REVIEW ARTICLE

Tamoxifen and Toremifene in Breast Cancer: Comparison of Safety and Efficacy

By Aman U. Buzdar and Gabriel N. Hortobagyi

Purpose: **Tamoxifen is currently the standard hormonal treatment of breast cancer, both for metastatic disease and in the adjuvant setting. A new antiestrogen, toremifene, was approved recently for use in managing metastatic breast cancer in postmenopausal women.**

Methods: **Toremifene is structurally similar to tamoxifen, differing only by a single chlorine atom, and has a similar pharmacologic profile. The major difference between the two compounds is in the preclinical activity; chronic, high-dose tamoxifen is hepatocarcinogenic in the rat, whereas toremifene is not. Neither agent is hepatocarcinogenic in mice, hamsters, or humans; therefore, clinical relevance of the rat data may not be significant.**

Results: **In a worldwide phase III trial, the two agents demonstrated comparable efficacy and safety against metastatic breast cancer. Both agents have shown a significant hypocholesterolemic effect after long-term administration.**

Conclusion: **Due to the paucity of long-term clinical data on toremifene, important unresolved questions remain, which include its effects on bone mineral density, the frequency of cardiac events, and the risk for endometrial cancer. Tamoxifen has been associated with maintenance of bone mineral density, a reduction in cardiac events, and a slightly increased risk of endometrial cancer. Toremifene is not likely to be used as second-line therapy after tamoxifen failure due to cross-resistance, and its ultimate place in therapy of advanced breast cancer remains to be determined.**

J Clin Oncol 16:348-353.

OVER THE NEARLY 20 YEARS since its introduction in the United States, tamoxifen has become firmly established as the standard in the hormonal treatment of both early and advanced breast cancer. First approved for the treatment of advanced breast cancer in postmenopausal women, tamoxifen's indications have expanded to include advanced breast cancer in premenopausal women, in men, and as adjuvant therapy for both node-positive and node-negative disease. The uses of tamoxifen have broadened due to its efficacy in prolonging disease-free survival and reducing mortality rates, as well as a 39% reduction in the risk for contralateral breast cancer.[1] Patients with estrogen receptor (ER)-positive breast cancer seem to derive the greatest benefit from tamoxifen therapy.

Recently, a variety of new antiestrogen compounds have begun to receive attention as potential successors to tamoxifen. One of these, toremifene, is a tamoxifen analog, differing chemically by only a single chlorine atom (Fig 1). Toremifene has received Food and Drug Administration approval for use in treating metastatic breast cancer in postmenopausal women. Because long-term data on toremifene are lacking, the drug is not yet indicated for adjuvant use. The purpose of this review is to address the similarities and differences of toremifene and tamoxifen, both in the laboratory and in the clinic.

PRECLINICAL PHARMACOLOGIC ACTIVITY

The pharmacologic profile of toremifene appears to be similar to that of tamoxifen in terms of ER binding, antitumor activity, and estrogenic activity.[2] Both agents bind ER with an affinity 5% of that of estradiol. In uterotrophic assays, toremifene exhibits lower estrogenic activity than tamoxifen at low and moderate doses; however, the maximum estrogenic and antiestrogenic activity of the two agents is similar.[3]

In a human ER-positive breast cancer cell line (MCF-7 cells), the effects of toremifene are similar to those of tamoxifen—growth inhibition at low concentrations and oncolytic activity at high concentrations.[4] Tamoxifen inhibited growth of MCF-7 cells more than toremifene in a comparative study of 10^{-6}-mol/L concentrations of various antiestrogens.[5]

The in vivo effects of the two agents were similar against dimethyl benzanthacene-induced rat mammary cancer, with the difference that 45 mg/kg toremifene showed an antitumor effect, while the same dose of tamoxifen was lethal to the rats.[4]

From Department of Breast and Gynecology Medical Oncology, The University of Texas, MD Anderson Cancer Center, Houston, TX.

Submitted February 18, 1997; accepted July 21, 1997.

Address reprint requests to Aman U. Buzdar, MD, MD Anderson Cancer Center, 1515 Holcombe Blvd, Box 56, Houston, TX 77030. Email abuzdar@notes.mdacc.tmc.edu.

