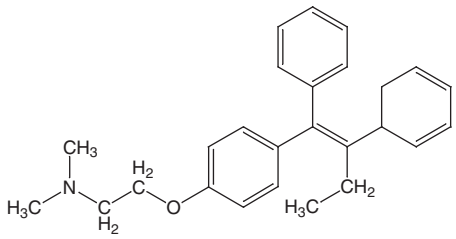
Tamoxifen
CAS No. 10540-29-1

Known to be a human carcinogen
First Listed in the *Ninth Report on Carcinogens* (2000)



Carcinogenicity

Tamoxifen is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity in humans that indicates a causal relationship between exposure to tamoxifen and cancers of the uterus (endometrium). 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 was reported in one adequate cohort study, four adequate case-control studies, and 14 randomized clinical trials.

The cohort study (Curtis *et al.* 1996) examined the effect of tamoxifen on risk of endometrial cancer in 87,323 women with breast cancer reported to the Surveillance, Epidemiology, and End Results (SEER) program in the United States and found a statistically significant elevation of endometrial cancer in women who had received tamoxifen therapy. In two of the four case-control studies (van Leeuwen *et al.* 1994, Sasco *et al.* 1996), a non-significant elevation of risk for endometrial cancer was found; however, a significant increase in risk was observed with increasing duration of therapy in one of these studies (van Leeuwen *et al.* 1994). In the United States case-control study (Cook *et al.* 1995), no increased risk was noted, but a shorter duration of tamoxifen use was reported. In the fourth case-control study (Hardell 1988), increased risk of endometrial cancer for tamoxifen use was found, but confounding factors could not be eliminated.

In the two largest randomized clinical trials (Fisher *et al.* 1994, Rutqvist *et al.* 1995), there was a strong and statistically significant association between risk for endometrial cancer and use of tamoxifen. In the 12 smaller trials, no statistically significant increases in endometrial cancer were seen, although 29 endometrial cancers were reported in tamoxifen-treated individuals compared to 14 in controls when these 12 studies were combined.

In 32 case studies, 102 cases of endometrial cancer were reported in women who received tamoxifen for breast cancer. One case series reported significantly more high-grade endometrial tumors in tamoxifen-treated breast cancer patients when compared to patients without tamoxifen use (Magriples *et al.* 1993); this difference, however, was not observed in six other studies.

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

Experimental animal studies also provide evidence of tamoxifen's carcinogenic effects. IARC (1996) reviewed experimental studies reported prior to 1996 and reached a similar conclusion. Tamoxifen, administered orally, was evaluated in one mouse study and eight rat studies. In mice, the incidences of benign ovarian and testicular tumors were significantly increased after 3 months of treatment. In rats, in eight studies that varied in treatment lengths, tamoxifen induced preneoplastic liver lesions and benign or malignant liver tumors. One rat study reported a decrease in tumors in hormone-dependent tissues; however, reduced weight gain may have been a contributing factor. In one additional study in which tamoxifen was given by subcutaneous administration, mammary tumor development was inhibited in intact and ovariectomized mice.

Uterine abnormalities, including endometrial carcinoma, also have been reported in experimental animals exposed to tamoxifen. Rats receiving tamoxifen daily by oral gavage for 20 to 52 weeks were reported to have squamous cell metaplasia, dysplasia, and squamous cell carcinoma of the uterus; no comparable lesions were observed in controls (Mantyla *et al.* 1996). Short-term developmental exposure to tamoxifen on days 1 to 5 of neonatal life has been reported to significantly increase the incidence of reproductive tract abnormalities in both female and male mice, including uterine carcinoma and seminal vesicle tumors (Newbold *et al.* 1996, Newbold *et al.* 1997).

Additional Information Relevant to Carcinogenicity

Several studies reviewed by IARC (1996) described tumor initiation/promotional and co-carcinogenicity attributes of tamoxifen. In several studies with male and female rats, it enhanced liver tumors induced by *N*-nitrosodiethylamine. In one rat study, it enhanced the development of *N*-nitrosodiethylamine-induced kidney tumors; however, in a number of other studies, it inhibited 7,12-dimethyl[*a*]benzanthracene-induced mammary tumors. In mice, tamoxifen inhibited 3-methylcholanthrene-induced cervical cancer and virus-induced leukemia. In hamsters, two studies reported the inhibition by tamoxifen of kidney and liver tumors induced by 17β-estradiol.

Several reports demonstrate that women receiving estrogen replacement therapy unopposed by progesterone have a highly elevated risk for endometrial cancer (IARC 1979, 1999). Because of these data, conjugated estrogens are considered *known human carcinogens* (See Estrogens, Steroidal profile). Tamoxifen acts as an estrogen agonist in the uterus, which is different than its action in the breast, where it is an anti-estrogen (used to treat breast cancer because of this property). Therefore, tamoxifen would likely produce the same effects as conjugated estrogens in the uterus. Available data strongly indicate that endometrial cancer following exposure to estrogens is caused by estrogen receptor-mediated responses. DNA adducts generally have not been detected in human samples; however, low levels of DNA adducts were observed in leukocytes and endometrial tissue of breast cancer patients receiving tamoxifen (Hemminki *et al.* 1996, Hemminki *et al.* 1997).

