Tamoxifen

CAS No. 10540-29-1

Known to be a human carcinogen
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 (Magriles 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 estrogen-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

**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.

<table>
<thead>
<tr>
<th>Property</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight</td>
<td>371.5(^a)</td>
</tr>
<tr>
<td>Melting point</td>
<td>96°C–98°C(^c)</td>
</tr>
<tr>
<td>Log (K_{ow})</td>
<td>6.3(^b)</td>
</tr>
<tr>
<td>Dissociation constant (pK_a)</td>
<td>5.31(^b)</td>
</tr>
</tbody>
</table>

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 \textit{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 2001, annual sales had declined to $114 million (AstraZeneca 2002). By 2005, annual sales had declined to $50 million for about 3,400,000 prescriptions in 2002, declining to $50 million for 1,670,000 prescriptions in 2007 (DrugTopics 2003a, 2008a, 2008b). 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).

**References**