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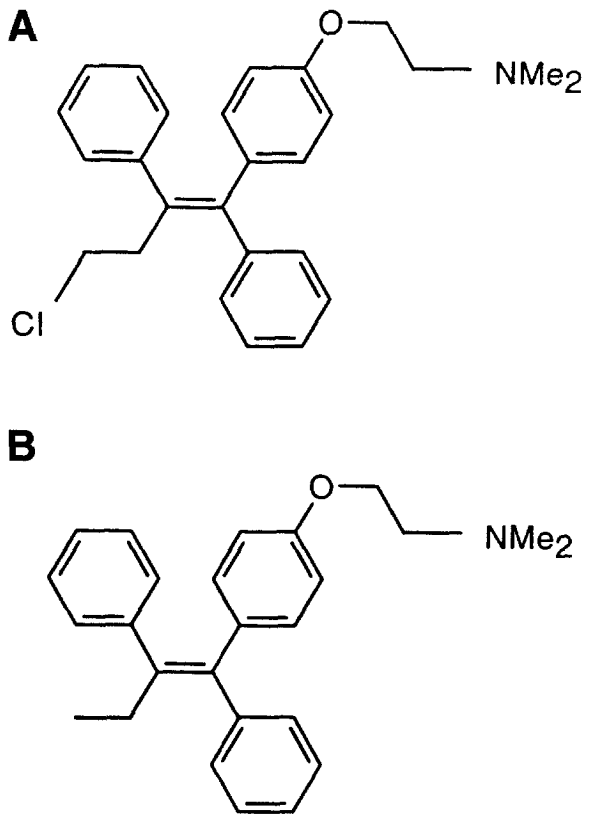

Fig 1. Structure of (A) toremifene and (B) tamoxifen.

RISK FOR SECONDARY CANCERS

Hepatocellular Cancer

One major difference between toremifene and tamoxifen is the hepatocarcinogenicity reported in animal studies. Chronic (3 to 12 months), high-dose tamoxifen (11.3 to 22.6 mg/kg, two doses per day) is hepatocarcinogenic in the rat (but not in other species), whereas toremifene at doses up to 48 mg/kg is not.[6] (Note that the recommended dose of tamoxifen for humans is 20 mg/d, which is roughly 0.3 mg/kg.) This effect of tamoxifen is both species- and strain-specific; tamoxifen is not hepatocarcinogenic in the mouse and may even exert a protective effect in the hamster.[7] In addition, Fischer rats seem to be markedly less sensitive to tamoxifen than Wistar or Lewis rats.

Toremifene is not devoid of genotoxicity. Both agents have shown genotoxic potential in MCL-5 cells,[8] and long-term toremifene has been linked to osteosarcoma in the mouse. Moreover, Dragan et al[9] demonstrated that both tamoxifen and toremifene can function as promoters of rat liver and kidney tumors initiated by the carcinogen diethylnitrosamine (DEN).

The genotoxicity of tamoxifen in the rat has been ascribed to the presence of DNA adducts in rat liver tissue. The frequency of DNA adducts may account for the species and strain differences in carcinogenicity, as DNA adduct levels are substantially higher in susceptible rat strains than in other rat strains, mice, hamsters, and humans.[7] For example, the level of DNA adducts in mice treated with tamoxifen is 30% to 40% of that seen in the rat.[10] Phillips et al[11] conducted a cross-species experiment and measured the levels of DNA adducts in rat, mouse, and human hepatocytes incubated with tamoxifen. In rat and mouse hepatocytes, the levels of DNA adducts were greater than 10^{-7} adducts per nucleotide following incubation with 1 to 10 μmol/L tamoxifen; however, in the human hepatocyte, no adducts were seen at a detection limit of 4×10^{-10} adducts per nucleotide (in the range of one adduct per cell).

Four studies have evaluated the presence of DNA adducts in human tissue after administration of tamoxifen in breast cancer patients. Martin et al[12] compared liver tissue DNA adduct levels in seven women treated with tamoxifen 20 mg for 6 to 44 months and seven control patients. DNA adduct levels ranged from 18 to 80 adducts per 10^8 nucleotides in tamoxifen-treated women, a level that was not significantly different from the control group.

In a different study,[13] DNA adducts were measured in the WBCs of seven women treated with tamoxifen (20 to 40 mg) for 3 months to 6 years for early breast cancer and compared with levels in three healthy control subjects. Similar levels of DNA adducts were seen in treated patients and controls, with a maximum reported level of 1.5 adducts per 10^8 nucleotides, and the adducts observed differed from those in treated rats.