In animal and *in vitro* experiments, tamoxifen readily forms DNA adducts in several tissues and cells, and either these adducts or the estrogenic activity of tamoxifen could be responsible for liver cancer observed in rodents exposed to tamoxifen.

Although tamoxifen is not mutagenic in bacteria, it is positive for micronuclei 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).

Available data indicate that the receptor-mediated mechanisms involved in the carcinogenic actions of tamoxifen are operative in humans. Genotoxic mechanisms may also be operative in humans, but preliminary studies suggest that they are quantitatively less than in rodents.

Properties

Tamoxifen belongs to the chemical class of triphenylethylenes and is considered to be an antiestrogen (i.e., estrogen inhibitor). It exists as white, odorless crystals with a molecular weight of 371.5 and a melting point of 96°C to 98°C. Tamoxifen citrate, the form of tamoxifen used in drug preparations, has a molecular weight of 563.6 and is a white, fine, crystalline powder with a melting point of 140°C to 142°C. The citrate salt form is slightly soluble in water and soluble in ethanol, methanol, and acetone. The compound is hygroscopic at high relative humidities and is sensitive to ultraviolet light and heat. It can form explosive dust clouds in air and releases flammable vapors when heated. Hazardous decomposition products include carbon monoxide, carbon dioxide, and nitrogen oxide (ICIA 1989, IARC 1996, HSDB 2003).

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 in many cases of 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 a period of 2 to 5 years (IARC 1996). Tamoxifen citrate is also used to reduce the risk of breast cancer in women who are at high risk for developing the disease (FDA 1998). Tamoxifen has been tested as a possible treatment for hepatocellular carcinoma, stomach carcinoma, renal-cell carcinoma, melanoma, pancreatic adenocarcinoma, cervical carcinoma, ovarian carcinoma, and other tumors; however, it is not widely used for these treatments (IARC 1996). Worldwide use of tamoxifen citrate 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 showed steady increases in the 1990s with 7 metric tons (15,400 lb) in 1989, 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). There is at least one U.S. producer of tamoxifen citrate (SRI 2003), and there are 15 U.S. suppliers for tamoxifen citrate and 2 suppliers of tamoxifen (ChemSources 2003). Nine U.S. pharmaceutical companies with drug products approved by the U.S. Food and Drug Administration (FDA) containing tamoxifen citrate as the active ingredient were identified (FDA 2003).

Exposure

Exposure to tamoxifen may occur by inhalation of dust or ingestion (ICIA 1989). Tamoxifen is available in 10- or 20-mg oral tablets (FDA 2003). The typical dose in the United States is 20 mg/day for 1 to 2 years. Doses in other countries may be as high as 30 to 40 mg/day. Tamoxifen citrate is available as 15.2-, 30.4-, and 45.6-mg tablets that contain 10, 20, and 30 mg of tamoxifen, respectively. Most patients with metastatic breast cancer (men and women) are treated with tamoxifen at some point in their therapy (IARC 1996). Tamoxifen was the world's most commonly prescribed breast cancer drug in 2002, and one pharmaceutical company reported sales totaling $337 million, down 27% from $462 million in 2001 (AstraZeneca 2003). Sales of generic forms of tamoxifen in 2002 totaled $420 million for approximately 3,400,000 prescriptions (DrugTopics 2003a, b).

Occupational exposure to tamoxifen may occur during its production, formulation, packaging, and administration. According to the National Occupational Exposure Survey (NOES) for 1981–1983, 339 employees were potentially exposed to tamoxifen in the workplace. Additionally, 2,077 employees were potentially exposed to tamoxifen citrate (NIOSH 1984).

Regulations

CPSC

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

FDA

Tamoxifen is a prescription drug subject to labeling and other requirements

REFERENCES

AstraZeneca. 2003. Annual Report and Form 20-F 2002. AstraZeneca United States. http://www.astrazeneca-us.com/investors/annualreport.asp. Last accessed: 2/6/04.

ChemSources. 2003. Chemical Sources International, Inc. http://www.chemsources.com.

Cook, L. S., N. S. Weiss, S. M. Schwartz, E. White, B. McKnight, D. E. Moore and J. R. Daling. 1995. Population-based study of tamoxifen therapy and subsequent ovarian, endometrial, and breast cancers. J Natl Cancer Inst 87(18): 1359-64.

