CHEMICALS UNDER CONSIDERATION FOR POSSIBLE LISTING VIA THE "FORMALLY REQUIRED TO BE LABELED OR IDENTIFIED" MECHANISM

Reproductive and Cancer Hazard Assessment Section
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

April 10, 1997

The chemicals listed in the table below appear to have been identified or labeled to communicate a risk of cancer or reproductive harm, in accordance with formal requirements of the U.S. Food and Drug Administration. They appear to meet the requirements for listing outlined in Title 22, California Code of Regulations, Section 12902 for the listing of a chemical which a state or federal agency has formally required to be labeled or identified as causing cancer or reproductive toxicity.

According to Title 22 CCR Section 12902,

- '"labeled' means that a warning message about the carcinogenicity or reproductive toxicity of a chemical is printed, stamped, written, or in any other manner placed upon the container in which the chemical is present or its outer or inner packaging including any material inserted with, attached to, or otherwise accompanying such a chemical;"
- "'identified' means that a required message about the carcinogenicity or reproductive toxicity of the chemical is to be disclosed in any manner to a person or legal entity other than the person or legal entity who is required to make such disclosure."

Chemical	CAS No.	Toxicological Endpoints	Reference
Estropipate	7280-37-7	cancer	FDA (1994)
Ganciclovir sodium	82410-32-0	cancer	FDA (1995a)
Amiodarone hydrochloride	19774-82-4	male reproductive toxicity female reproductive toxicity developmental toxicity	FDA (1995b)
Atenolol	29122-68-7	developmental toxicity	FDA (1996a)
Estropipate	7280-37-7	developmental toxicity	FDA (1994)
Ethionamide	536-33-4	developmental toxicity	FDA (1969)
Ganciclovir sodium	82410-32-0	male reproductive toxicity developmental toxicity	FDA (1995a)

Chemical	CAS No.	Toxicological Endpoints	Reference
Goserelin acetate	65807-02-5	male reproductive toxicity female reproductive toxicity developmental toxicity	FDA (1995c)
Leuprolide acetate	74381-53-6	male reproductive toxicity female reproductive toxicity developmental toxicity	FDA (1996b)
Paclitaxel	33069-62-4	male reproductive toxicity female reproductive toxicity developmental toxicity	FDA (1996c)
Quazepam	36735-22-5	developmental toxicity	FDA (1991)
Trimetrexate glucuronate	82952-64-5	developmental toxicity	FDA (1993)

Language taken directly from the FDA-approved product labels which appears to meet the requirements outlined in Title 22 CCR Section 12902 is quoted below for each of these substances.

CARCINOGENS

Estropipate (boxed WARNINGS section and under WARNINGS)
Boxed WARNINGS in bold type: "Estrogens have been reported to increase the risk of endometrial carcinoma in post-menopausal women."

"Studies of women who received diethylstilbestrol (DES) during pregnancy have shown that female offspring have an increased risk of vaginal adenosis, squamous cell dysplasia of the uterine cervix, and clear cell vaginal cancer later in life; male offspring have an increased risk of urogenital abnormalities and possibly testicular cancer later in life."

Under WARNINGS: "Induction of malignant neoplasms. Endometrial cancer. The reported endometrial cancer risk among unopposed estrogen users is about 2-12 fold greater than in nonusers, and appears dependent on duration of treatment and on estrogen dose."

"The greatest risk appears associated with prolonged use--with increased risks of 15-24-fold for five to ten years or more."

Ganciclovir sodium (boxed section and under PRECAUTIONS)
Boxed section in bold type: "In animal studies cytovene was carcinogenic, teratogenic, and caused aspermatogenesis."

Under PRECAUTIONS: "Carcinogenesis, Mutagenesis. Ganciclovir was carcinogenic in the mouse at oral doses of 20 and 1,000 mg/kg/day (approximately 0.1x and 1.4x, respectively, the mean drug exposure in humans following the recommended intravenous dose of 5 mg/kg, based on area under the plasma concentration curve (AUC) comparisons). At the dose of

1,000 mg/kg/day there was a significant increase in the incidence of tumors of the preputial gland in males, forestomach (nonglandular mucosa) in males and females, and reproductive tissues, (ovaries, uterus, mammary gland, clitoral gland, and vagina) and liver in females."

DEVELOPMENTAL AND REPRODUCTIVE TOXICANTS

Amiodarone hydrochloride (under WARNINGS and PRECAUTIONS)
Under WARNINGS: "Neonatal hypo- or hyperthyroidism. Although oral Cordarone use during pregnancy is uncommon, there have been a small number of published reports of congenital goiter/hypothyroidism and hyperthyroidism. If Cordarone I.V. is administered during pregnancy, the patient should be apprised of the potential hazard to the fetus."

