, it inhibited the development of kidney and liver tumors induced by 17β-estradiol.

Properties

Tamoxifen is a triphenylethylene compound that is a white, odorless crystal at room temperature (HSDB 2009). It is practically insoluble in water, but soluble in ethanol, methanol, and acetone. Physical and chemical properties of tamoxifen are listed in the following table.

Property	Information
Molecular weight	371.5[a]
Melting point	96°C to 98°C[a]
Log K_{ow}	6.3[a]
Dissociation constant (pK_b)	5.31 (pK_b)[b]

Sources: [a]HSDB 2009, [b]Akron 2009.

Use

Tamoxifen was approved for pharmaceutical use in the United States in 1977. It is registered for use in more than 90 countries. Tamoxifen has proven to be a successful palliative therapy for advanced breast cancer, yielding response rates similar to those seen with other endocrine treatments but with fewer side effects. It is commonly used as a primary therapy for breast cancer in elderly women who are considered poor candidates for surgery. Tamoxifen has been the adjuvant therapy of choice for postmenopausal, node-positive, and estrogen- or progesterone-receptor-positive women since the mid 1980s, and for postmenopausal, node-negative, and estrogen- or progesterone-receptor-positive women since the early 1990s. It is also being used to treat breast cancer in node-negative and receptor-positive premenopausal women. A high proportion (40% to 60%) of all women who undergo potentially curative surgery for breast cancer now receive adjuvant tamoxifen therapy for two to five years (IARC 1996). Tamoxifen is also used to reduce the risk of breast cancer in women who are at high risk for developing the disease (HHS 1998). Tamoxifen has been tested as a possible treatment for other types of cancer, including melanoma and cancer of the liver (hepatocellular carcinoma), stomach, kidney (renal-cell carcinoma), pancreas (adenocarcinoma), cervix of the uterus, and ovary; however, it is not widely used for these purposes (IARC 1996). Worldwide use of tamoxifen from its market introduction through July 2001 was estimated at more than 12 million patient-years (Wickerham *et al.* 2002).

Production

Worldwide production of tamoxifen citrate (the salt used as the active ingredient in most drug products) increased steadily in the 1990s, from 7 metric tons (15,400 lb) in 1989 to 8.5 metric tons (18,700 lb) in 1991, 10.1 metric tons (22,300 lb) in 1993, and 10.3 metric tons (22,700 lb) in 1995 (IARC 1996). In 2009, one company (in Europe) produced tamoxifen, and twelve companies worldwide produced tamoxifen citrate (none in the United States) (SRI 2009); tamoxifen was available from seven U.S. suppliers, and tamoxifen citrate from fourteen U.S. suppliers (ChemSources 2009). In 2009, five U.S. pharmaceutical companies produced 10 drug products approved by the U.S. Food and Drug Administration that contained tamoxifen citrate as the active ingredient (FDA 2009).

Exposure

Exposure to tamoxifen may occur by ingestion or by inhalation of dust (ScienceLab 2008). Tamoxifen is available in 10- and 20-mg oral tablets, taken in the United States at a typical dose of 20 mg per day for one to two years. Daily doses in other countries may be as high as 30 to 40 mg. Tamoxifen citrate is available in 15.2-, 30.4-, and 45.6-mg tablets that contain 10, 20, and 30 mg of tamoxifen, respectively (FDA 2009). Most patients with metastatic breast cancer (men and women) are treated with tamoxifen at some point in their therapy (IARC 1996). In 2002, tamoxifen was the world's most commonly prescribed breast-cancer drug; one pharmaceutical company reported sales totaling $480 million, down 21% from $618 million in 2001. By 2005, annual sales had declined to $114 million (AstraZeneca 2003, 2006). Sales of generic forms of tamoxifen totaled $420 million for about 3,400,000 prescriptions in 2002, declining to $50 million for 1,670,000 prescriptions in 2007 (DrugTopics 2003a,b, 2008a,b)

Occupational exposure to tamoxifen may occur during its production, formulation, packaging, and administration. According to the National Occupational Exposure Survey (conducted from 1981 to 1983), 339 workers potentially were exposed to tamoxifen, and 2,077 workers potentially were exposed to tamoxifen citrate (NIOSH 1990).