Two studies have investigated DNA adduct levels in the human endometrium after tamoxifen treatment. These studies used different methods to measure DNA adduct levels, which produced contrasting results. Carmichael et al[14] determined endometrial DNA adduct levels in 18 patients who received tamoxifen (10 to 40 mg) for 3 months to 9 years and compared the levels with those in 16 control patients. Although both groups displayed a low level of DNA adducts as detected by phosphorus 32–postlabeling, the results of the two groups were indistinguishable. In the other study,[15] a low level of DNA adducts (2.7 adducts per 10^9 nucleotides) was observed in the endometria of five of seven tamoxifen-treated patients (20 to 40 mg/d for 3 months to 5 years), but none of five control patients. This study used high-performance liquid chromatography (HPLC) to analyze DNA adducts and used liver DNA from tamoxifen-treated rats as a positive standard. The differing methodologies used in these studies require further analysis. It should be noted that the level of DNA adducts seen in the study reported by Hemminki et al[15] was far below that seen in the

livers of chronically treated rats (3,000 adducts per 10^8 nucleotides).[16]

The contrasting results regarding DNA adducts in different species have been attributed to the profound differences in rodent and human metabolism of tamoxifen.[17] It is also thought that human cells may have a greater ability to remove DNA adducts via detoxifying enzymes. Animal studies may not be a fair representation of the clinical use of tamoxifen; besides the substantial metabolic differences between rodents and humans, the threshold dose for carcinogenicity in the rat is an order of magnitude larger than the clinical therapeutic dose, and the drug is given for a greater proportion of the animal's life span.[7]

Although toremifene has not produced DNA adducts in rat liver, high doses of both compounds induced low levels of DNA adducts in rat and human microsomal systems and in cultured lymphocytes in vitro.[18]

As no increase in hepatocellular cancer risk has been observed in more than 7.5 million woman-years of clinical experience with tamoxifen, the clinical relevance of its rodent carcinogenicity does not appear to be significant. Moreover, it is possible that the rare instances of liver cancer reported thus far could actually be cases of metastatic breast cancer.

Endometrial Cancer

Tamoxifen has been associated with an increased risk of endometrial cancer in breast cancer patients, on the order of two cases per 1,000 patients annually.[19] There is currently not enough evidence to prove causality definitely; however, this effect has been attributed to the estrogenic activity of tamoxifen on the uterus.[20] As toremifene is solely indicated for the treatment of metastatic breast cancer and few patients have received adjuvant therapy, there are clearly not enough data to assess the endometrial cancer risk of toremifene at this time. It will probably take many years and thousands of treated patients before the answer is known. However, it is important to note that tamoxifen and toremifene produce similar increases in the endometrial thickness of postmenopausal breast cancer patients, thereby demonstrating comparable estrogenic activity.[21]

CLINICAL EFFICACY AND SAFETY

The clinical trials' data base on tamoxifen for both adjuvant therapy of early breast cancer and palliative therapy of late-stage breast cancer is enormous. Clinical experience with toremifene is limited at this time and only one large-scale study has compared the two agents.[22]

First-Line Therapy of Metastatic Breast Cancer

The efficacy and safety of two doses of toremifene (60 and 200 mg/d) and a standard dose of tamoxifen (20 mg/d) were compared in a worldwide phase III trial.[22] The study population included postmenopausal women with measurable or assessable metastatic breast cancer with either hormone receptor-positive or unknown receptor status. Exclusion criteria included prior hormonal treatment or chemotherapy for recurrent or metastatic disease, but adjuvant therapy was acceptable. Six hundred forty-eight patients were enrolled at 129 sites in six countries. Primary efficacy end points included response rate and progression-free interval, and secondary end points consisted of survival, response duration, and quality of life.

There were no significant differences among the three treatment groups in response rate, median response duration, median time to progression, or overall survival (Fig 2 and Table 1).