Under PRECAUTIONS: "No fertility studies were conducted with Cordarone I.V. However, oral Cordarone administration resulted in reduced fertility of rats at a dose of 90 mg/kg/day (about 1.3 times the maximum recommended oral human maintenance dose in mg/m^2)."

"Pregnancy Category D. In addition to causing infrequent congenital goiter/hypothyroidism and hyperthyroidism, amiodarone has caused a variety of adverse effects in animals."

Atenolol (under WARNINGS and PRECAUTIONS)
Under WARNINGS: "Pregnancy and Fetal Injury: Atenolol can cause fetal harm when administered to a pregnant woman. Atenolol crosses the placental barrier and appears in cord blood. Administration of atenolol, starting in the second trimester of pregnancy, has been associated with the birth of infants that are small for gestational age. No studies have been performed on the use of atenolol in the first trimester and the possibility of fetal injury cannot be excluded. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus."

"Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg/day or 25 or more times the maximum recommended human antihypertensive dose."

Under PRECAUTIONS: Use in Pregnancy: Pregnancy Category D.

Estropipate (under boxed WARNINGS, CONTRAINDICATIONS and PRECAUTIONS)
Under boxed WARNINGS in bold type: "Estrogens should not be used during pregnancy."

"Estrogen therapy during pregnancy is associated with an increased risk of congenital defects in the reproductive organs of the fetus, and possibly other birth defects. Studies of women who received diethylstilbestrol (DES) during pregnancy have shown that female offspring have an increased risk of vaginal adenosis, squamous cell dysplasia of the uterine cervix, and clear cell vaginal cancer later in life; male offspring have an increased risk of urogenital abnormalities and possibly testicular cancer later in life."

Under CONTRAINDICATIONS: "Estrogens may cause fetal harm when administered to a pregnant woman."

Under PRECAUTIONS: Pregnancy Category X.

Ethionamide (under WARNINGS)
USE IN PREGNANCY
"Teratogenic effects have been demonstrated in animals (rabbits, rats) receiving doses in excess of those recommended in humans. Use of the drug should be avoided during pregnancy or in women of childbearing potential unless the benefits outweigh its possible hazard."

Ganciclovir sodium (boxed section and under WARNINGS and PRECAUTIONS)
Boxed section in bold type: "In animal studies cytovene was carcinogenic, teratogenic, and caused aspermatogenesis."

Under WARNINGS: "Impairment of Fertility: Animal data indicate that administration of Cytovene causes inhibition of spermatogenesis and subsequent infertility."

"Although data in humans have not been obtained regarding this effect, it is considered probable that intravenous Cytovene at the recommended doses causes temporary or permanent inhibition of spermatogenesis. Animal data also indicate that suppression of fertility in females may occur."

"Teratogenesis: Because of the mutagenic potential of Cytovene, women of childbearing potential should be advised to use effective contraception during treatment."

Under PRECAUTIONS: "Cytovene has been shown to be embryotoxic in rabbits and mice following intravenous administration. Fetal resorptions were present in at least 85% of rabbits and mice administered 60 mg/kg/day and 108 mg/kg/day (2x the human exposure based on AUC comparisons), respectively. Effects observed in rabbits included: fetal growth retardation, embryolethality, teratogenicity, and/or maternal toxicity. Teratogenic changes included cleft palate, anophthalmia/microphthalmia, aplastic organs (kidney and pancreas), hydrocephaly, and brachygnathia. In mice, effects observed were maternal/fetal toxicity and embryolethality."

Goserelin acetate (under WARNINGS, CONTRAINDICATIONS and PRECAUTIONS)
Under WARNINGS: "Before starting treatment with Zoladex, pregnancy must be excluded. Safe use of Zoladex in pregnancy has not been established. Zoladex <u>can</u> cause fetal <u>harm</u> when administered to a pregnant woman."

Under CONTRAINDICATIONS: "There are no adequate and well-controlled studies in pregnant women using Zoladex. If this drug is used during pregnancy, or the patient being treated for endometriosis becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus or potential risk for loss of pregnancy. Women of childbearing potential should be advised to avoid becoming pregnant."

Under PRECAUTIONS: "Administration of goserelin led to changes that were consistent with gonadal suppression in both male and female rats as a result of its endocrine action. In male rats administered 500-1000 ug/kg/day (about 30-60 times the recommended human dose on a mg/m^2 basis), a decrease in weight and atrophic histological changes were observed in the testes, epididymis, seminal vesicle, and prostate gland with complete suppression of spermatogenesis. In female rats administered 50-1000 ug/kg/day (about 3-60 times the recommended daily human dose on a mg/m^2 basis), suppression of ovarian function led to decreased size and weight of ovaries and secondary sex organs; follicular development was arrested at the antral stage and the corpora lutea were reduced in size and number."