Curtis, R. E., J. D. Boice, Jr., D. A. Shriner, B. F. Hankey and J. F. Fraumeni, Jr. 1996. Second cancers after adjuvant tamoxifen therapy for breast cancer. J Natl Cancer Inst 88(12): 832-4.

DrugTopics. 2003a. Top 200 Brand Drugs by Retail Dollars in 2002. DrugTopics.com. http://www.drugtopics.com and search Past Issues, Apr. 7, 2003. Last accessed: 2/14/04.

DrugTopics. 2003b. Top 200 Brand-Name Drugs by Units in 2002. DrugTopics.com. http://www.drugtopics.com and search Past Issues, Mar. 17, 2003. Last accessed: 2/14/04.

FDA. 1998. Tamoxifen Approved for Reducing Breast Cancer Incidence. Food and Drug Administration, U.S. Department of Health and Human Services News. http://www.fda.gov/bbs/topics/NEWS/NEW00662.html.

FDA. 2003. The Electronic Orange Book. Food and Drug Administration. http://www.fda.gov/cder/ob/default.htm (then select "Search by Active Ingredient" and type in tamoxifen).

Fisher, B., J. P. Costantino, C. K. Redmond, E. R. Fisher, D. L. Wickerham and W. M. Cronin. 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): 527-37.

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

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

Hemminki, K., H. Rajaniemi, B. Lindahl and B. Moberger. 1996. Tamoxifen-induced DNA adducts in endometrial samples from breast cancer patients. Cancer Res 56(19): 4374-7.

HSDB. 2003. Hazardous Substances Database. National Library of Medicine. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB.

IARC. 1979. 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. 583 pp.

IARC. 1996. 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. 514 pp.

IARC. 1999. Hormonal Contraception and Post-Menopausal Hormonal Therapy. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 71. Lyon, France: International Agency for Research on Cancer. 1095 pp.

ICIA. 1989. Material Safety Data Sheet. Tamoxifen Citrate Tablets. ICI Americas Pharmaceuticals Division. http://hazard.com/msds2/.

MacMahon, B. 1997. Overview of studies on endometrial cancer and other types of cancer in humans: perspectives of an epidemiologist. Semin Oncol 24(1 Suppl 1): S1-122-S1-39.

Magriples, U., F. Naftolin, P. E. Schwartz and M. L. Carcangiu. 1993. High-grade endometrial carcinoma in tamoxifen-treated breast cancer patients. J Clin Oncol 11(3): 485-90.

Mantyla, E. T. E., S. H. Karlsson and L. S. Nieminen. 1996. Induction of Endometrial Cancer by Tamoxifen in the Rat. In Hormonal Carcinogenesis II Proceedings of the Second International Symposium. J. J. Li, S. A. Li, J.-C. Gustafsson, S. Nandi and L. I. Sekely, eds. New York: Springer Verlag. p. 442-445.

Newbold, R. R., B. C. Bullock, W. N. Jefferson and E. Padilla-Burgos. 1996. Effects of developmental exposure of mice to tamoxifen. Abstract no. 753. Proc Am Assoc Cancer Res 37: 109.

Newbold, R. R., W. N. Jefferson, E. Padilla-Burgos and B. C. Bullock. 1997. Uterine carcinoma in mice treated neonatally with tamoxifen. Carcinogenesis 18(12): 2293-8.

NIOSH. 1984. National Occupational Exposure Survey (1981-83). Cincinnati, OH: U. S. Department of Health and Human Services. http://www.cdc.gov/noes/noes3/empl0003.html.

Otto, A. M., R. Paddenberg, S. Schubert and H. G. Mannherz. 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): 603-12.

Rutqvist, L. E., H. Johansson, T. Signomklao, U. Johansson, T. Fornander and N. Wilking. 1995. Adjuvant tamoxifen therapy for early stage breast cancer and second primary malignancies. Stockholm Breast Cancer Study Group. J Natl Cancer Inst 87(9): 645-51.

Sargent, L. M., Y. P. Dragan, C. Sattler, N. Bahnub, G. Sattler, P. Martin, *et al.* 1996. Induction of hepatic aneuploidy *in vivo* by tamoxifen, toremifene and idoxifene in female Sprague-Dawley rats. Carcinogenesis 17(5): 1051-6.

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

SRI. 2003. Directory of Chemical Producers. http://dcp.sric.sri.com/Public/ (Visitor Search).
van Leeuwen, F. E., J. Benraadt, J. W. Coebergh, L. A. Kiemeney, C. H. Gimbrere, R. Otter, *et al*. 1994. Risk of endometrial cancer after tamoxifen treatment of breast cancer. Lancet 343(8895): 448-52.
Wickerham, D. L., B. Fisher, N. Wolmark, J. Bryant, J. Costantino, L. Bernstein and C. D. Runowicz. 2002. Association of tamoxifen and uterine sarcoma. J Clin Oncol 20(11): 2758-60.