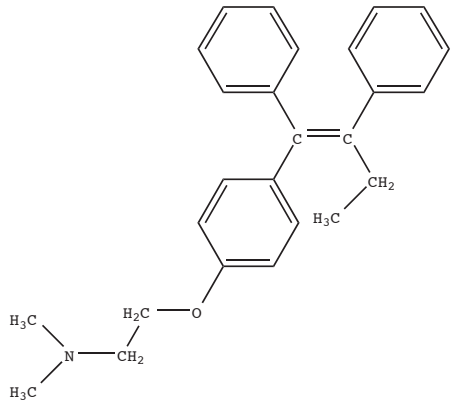
TAMOXIFEN
CAS No. 10540-29-1
First Listed in the *Ninth Report on Carcinogens*



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 uterine endometrium. However, there is also 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). The potential effect of tamoxifen in increasing the risk of endometrial cancer has been 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 (Sasco *et al*. 1996, van Leeuwen *et al.* 1994), a non-significant elevation of risk for endometrial cancer was found; further, a significant increase in risk was observed with increasing duration of therapy in one of these studies (van Leeuwen *et al.* 1994). In the U.S. 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 other 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. Examining the same confounding factors, an IARC Working Group concluded that there is a positive association between tamoxifen use and endometrial cancer and cited several studies in support of this conclusion; the same potential confounders were considered unlikely to have a major effect on the reported relative risks (IARC 1996).

Experimental animal studies also provide evidence of tamoxifen's carcinogenic effects. An IARC Working Group (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 (IARC 1996).

Uterine abnormalities including endometrial carcinoma have also 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 recently 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, 1997).

ADDITIONAL INFORMATION RELEVANT TO CARCINOGENESIS OR POSSIBLE MECHANISMS OF CARCINOGENESIS

Several studies (IARC 1996) described tumor initiation/promotional and co-carcinogenicity attributes of tamoxifen. In mice, tamoxifen inhibited 3-methylcholanthrene-induced cervical cancer and virus-induced leukemia. 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 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. Unlike the breast, where tamoxifen is an anti-estrogen (used to treat breast cancer because of this property), it acts as an estrogen agonist in the uterus. 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 have not been detected in human samples (IARC 1996) with one exception where low levels of DNA adducts were observed in leukocytes and endometrial tissue of breast cancer patients receiving tamoxifen (Hemminki *et al.* 1996, 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 increases 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 people, but preliminary studies suggest that they are quantitatively less than in rodents.

PROPERTIES

Tamoxifen exists as white, odorless crystals with a melting point of 96 to 98°C. Tamoxifen citrate ($C_{32}H_{37}NO_8$, mol. wt. = 563.65, CAS Registry No. 54965-24-1), the form of tamoxifen used in drug preparations, is a white, fine, crystalline powder with a melting point of 140 to 142°C. It 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 (ICI Americas 1989, IARC 1996, HSDB 2001).

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). Nolvadex (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. Tamoxifen's worldwide use was estimated at more than 7 million patient-years by the mid 1990s (IARC 1996).

PRODUCTION

Worldwide production of tamoxifen citrate showed steady increases in the 1990s with 7, 8.5, 10.1, and 10.3 metric tons reported for 1989, 1991, 1993, and 1995, respectively (IARC 1996). There is at least one current U.S. supplier for tamoxifen (Chem Sources 2001).

EXPOSURE

Exposure to tamoxifen may occur by inhalation of dust or ingestion (ICI Americas 1989). 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/kg. 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).

According to the National Occupational Exposure Survey (NOES) for 1981-1983, approximately 350 employees were potentially exposed to tamoxifen in the workplace. Additionally, 2100 employees were potentially exposed to tamoxifen citrate (IARC 1996).

REGULATIONS

The FDA regulates tamoxifen as a new drug with reporting and labeling requirements.

The OSHA regulates tamoxifen under the Hazard Communication Standard and as a chemical hazard in laboratories. Regulations are summarized in Volume II, Table 167.

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