TAMOXIFEN:

SAFE WORK PRACTICES INFORMATION PAGE

Revised 11/3/09

BACKGROUND

Tamoxifen is a commonly prescribed antiestrogen drug marketed under the trade name Nolvadex®. Tamoxifen is widely used for the treatment of hormone-dependent breast cancer in postmenopausal women (Baum, 1985; Jordan and Murphy, 1990) and more recently as a prophylactic for women who have a high risk of breast cancer (Jordan, 1993). Tamoxifen is a selective estrogen receptor modulator (SERM). This is a compound which competes with estrogen for binding to the estrogen receptor and exhibits estrogen agonist or antagonist action depending on the site of action (Johnson et al., 2004). Tamoxifen citrate, in a pure state, is a white to off-white crystalline solid that is easily soluble in methanol and very slightly soluble in cold water (Calbiochem, 2006). Tamoxifen is extensively metabolized by the liver into several active metabolites that may exhibit altered affinity for the estrogen receptors (ER) (Furr and Jordan, 1984; Johnson et al., 1989). N-desmethyl-tamoxifen, 4-hydroxy-tamoxifen, 4-Hydroxy-N-desmethyl tamoxifen, α-hydroxy-tamoxifen, and α-hydroxy-N-desmethyl-tamoxifen are common metabolites found in plasma samples after long-term exposure to tamoxifen (Johnson et al., 2004). It is the latter two metabolites that give rise for concern given the supposition that α-hydroxylation can lead to formation of DNA adducts and possible carcinogenicity, teratogenicity, genotoxicity, and reproductive toxicity (Potter et al., 1994; Cunha et al., 1987; Poirier, 2003; Gray et al., 1989). These potentially severe side effects make tamoxifen exposure a significant health and safety threat to laboratory staff, animal handlers, and other personnel who may be subject to accidental exposure. Due to this health and safety threat the Institutional Biosafety Committee (IBC) has classified tamoxifen as a reportable hazardous chemical that must be reported on Institutional Animal Care and Use Committee (IACUC) protocols.

PURPOSE

The purpose of this page is to provide principal investigators (PIs) with information regarding health threats, exposure routes, proper work methods, and provision of suitable personal protective equipment for development of research protocols that effectively reduce risk of occupational exposure to tamoxifen.

OCCUPATIONAL EXPOSURE HAZARDS

Primary routes of occupational exposure to tamoxifen include: aerosol exposure, ingestion, accidental injection, and tissue/transplacental absorption (Phillips et al., 2005; Saunders and Cunningham, 2002). Industrial hygiene and epidemiological case studies involving tamoxifen are limited. The available scientific literature indicates that chronic long-term exposure to tamoxifen could lead to a number of potentially serious health effects.

1. Carcinogenicity: Exposure to tamoxifen or tamoxifen metabolites has been associated with an increased risk of cancer. Specifically, orally administered tamoxifen has been shown to significantly increase the incidence of hepatocellular carcinoma in female laboratory rats (Williams et al., 1993) and in human MCL-5 cells (Styles et al., 1994) by the formation of DNA adjuncts (Han and Liehr, 1992). In addition, tamoxifen has been associated with an increased risk of endometrial carcinoma (Riek et al., 2005) and an increase of rare forms of uterine cancer, specifically malignant mixed mullerian tumors (MMMTs), and uterine sarcomas, (Curtis et al., 2004) in women undergoing long-term treatment of breast cancer with tamoxifen. The International Agency for Research on Cancer (IARC) lists tamoxifen as a Group 1 carcinogen, carcinogenic to humans (IARC, 1996).

2. Teratogenicity: Research has indicated that tamoxifen may induce mutations in the developing (fetal through adolescent) human genital tract (Cunha GR et al., 1987). Thus, emphasizing the need for caution to prevent inadvertent exposure of the developing fetus to this compound. Tamoxifen is included on the "Dangerous Properties of Industrial Materials" listing of know human carcinogens (Lewis, 2004).