Thirty-six patients died; the frequency of study deaths was 4% (tamoxifen), 9% (toremifene 60 mg), and 5% (toremifene 200 mg). The three groups also showed similar rates for tumor flare, elevated calcium levels, and cardiac events. Although rare, ocular abnormalities and thromboembolic events are known to be associated with tamoxifen and phase II studies have found similar effects with toremifene.[23] The phase III trial[22] reported that tamoxifen and toremifene had similar effects on rates of cataracts (new or worsened) and thromboembolic events. However, corneal keratopathies were more common with 200 mg toremifene (n = 8)

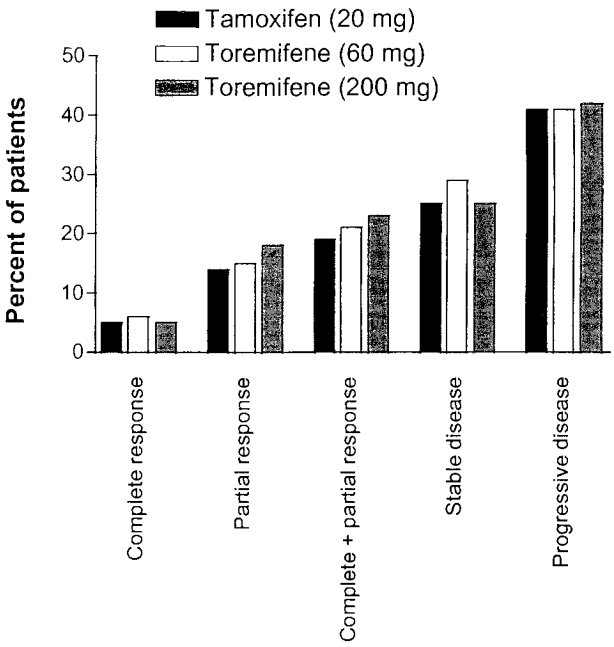

Fig 2. Clinical response rates for tamoxifen and toremifene (intent-to-treat analysis). Data from Hayes et al.[22]

Table 1. Clinical Trial Data Comparing Toremifene and Tamoxifen (intent-to-treat analysis)

Variable	Tamoxifen 20 mg	Toremifene 60 mg	Toremifene 200 mg
No. of randomized patients	215	221	212
Median response duration (months)*	19.1	16.9	18.4
Median time to progression (months)	5.8	5.6	5.6
Overall survival (months)	31.7	38.3	30.1

NOTE. Complete response + partial response + stable disease.
Data from Hayes et al.[22]

than with 60 mg toremifene (n = 4) or tamoxifen (n = 2). This condition resolved in all patients after cessation of treatment.

Three percent of patients discontinued treatment due to toxicity, including three patients on tamoxifen, six on toremifene 60 mg, and 12 on toremifene 200 mg.

The most common subjective complaints were pain, asthenia, anorexia, headache, diarrhea, vaginitis, rash, pruritis, depression, and insomnia; the distribution for these symptoms in the three groups was similar. The frequencies of prospectively assessed side effects are shown in Fig 3.

There was an excess of AST abnormalities (≥100 IU/L) not attributable to progressive disease in the high-dose toremifene arm compared with tamoxifen (10% *v* 2%; $P < .05$). In the low-dose toremifene group, more patients developed alkaline phosphatase abnormalities (≥200 IU/L) than in the tamoxifen group (19% *v* 11%; $P < .05$).

Quality-of-life analyses showed no differences among the three treatments with respect to enjoyment of life, pain, mood, or analgesic requirements.

This study showed no advantage in using toremifene over tamoxifen for the management of metastatic breast cancer. Like tamoxifen, toremifene does not exhibit a dose-response relationship, and thus there appears to be no benefit of increasing the dose from 60 mg to 200 mg.

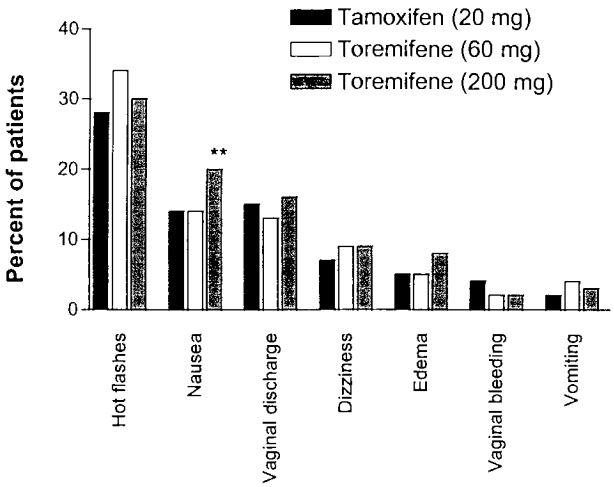

Fig 3. Prospectively assessed side effects of tamoxifen and toremifene (drug-related or indeterminate cause). **$P < .05$ *v* tamoxifen. Data from Hayes et al.[22]