Regulations

Consumer Product Safety Commission (CPSC)

Orally administered prescription drugs for human use require child-resistant packaging.

Food and Drug Administration (FDA)

Tamoxifen is regulated as a prescription drug subject to labeling and other requirements.

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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References

Akron. 2009. *The Chemical Database.* The Department of Chemistry at the University of Akron. http://ull.chemistry.uakron.edu/erd and search on CAS number. Last accessed: 11/5/09.

AstraZeneca. 2003. Key product summary. *Annual Review 2002*. AstraZeneca United States. http://www2.astrazeneca.com/annualrep2002/inbrief/keyproductsummary.asp#nw.

AstraZeneca. 2006. *Annual Review 2005*. AstraZeneca United States. http://www.astrazeneca-annualreports.com/2005/astrazeneca-2005-annual-review.pdf.

ChemSources. 2009. *Chem Sources - Chemical Search.* Chemical Sources International. http://www.chemsources.com/chemonline.html and search on tamoxifen. Last accessed: 11/5/09.

Cook LS, Weiss NS, Schwartz SM, White E, McKnight B, Moore DE, Daling JR. 1995. Population-based study of tamoxifen therapy and subsequent ovarian, endometrial, and breast cancers. *J Natl Cancer Inst* 87(18): 1359-1364.

Curtis RE, Boice JD Jr, Shriner DA, Hankey BF, Fraumeni JF Jr. 1996. Second cancers after adjuvant tamoxifen therapy for breast cancer. *J Natl Cancer Inst* 88(12): 832-834.

DrugTopics. 2003a. Top 200 brand and generic drugs by retail dollars in 2002. *DrugTopics.* ModernMedicine. http://drugtopics.modernmedicine.com/drugtopics/Generics/Top-200-brand-and-generic-drugs-by-retail-dollars-/ArticleStandard/Article/detail/115428. Last accessed: 2/14/04.

DrugTopics. 2003b. Top 200 brand and generic drugs sold in 2002 by units. *DrugTopics.* ModernMedicine. http://drugtopics.modernmedicine.com/drugtopics/Supplements/Top-200-brand-and-generic-drugs-sold-in-2002-by-un/ArticleStandard/Article/detail/110839. Last accessed: 2/14/04.

DrugTopics. 2008a. Top 200 generic drugs by retail dollars in 2007. *DrugTopics.* ModernMedicine. http://drugtopics.modernmedicine.com/drugtopics/data/articlestandard//drugtopics/102008/500218/article.pdf.

DrugTopics. 2008b. Top 200 generic drugs by units in 2007. *DrugTopics.* ModernMedicine. http://drugtopics.modernmedicine.com/drugtopics/data/articlestandard//drugtopics/072008/491181/article.pdf.

FDA. 2009. *The Electronic Orange Book*. U.S. Food and Drug Administration. http://www.fda.gov/cder/ob/default.htm and select Search by Active Ingredient and search on tamoxifen. Last accessed: 10/26/09.

Fisher B, Costantino JP, Redmond CK, Fisher ER, Wickerham DL, Cronin WM. 1994. Endometrial cancer in tamoxifen-treated breast cancer patients: findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14. *J Natl Cancer Inst* 86(7): 527-537.

Hardell L. 1988. Pelvic irradiation and tamoxifen as risk factors for carcinoma of corpus uteri. *Lancet* 2(8625): 1432.

Hemminki K, Rajaniemi H, Lindahl B, Moberger B. 1996. Tamoxifen-induced DNA adducts in endometrial samples from breast cancer patients. *Cancer Res* 56(19): 4374-4377.

Hemminki K, Rajaniemi H, Koskinen M, Hansson J. 1997. Tamoxifen-induced DNA adducts in leucocytes of breast cancer patients. *Carcinogenesis* 18(1): 9-13.

HHS. 1998. Tamoxifen approved for reducing breast cancer incidence [press release]. Washington, DC: U.S. Department of Health and Human Services. Oct. 29.