Pregnancy: Pregnancy Category X for treatment of endometriosis. Pregnancy Category D for treatment of advanced breast cancer in pre- and peri-menopausal women..

Leuprolide acetate (under CLINICAL PHARMACOLOGY, CONTRAINDICATIONS and PRECAUTIONS)
Under CLINICAL PHARMACOLOGY: "In humans, subcutaneous administration of single daily doses of leuprolide acetate results in an initial increase in circulating levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), leading to a transient increase in levels of the gonadal steroids (testosterone and dihydrotestosterone in males, and estrone and estradiol in pre-menopausal females). However, continuous daily administration of leuprolide acetate results in decreased levels of LH and FSH in all patients. In males, testosterone is reduced to castrate levels. In pre-menopausal females, estrogens are reduced to post-menopausal levels."

Under CONTRAINDICATIONS: "Lupron is contraindicated in women who are or may become pregnant while receiving the drug. When administered on day 6 of pregnancy at test dosages of 0.00024, 0.0024, and 0.024 mg/kg (1,600 to 1/6 the human dose) to rabbits, Lupron produced a dose related increase in major fetal abnormalities. Similar studies in rats failed to demonstrate an increase in fetal malformations. There was increased fetal mortality and decreased fetal weights with the two higher doses of Lupron in rabbits and with the highest dose in rats. The effects on fetal mortality are logical consequences of the alterations in hormonal levels brought about by this drug. Therefore, the possibility exists that spontaneous abortion may occur if the drug is administered during pregnancy."

Under PRECAUTIONS: Pregnancy Category X.

Paclitaxel (under WARNINGS and PRECAUTIONS)
Under WARNINGS: "Taxol may cause fetal harm when administered to a pregnant woman. Taxol has been shown to be embryo- and fetotoxic in rats and rabbits and to decrease fertility in rats. In these studies, Taxol was shown to result in abortions, decreased corpora lutea, a decrease in implantations and live fetuses, and increased resorptions and embryo-fetal deaths. If Taxol is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with Taxol."

Under PRECAUTIONS: "Taxol at an I.V. dose of 1 mg/kg (6 mg/m^2) produced low fertility and fetal toxicity in rats. Taxol has also been shown to be maternal and embryo-fetal toxic in rabbits receiving the drug at an I.V. dose of 3 mg/kg (33 mg/m^2) during organogenesis. (See "WARNINGS" section.)"

Pregnancy Category D.

Quazepam (under CONTRAINDICATIONS and PRECAUTIONS*)*
Under CONTRAINDICATIONS: "Usage in Pregnancy: Benzodiazepines may cause fetal damage when administered during pregnancy. An increased risk of congenital malformations associated with the use of diazepam and chlordiazepoxide during the first trimester of pregnancy has been suggested in several studies."

"If there is a likelihood of the patient becoming pregnant while receiving Doral, she should be warned of the potential risk to the fetus. Patients should be instructed to discontinue the drug prior to becoming pregnant."

Under PRECAUTIONS: Pregnancy: Teratogenic Effects: Pregnancy Category X.

Trimetrexate glucuronate (Under WARNINGS and PRECAUTIONS)
Under WARNINGS: "Neutrexin can cause fetal harm when administered to a pregnant woman. Trimetrexate has been shown to be fetotoxic and teratogenic in rats and rabbits."

"If Neutrexin is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant."

Under PRECAUTIONS: Pregnancy Category D.

References

Food and Drug Administration (FDA, 1969). Final printed labeling for the drug ethionamide. FDA approved February 1969.

Food and Drug Administration (FDA, 1994). Final printed labeling for the drug estropipate. FDA approved June 1994.

Food and Drug Administration (FDA, 1995a). Final printed labeling for the drug ganciclovir sodium. FDA approved October 1995.

Food and Drug Administration (FDA, 1995b). Final printed labeling for the drug amiodarone hydrochloride. FDA approved October 1995.

Food and Drug Administration (FDA, 1995c). Final printed labeling for the drug goserelin acetate. FDA approved December 1995.

Food and Drug Administration (FDA, 1996a). Final printed labeling for the drug atenolol. FDA approved February 1996.

Food and Drug Administration (FDA, 1996b). Final printed labeling for the drug leuprolide acetate. FDA approved April 1996.

Food and Drug Administration (FDA, 1996c). Final printed labeling for the drug paclitaxel. FDA approved April 1996.

Food and Drug Administration (FDA, 1991). Final printed labeling for the drug quazepam. FDA approved August 1991.

Food and Drug Administration (FDA, 1993). Final printed labeling for the drug trimetrexate glucuronate. FDA approved December 1993.