3. Genotoxicity: As a genotoxin, tamoxifen can be converted to reactive intermediates capable of binding to DNA. Subsequent replication on a damaged DNA template may lead to mutagenesis in critical genes and a heritable loss of growth control (Poirier and Schild, 2003). Research has established that tamoxifen is a potent rat hepatocarcinogen (Greaves et al., 1993). In the rat liver tamoxifen acts as a classical genotoxic chemical carcinogen by forming DNA adducts, which induce mutation in genes required for growth and control (Greaves et al., 1993; Carthew et al., 1995; Phillips, 2001; White, 2001; Brown, 2002). Available research on tamoxifen-DNA adduct formation in human tissue is incomplete (Poirier and Schild, 2003). However, proper safety precautions should be implemented when working with this compound due to potential DNA adduct formation that have been observed in animal studies.

4. Reproductive Toxicity: Prenatal, neonatal, and postnatal exposure to tamoxifen could lead to varying levels of reproductive toxicity. Neonatal laboratory animals exposed to tamoxifen develop defects of the reproductive tract, such as: hypoplastic testes, epididymal cysts, and metaplasia of accessory glands in males, and hyperplasia of vaginal epithelium, adenosis, and cervico-vaginal tumors in females (Taguchi, 1987). Early postnatal exposure to tamoxifen could lead to hypertrophy in luminal epithelium, permanent inhibition of uterine gland differentiation, and uterine neoplasia (Branham et al., 1996). Tamoxifen is also associated with ovarian follicular atrophy and degeneration, severe to mild uterine atrophy, and endometriosis (Yang et al., 1995). The limited available human tamoxifen studies indicate that long-term administration to women leads to a greater incidence of endometrial cancer and thickening of the endometrial tissue (Phillips 2001). Based on the resounding evidence of tamoxifen-related reproductive toxicity exhibited in animal models and in the limited available human studies, research involving tamoxifen should be conducted with the utmost care.

SAFE WORK METHODS

The list of potential tamoxifen-related health hazards identified above makes it imperative that PIs conduct thorough risk assessments and prepare protocols which include measures for minimizing staff exposure potential. To date, governmental regulatory agencies have not established exposure limits for tamoxifen. In lieu of the availability of regulatory guidance, the prudent course for PIs to follow is to either eliminate or reduce exposure potential as much as feasible through implementation of the safe work methods listed below.

1. Administrative Controls

a. Management considerations for tamoxifen and other potentially hazardous chemicals must be included in the laboratory Chemical Hygiene Plan.

b. Protocols involving the *in vivo* use of tamoxifen must include completion of IACUC Hazardous Chemical Information Page and approval through the Institutional Animal Care and Use Committee.

c. Principal investigators will develop and implement standard operating procedures (SOPs) by which laboratory staff will prepare/administer tamoxifen with minimal potential for exposure.

d. All tasks having potential for occupational tamoxifen exposure (mixing of doses, dose preparation, administering of injections, etc.) will only be conducted by competent staff who have received appropriate training (OSHA: "Worker Right to Know") regarding the specific tamoxifen-related health and safety risks, SOPs, and procedures to be followed in event of an exposure incident.

e. Laboratory personnel must be instructed to use extreme caution when performing injections involving tamoxifen, since accidental needle stick appears to potentially present the greatest exposure threat.

f. Laboratory personnel using tamoxifen in any of the procedures noted above are also required to complete applicable modules of the VCU Laboratory Safety Training Modules.

g. Exposures involving tamoxifen or any other acutely hazardous material should be reported to Employee Health as soon as possible.

2. Personal Protective Equipment: Tamoxifen exposure is often attributable to the wearing of inadequate PPE. Staff involved with any tasks where potential for tamoxifen exposure exists must don the following PPE:

a. Examination gloves: Two pairs of powder-free latex or nitrile examination gloves which cover hands and wrists completely through overlapping sleeve of lab coat should be donned as a minimum level of protection whenever working with tamoxifen.

Laboratory personnel should thoroughly wash hands with soap and water immediately upon removing examination gloves.

b. Safety glasses or safety goggles (ANSI Z-87 approved) are considered the minimum appropriate level of eye protection. The IBC recommends donning of full-face shield when conducting tasks posing potential for any generation of aerosol or droplets.

c. Lab coats or disposable coveralls that provide complete coverage of skin not otherwise protected by PPE and/or attire.

d. Appropriate laboratory attire: workers handling tamoxifen should don attire which when worn in combination with lab coat and PPE provides entire coverage of the body. Short pants/dresses and open sole shoes are not appropriate laboratory attire.

e. If an aerosol exposure threat exists, all procedures must be conducted in an approved chemical fume hood (see Engineering Controls below). If an approved chemical fume hood cannot be utilized, provision of suitable respiratory protection will be required. Prior to instituting respiratory protection to personnel, the laboratory must participate in the university Respiratory Protection Program.