Efficacy of Toremifene in Tamoxifen-Resistant Metastatic Breast Cancer

Two studies have evaluated the potential use of toremifene as second-line therapy after tamoxifen for the treatment of advanced breast cancer. Vogel et al[23] conducted a phase II trial of toremifene (200 mg/d) in perimenopausal or postmenopausal women with advanced breast cancer who had either failed to respond to tamoxifen (n = 28), who had relapsed after a tamoxifen response (n = 43), or who had relapsed on adjuvant tamoxifen (n = 31). Patients had hormone receptor-positive disease or had achieved a prior response on hormonal therapy. The objective response rate of toremifene was only 5% (median duration, 10.9 months), with an additional 23% of patients achieving stable disease (median duration, 7.8 months). The investigators were uncertain as to whether patients with stable disease derived a benefit from toremifene or just had an indolent disease course. Although patients were substantially pretreated, the investigators attributed the low objective response rate to major cross-resistance between toremifene and tamoxifen.

Stenbygaard et al[24] conducted a double-blind crossover trial of toremifene (240 mg/d) and tamoxifen (40 mg/d) in 66 postmenopausal women with advanced breast cancer (ER-positive or receptor status unknown). After disease progression on either toremifene or tamoxifen, patients were crossed over to the opposite treatment. Objective response rates for first-line therapy were 29% with toremifene and 42% with tamoxifen (*P* not significant between treatments). Forty-four patients who progressed on first-line toremifene or tamoxifen were assessable for second-line response. No objective responses were observed, which indicates cross-resistance of the two agents.

EFFECTS ON LIPIDS

Two clinical studies have demonstrated a hypocholesterolemic effect of both tamoxifen and toremifene after 1 year of treatment.[25,26] In the first study,[25] 24 postmenopausal women with advanced breast cancer were randomized to tamoxifen (40 mg/d) or toremifene (60 mg/d). After 12 months, serum cholesterol levels decreased by 8% (from a baseline of 5.2 ± 0.4 mmol/L) with tamoxifen and 12% (from a baseline of 5.8 ± 0.3 mmol/L) with toremifene ($P < .05$ for both treatments). Low-density lipoprotein (LDL)-cholesterol levels decreased by 16% (from a baseline of 3.3 ± 0.3 mmol/L) with tamoxifen and 15% (from a baseline of 3.5 ± 0.3 mmol/L) with toremifene ($P < .05$ for both treatments),

with no changes in high-density lipoprotein (HDL)-cholesterol or serum triglycerides. The investigators attributed these effects to an interference in cholesterol synthesis via inhibition of the conversion of D^8-cholestenol to lathosterol; each agent produced substantial accumulation of D^8-cholestenol (40- to 55-fold of baseline levels).

In the second study,[26] 49 postmenopausal breast cancer patients were randomized to 20 mg/d tamoxifen or 60 mg/d toremifene. In both groups, total cholesterol and LDL-cholesterol were reduced by 11% and 20%, respectively ($P \leq .01$). Baseline total cholesterol levels were 6.16 ± 1.03 mmol/L and 5.88 ± 1.16 mmol/L with tamoxifen and toremifene, respectively; baseline LDL-cholesterol levels were 4.01 ± 0.91 mmol/L (tamoxifen) and 3.74 ± 1.03 mmol/L (toremifene). HDL-cholesterol levels, which were lower in the toremifene group at baseline (1.36 ± 0.33 mmol/L *v* 1.63 ± 0.40 mmol/L), decreased by 5% with tamoxifen and increased by 14% with toremifene, a difference that was statistically significant ($P = .001$ between treatments). Triglycerides increased by 28% with tamoxifen ($P = .013$) and were unchanged in the toremifene group; however, weight gain was higher with tamoxifen (mean, 1.8 kg *v* 1 kg). Apolipoprotein (Apo) B levels decreased by 7% with tamoxifen ($P = .013$) and by 10% with toremifene ($P = .025$). Apo A-I and A-II levels were unchanged with tamoxifen, but increased with toremifene. Lipoprotein Lp, an independent risk factor for coronary heart disease, decreased by 34% with tamoxifen ($P = .00002$) and by 41% with toremifene ($P = .00004$). The clinical trials of adjuvant tamoxifen suggest that the favorable effects of tamoxifen on blood lipids may reduce the risk of cardiac events.[1] Additional studies are necessary to establish these findings and to determine if toremifene has a similar effect.