HSDB. 2009. *Hazardous Substances Data Bank*. National Library of Medicine. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB and search on CAS number. Last accessed: 10/22/09.

IARC. 1979. Conjugated oestrogens. In *Sex Hormones (II)*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 21. Lyon, France: International Agency for Research on Cancer. pp. 147-159.

IARC. 1996. Tamoxifen. In *Some Pharmaceutical Drugs*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 66. Lyon, France: International Agency for Research on Cancer. pp. 253-366.

IARC. 1999. Post-menopausal oestrogen therapy. In *Hormonal Contraception and Post-Menopausal Hormonal Therapy*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 72. Lyon, France: International Agency for Research on Cancer. pp. 399-530.

MacMahon B. 1997. Overview of studies on endometrial cancer and other types of cancer in humans: perspectives of an epidemiologist. *Semin Oncol* 24(suppl 1): 122-139.

Magriples U, Naftolin F, Schwartz PE, Carcangiu ML. 1993. High-grade endometrial carcinoma in tamoxifen-treated breast cancer patients. *J Clin Oncol* 11(3): 485-490.

Mantyla ETE, Karlsson SH, Nieminen LS. 1996. Induction of endometrial cancer by tamoxifen in the rat. In *Hormonal Carcinogenesis II. Proceedings of the Second International Symposium*. Li JJ, Li SA, Gustafsson JA, Nandi S, Sekely LI, eds. New York: Springer Verlag. pp. 442-445.

Newbold RR, Bullock BC, Jefferson WN, Padilla-Burgos E. 1996. Effects of developmental exposure of mice to tamoxifen. *Proc Am Assoc Cancer Res* 37: 109.

Newbold RR, Jefferson WN, Padilla-Burgos E, Bullock BC. 1997. Uterine carcinoma in mice treated neonatally with tamoxifen. *Carcinogenesis* 18(12): 2293-2298.

NIOSH. 1990. *National Occupational Exposure Survey (1981-83)*. National Institute for Occupational Safety and Health. Last updated: 7/1/90. http://www.cdc.gov/noes/noes1/x7229sic.html, http://www.cdc.gov/noes/noes1/x4010sic.html.

Otto AM, Paddenberg R, Schubert S, Mannherz HG. 1996. Cell-cycle arrest, micronucleus formation, and cell death in growth inhibition of MCF-7 breast cancer cells by tamoxifen and cisplatin. *J Cancer Res Clin Oncol* 122(10): 603-612.

Rutqvist LE, Johansson H, Signomklao T, Johansson U, Fornander T, Wilking N. 1995. Adjuvant tamoxifen therapy for early stage breast cancer and second primary malignancies. *J Natl Cancer Inst* 87(9): 645-651.

Sargent LM, Dragan YP, Sattler C, Bahnub N, Sattler G, Martin P, *et al.* 1996. Induction of hepatic aneuploidy *in vivo* by tamoxifen, toremifene and idoxifene in female Sprague-Dawley rats. *Carcinogenesis* 17(5): 1051-1056.

Sasco AJ, Chaplain G, Amoros E, Saez S. 1996. Endometrial cancer following breast cancer: Effect of tamoxifen and castration by radiotherapy. *Epidemiology* 7(1): 9-13.

ScienceLab. 2008. *Material Safety Data Sheet: Tamoxifen Citrate MSDS*. ScienceLab.com. Last updated: 11/6/08. http://www.sciencelab.com/msds.php?msdsId=9925160.

SRI. 2009. *Directory of Chemical Producers*. Menlo Park, CA: SRI Consulting. Database edition. Last accessed: 11/5/09.

Van Leeuwen FE, Benraadt J, Coebergh JW, Kiemeney LA, Gimbrere CH, Otter R, *et al.* 1994. Risk of endometrial cancer after tamoxifen treatment of breast cancer. *Lancet* 343(8895): 448-452.

Wickerham DL, Fisher B, Wolmark N, Bryant J, Costantino J, Bernstein L, Runowicz CD. 2002. Association of tamoxifen and uterine sarcoma. *J Clin Oncol* 20(11): 2758-2760.