3. Work Methods:

a. Procedures with the potential for producing tamoxifen aerosols should be conducted within an approved chemical fume hood.

b. Needles used for tamoxifen injection will be disposed of in approved sharps containers immediately following use.

c. Needles used for tamoxifen injection should never be bent, sheared, or recapped. If recapping is absolutely necessary, a "Needle Recapping Waiver" must be submitted for IBC review/approval prior to proceeding.

d. Bench paper utilized during preparation of tamoxifen stock should be lined with an impervious backing to limit potential for contamination of work surfaces in the event of the occurrence of minor spills.

e. Areas where tamoxifen is prepared and/or administered should be cleaned and decontaminated (1:5 bleach-water solution recommended) immediately following each task. Prepare fresh stock only as needed.

4. Engineering Controls:

a. In cases where the recommended level of PPE does not provide sufficient protection (splash potential, aerosolization potential, etc.) tasks should be conducted within a chemical fume hood utilizing sash for added protection.

b. Syringes used for tamoxifen injection must be safety engineered (self-sheathing syringes, luer-lock syringes, etc.). Exceptions will be considered by the IBC on a case-by-case basis.

c. Animals should be appropriately restrained and/or sedated prior to administering injections and other dosing methods.

d. Laboratories and other spaces where handling of tamoxifen occurs must be equipped with an eyewash station that meets the requirements of the American National Standards Institute (ANSI).

5. Waste Disposal:

a. Surplus tamoxifen must be disposed of as a hazardous chemical through the OEHS Chemical Waste Management Program.

b. The available scientific research indicates that tamoxifen and its metabolites are primarily excreted in feces, and to a much lesser extent in urine. The drug is excreted as polar conjugates, with the bulk of the excretion being unchanged drug and unconjugated metabolites (Goodman and Gilman, 2006). The metabolism and potential risks associated with tamoxifen use make it necessary that all potentially contaminated carcasses, bedding, and other non-sharps materials be disposed of as Regulated Medical Waste (RMW) through incineration.

c. All contaminated sharps waste materials must be placed in proper sharps container and disposed of as RMW.

6. Spills:

a. Small spills of powder tamoxifen should be brushed into an appropriate waste disposal container. Following cleaning of the powder, the spill area should be thoroughly cleansed with absorbent paper, bleach solution (20%) and soap and water.

b. Small spills of liquid tamoxifen should be treated with a mist of 20% bleach solution (allow at least 15 minutes oxidation time) and covered/absorbed with absorbent paper. Spill areas should be treated with bleach solution again following removal of absorbent paper, and finally cleaned with soap and water.

c. Use appropriate PPE during spill clean-up and dispose of all waste generated through OEHS hazardous waste management program. For larger spills of tamoxifen, contact the OEHS emergency line (828-9834) for assistance.

LITERATURE CITED

Baum M. Nolvadex adjuvant trial organization controlled trial of tamoxifen as a singe adjuvant agent in the management of early breast cancer. *Lancet* (1) 836-840, 1985

Branham WS, Fishman R, et al. ICI 182,780 inhibits endogenous estrogen-dependent rat uterine growth and tamoxifen–induce developmental toxicity. *Bio of Repro* (54) 160-167, 1996

Brown K. Breast cancer chemoprevention: risk-benefit effects of anti-oestorgen tamoxifen. *Expert Opin Drug Saf* (1) 253-267, 2002

Carthew P, Rich KJ, deMatteis F, Lim CK, Manson MM, Festing MF, White IN, Smith LL. DNA damage as assessed by ^{32}P-postlabeling in three rat strains exposed to dietary tamoxifen: the relationship between cell proliferation and liver toumour formation. *Carcinogenisis* (16) 1299-1304, 1995

Cunha GR, Taguchio, Namikawa R, Nishizuka Y, Robboy SJ. Teratogenic effects of clomihene, tamoxifen, and diethysilbesterol on the developing human female genital tract. *Human Path*. 18(11) 1132-43, 1987

Curtis RE, Freedman DM, Sherman ME, Fraumini JF. Risk of malignant mullerian tumor after tamoxifen therapy for breast cancer. *J National Cancer Inst.* (96) 1 40-74, 2004