EFFECTS ON BONE

Several studies have documented preservation of lumbar spine bone mineral density in postmenopausal women who receive long-term tamoxifen therapy.[27,28] No studies have been published on toremifene and bone mineral density; however, the drug is not yet approved for adjuvant use, and clinical experience with long-term toremifene (>1 year) is limited.

CONCLUSION

Toremifene is a new antiestrogen for the management of metastatic breast cancer. It appears to have a similar pharmacologic profile as tamoxifen, with the exception that it is not hepatocarcinogenic in laboratory rats. The clinical relevance of this difference does not appear to be significant, as tamoxifen has not been linked to an increased risk of liver cancer in patients. A more important, unresolved question is how toremifene will affect the risk for endometrial cancer in breast cancer patients, as this new agent shows similar estrogenic activity to tamoxifen in the human uterus. As toremifene has not yet been adequately studied in the adjuvant setting, long-term data are not available to address endometrial cancer risk, as well as its effect on bone mineral density and the frequency of cardiac events. Therefore, a true comparison is not possible at this time.

The results of the toremifene phase III trial demonstrated comparable efficacy to tamoxifen against metastatic breast cancer. The rate of adverse events was similar with the exception of an excess of liver abnormalities in the high-dose toremifene group. Like tamoxifen, toremifene shows a lack of dose-response relationship, and this, in addition to increased toxicity, obviates use of the 200-mg dose.

The ultimate place of toremifene in therapy will probably be determined only after the clinical database expands substantially. This agent is unlikely to be used as second-line therapy after tamoxifen failure due to the likelihood of cross-resistance.

Although toremifene was being marketed as a safer antiestrogen in Great Britain,[29] the available data are not sufficient to make such a claim; it would require careful controlled studies to demonstrate any safety benefit, if one actually exists.

REFERENCES

1. Early Breast Cancer Trialists' Collaborative Group: Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. Lancet 339:1-15, 71-85, 1992

2. Howell A, Downey S, Anderson E: New endocrine therapies for breast cancer. Eur J Cancer 32A:576-588, 1996

3. Kangas L: Introduction to toremifene. Breast Cancer Res Treat 16:S3-S7, 1990 (suppl)

4. Kangas L: Review of the pharmacological properties of toremifene. J Steroid Biochem 36:191-195, 1990

5. Tominaga T, Yoshida Y, Matsumoto A, et al: Effects of tamoxifen and the derivative (TAT) on cell cycle of MCF-7 in vitro. Anticancer Res 13:661-666, 1993

6. Hard GC, Iatropoulos MJ, Jordan K, et al: Major difference in the hepatocarcinogenicity and DNA adduct forming ability between toremifene and tamoxifen in female Crl:CD(BR) rats. Cancer Res 53:4534-4541, 1993

7. Guzelian PS: Relevance of rat liver tumors to human hepatic and endometrial cancer. Semin Oncol 24:s1-105-s1-121, 1997 (suppl 1)

8. Styles JA, Davies A, Lim CK, et al: Genotoxicity of tamoxifen, tamoxifen epoxide and toremifene in human lymphoblastoid cells containing human cytochrome P450s. Carcinogenesis 15:5-9, 1994

9. Dragan YP, Vaughan J, Jordan VC, et al: Comparison of the effects of tamoxifen and toremifene on liver and kidney tumor promotion in female rats. Carcinogenesis 16:2733-2741, 1995

10. White INH, de Matteis F, Davies A, et al: Genotoxic potential of tamoxifen and analogues in female Fischer F344/n rats, DBA/2 and C57BL/6 mice and in human MCL-5 cells. Carcinogenesis 13:2197-2203, 1992

11. Phillips DH, Carmichael PL, Hewer A, et al: Activation of tamoxifen and its metabolite a-hydroxytamoxifen to DNA-binding products: Comparisons between human, rat, and mouse hepatocytes. Carcinogenesis 17:89-94, 1996

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