CHEMICALS MEETING THE CRITERIA FOR LISTING AS CAUSING CANCER OR REPRODUCTIVE TOXICITY VIA THE "FORMALLY REQUIRED TO BE LABELED OR IDENTIFIED" MECHANISM

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California Environmental Protection Agency

PACKAGE 19a1
August 25, 2000

The chemicals in the table below meet the requirements outlined in Title 22, California Code of Regulations, Section 12902 for the listing of a chemical that 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"; and

- "as causing cancer or reproductive toxicity" means: "For chemicals that cause cancer, the required label or identification uses any words or phrases intended to communicate a risk of cancer or tumors." "For chemicals that cause reproductive toxicity, the required label for identification uses any words or phrases intended to communicate a risk of reproductive harm to men or women or both, or a risk of birth defects or other developmental harm."

The chemicals in the table below have been identified or labeled to communicate a risk of cancer or reproductive or developmental harm, in accordance with formal requirements by the U.S. Food and Drug Administration (FDA). Following the table, language taken directly from the FDA-approved product labels which meets the requirements outlined in Title 22 CCR Section 12902 is quoted for each of the substances listed.

Chemical	CAS No.	Toxicological Endpoints	References
Gemfibrozil	25812-30-0	Cancer	FDA (1998)
Zileuton	111406-87-2	Cancer Developmental toxicity Female reproductive toxicity	FDA (1996)

Gemfibrozil (under WARNINGS and PRECAUTIONS)

Under WARNINGS: "A comparative carcinogenicity study was also done in rats comparing three drugs in this class: fenofibrate (10 and 60 mg/kg; 0.3 and 1.6 times the human dose), clofibrate (400 mg/kg; 1.6 times the human dose), and gemfibrozil (250 mg/kg, 1.7 times the human dose). Pancreatic acinar adenomas were increased in males and females on fenofibrate; hepatocellular carcinoma and pancreatic acinar adenomas were increased in males and hepatic neoplastic nodules in females treated with clofibrate; hepatic neoplastic nodules were increased in males and females treated with gemfibrozil while testicular interstitial cell (Leydig cell) tumors were increased in males on all three drugs."

Under PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility. "Long-term studies have been conducted in rats at 0.2 and 1.3 times the human exposure (based on AUC). The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p=0.1). Male rats had a dose-related and statistically significant increase in benign Leydig cell tumors. The higher dose female rats had a significant increase in the combined incidence of benign and malignant liver neoplasms."

"Long-term studies have been conducted in mice at 0.1 and 0.7 times the human exposure (based on AUC). There were no statistically significant differences from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates."

"Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lopid [gemfibrozil] administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual."

Zileuton

For listing as causing cancer (under PRECAUTIONS)

Carcinogenesis, Mutagenesis, Impairment of Fertility: "In 2-year carcinogenicity studies, increases in the incidence of liver, kidney, and vascular tumors in female mice and a trend towards an increase in the incidence of liver tumors in male mice were observed at 450 mg/kg/day (providing approximately 4 times [females] or 7 times [males] the systemic exposure [AUC] achieved at the maximum recommended human daily oral dose).... In rats, an increase in the incidence of kidney tumors was observed in both sexes at 170 mg/kg/day (providing approximately 6 times [males] or 14 times [females] the systemic exposure [AUC] achieved at the maximum recommended human daily oral dose)..."

Nursing Mothers: "...because of the potential for tumorigenicity shown for Zyflo [zileuton] in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother."

For listing as causing reproductive toxicity (under PRECAUTIONS)
Carcinogenesis, Mutagenesis, Impairment of Fertility: "...Reduction of fetal implants was observed at oral doses of 150 mg/kg/day and higher (providing approximately 9 times the systemic exposure [AUC] achieved at the maximum recommended human daily oral dose). Increases in gestation length, prolongation of estrous cycle, and increases in stillbirths were observed at oral doses of 70 mg/kg/day and higher (providing approximately 4 times the systemic exposure (AUC) achieved at the maximum recommended human daily oral dose)."
Pregnancy: Pregnancy Category C: "Developmental studies indicated adverse effects (reduced body weight and increased skeletal variations) in rats at an oral dose of 300 mg/kg/day (providing approximately 18 times the systemic exposure [AUC] achieved at the maximum recommended human daily oral dose). Comparative systemic exposure [AUC] is based on measurements in nonpregnant female rats at a similar dosage. Zileuton and/or its metabolites cross the placental barrier of rats. Three of 188 (2.5%) rabbit fetuses had cleft palates at an oral dose of 150 mg/kg/day (equivalent of the maximum recommended human daily oral dose on a mg/m^2 basis). There are no adequate and well-controlled studies in pregnant women. Zyflo [zileuton] should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus."

References

Food and Drug Administration (FDA, 1998). Final printed labeling for the drug gemfibrozil. FDA approved 1998.

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