EMD Biosciences. Calbiochem: Tamoxifen information brief. http://www.emdbiosciences.com/product/579000 , 2006

Furr BJ, Jordan. The pharmacology of and clinical uses of tamoxifen. *Pharmco Ther* (25) 127-205, 1984

Gray Le, Ostby J, Ferrell J, Signom R, et al. Correlation of sperm and endocrine measures with reproductive success in rodents. *Prog Clin Biol Res*. (302) 193-206, 1989

Goodman LS, Gilman AG. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 11th ed. p1382 & 1556, 2006

Greaves P, Goonetilleke R, Nunn G, Topham J, Orton T. Two–year carcinogenicity study of tamoxifen in Alderley Park Wistar-derived rats. *Cancer Press* (53) 3919-3924, 1993

Han, Liehr JG. Induction of covalent DNA adducts in rodents by tamoxifen. *Cancer Res* (52) 1360-1363, 1992

International Agency for Research on Cancer (2004). IARC Monographs, 66 (1996) p. 253.

Johnson MD, Westley BR, May FE. Oestrogenic activity of tamoxifen and its metabolites on gene regulation and cell proliferation in MCF-7 breast cancer cells. *Br J Cancer* 59: 727-728, 1989

Johnson MD, Zuo Hong, Lee K, et al. Pharmacological characterization of 4-hydroxy-N-desmethyl tamoxifen, a novel active metabolite of tamoxifen. *Breast Can Res Treat*. (207) 1-9, 2004

Jordan VC. A current view of tamoxifen for the treatment and prevention of breast cancer. *Br J Pharmcol* (110) 507-517, 1993

Jordan VC, Murphy CS. Endocrine pharmacology of antiestrogen and antitumor agents. *Endocr Rev* (11) 578-610, 1990

Lewis, RJ. "Sax's dangerous properties of industrial materials" 11th ed. Hoboken, N.J.: J. Wiley and Sons, c2004

Phillips DH. Understanding the genotoxicity of tamoxifen? *Carcinogenesis* (22) 839-849, 2001

Phillips DH, Hewer A, Osborne MR, Cole KJ, Churchill C, Arlt VM. Organ specificity of DNA adduct formation by tamoxifen and alpha-hydroxytamoxifen in the rat: implications for understanding the mechanism(s) of tamoxifen carcinogenicity and for human risk assessment. *Mutagenesis.* 20(4):297-303

Poirier MC, Schild LJ. The genotoxicity of tamoxifen: extent and consequences, Kona, Hawaii, Jan 23, 2003. *Mutagenesis* (18) 395-399, 2003

Poon GK, Walter B, Lonning PE, Horton MN, McCague R. Identification of tamoxifen metabolites in human Hep G2 cell line, human liver homogenate, and patients on long-term therapy for breast cancer. *Drug Metabo and Disp* (23) 377-382, 1994

Potter GA, McCague, Jarman M. A mechanistic hypothesis for DNA adduct formation by tamoxifen following hepatic oxidative metabolism. *Carcinogenesi*s (15) 439-442, 1994

Reik GC, Freites ON, Williams S. Is tamoxifen associated with high-risk endometrial carcinomas? A retrospective case series of 196 women with endometrial cancer. *J of Obstet and Gynocol* 25(1) 39-41, 2005

Saunders JM, Cunningham ML. Determination of tamoxifen and metabolites in mouse fetal tissue using nonaqueous capillary electrophoresis. Electrophoresis 23(3) 502-5, 2002

Styles JA, Davies A, Lim CK, et al. *Carcinogenesis* (15) 5-9, 1994

Taguchi O. Reproductive tract lesions in male mice treated neonatally with tamoxifen. *Bio of Repro* (37) 113-116, 1987

White IN. Anti-oestrogenic drugs and endometrial cancers. *Toxicol Lett*., (120) 21-29, 2001

Williams MJ, Iatropoulos MV, Djordjevic MV, Kaltenberg OP. Tamoxifen is a strong liver carcinogen the rat. *Carcinogenesis* (14) 315-317, 1993

Yang HH, Aulerich RJ, Helferich W, Yamini B, Chou KC, Miller ER, Bursian SJ. Effects of zearlenone and /or tamoxifen on swine and mink reproduction. *J Appl Toxicol* 15 (3) 223-32, 1995