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

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Reproductive and Cancer Hazard Assessment Section
Office of Environmental Health Hazard Assessment
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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
Amantadine hydrochloride	665-66-7	Developmental toxicity	FDA (1993a)
Diazoxide	364-98-7	Developmental toxicity	FDA (1994a)
Dichlorphenamide	120-97-8	Developmental toxicity	FDA (1994b)
Diltiazem hydrochloride	42399-41-7	Developmental toxicity	FDA (1996b)
Filgrastim	121181-53-1	Developmental toxicity	FDA (1992)
Ribavirin*	36791-04-5	Male reproductive toxicity	FDA (1993b)
Rifampin	13292-46-1	Developmental toxicity Female reproductive toxicity	FDA (1997b)
Trientine hydrochloride	38260-01-4	Developmental toxicity	FDA (1988)

* Ribavirin was added to the list of chemicals known to cause reproductive toxicity on the basis of a developmental toxicity endpoint on April 1, 1990.

Amantadine hydrochloride (under PRECAUTIONS)
Pregnancy Category C: "Symmetrel [amantadine hydrochloride] has been shown to be embryotoxic and teratogenic in rats at 50 mg/kg/day (estimated human equivalent dose of 7.1 mg/kg/day based on body surface area conversion)… There are no adequate and well-controlled studies in pregnant women. Symmetrel [amantadine hydrochloride] should be used during pregnancy only if the potential benefit justifies potential risk to the embryo or fetus."

Diazoxide (Under PRECAUTIONS)

Pregnancy Category C. "Reproduction studies using the oral preparation in rats have revealed increased fetal resorptions and delayed parturition, as well as fetal skeletal anomalies; evidence of skeletal and cardiac teratogenic effects in rabbits has been noted with intravenous administration. The drug has also been demonstrated to cross the placental barrier in animals and to cause degeneration of the fetal pancreatic beta cells (see ANIMAL PHARMACOLOGY AND/OR TOXICOLOGY) . . .. When the use of PROGLYCEM is considered, the indications should be limited to those specified above for adults (See INDICATIONS AND USAGE) and the potential benefits to the mother must be weighed against possible harmful effects to the fetus."

Non-teratogenic effects: "Diazoxide crosses the placental barrier and appears in cord blood. When given to the mother prior to delivery of the infant, the drug may produce fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism, and possibly other side effects that have occurred in adults."

*Dichlorphenamide (*Under PRECAUTIONS)
Pregnancy: Pregnancy Category C. "Dichlorphenamide has been shown to be teratogenic in the rat (skeletal anomalies) when given in doses 100 times the human dose.

There are no adequate and well-controlled studies in pregnant women. DARANIDE [dichlorphenamide] should not be used in women of childbearing age or in pregnancy, especially during the first trimester, unless the potential benefits outweigh the potential risks."

Diltiazem hydrochloride (under PRECAUTIONS)
Pregnancy: Category C. "Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater."

"There are no well-controlled studies in pregnant women; therefore, use CARDIZEM [diltiazem hydrochloride] in pregnant women only if the potential benefit justifies the potential risk to the fetus."

Filgrastim (under PRECAUTIONS)
Use in Pregnancy: "NEUPOGEN [filgrastim] has been shown to cause adverse effects in pregnant rabbits when given in doses 2 to 10 times the human dose."

"In rabbits, increased abortion and embryolethality were observed in animals treated with NEUPOGEN at 80 μg/kg/day. NEUPOGEN administered in pregnant rabbits at doses of 100 μg/kg/day during the period of organogenesis was associated with increased fetal resorption, genitourinary bleeding, developmental abnormalities and decreased body weight, live births and food consumption…"

"There are no adequate, well controlled studies in pregnant women, therefore, NEUPOGEN is not recommended for use in pregnant women."

Ribavirin (under WARNINGS, CONTRAINDICATIONS, and PRECAUTIONS)
Under boxed WARNINGS in bold type: "Physicians and patients should be aware that ribavirin has been shown to produce testicular lesions in rodents..."

Under PRECAUTIONS: Impairment of Fertility: "The fertility of ribavirin-treated animals (male or female) has not been fully investigated. However, in the mouse, administration of ribavirin at doses between 35-150 mg/kg/day (estimated human equivalent of 2.92-12.5 mg/kg/day, based on body surface area adjustment for the adult) resulted in significant seminiferous tubule atrophy, decreased sperm concentrations, and increased numbers of sperm with abnormal morphology. Partial recovery of sperm production was apparent 3-6 months following dose cessation. In several additional toxicology studies, ribavirin has been shown to cause testicular lesions (tubular atrophy) in adult rats at oral dose levels as low as 16 mg/kg/day (estimated human equivalent of 2.29 mg/kg/day, based on body surface area adjustment…)."

Rifampin (under PRECAUTIONS)
Pregnancy-Teratogenic Effects. "Category C. Rifampin has been shown to be teratogenic in rodents given oral doses of rifampin 15-25 times the human dose. . . Neonates of rifampin-treated mothers should be carefully observed for any evidence of

adverse effects. Isolated cases of fetal malformation have been reported; however, there are no adequate and well-controlled studies in pregnant women. Rifampin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Rifampin in oral doses of 150 to 250 mg/kg produced teratogenic effects in mice and rats. Malformations were primarily cleft palate in the mouse and spina bifida in the rat. The incidence of these anomalies was dose-dependent. When rifampin was given to pregnant rabbits in doses up to 20 times the usual daily human dose, imperfect osteogenesis and embryotoxicity were reported."

Pregnancy-Non-Teratogenic Effects: "When administered during the last few weeks of pregnancy, rifampin can cause post-natal hemorrhages in the mother and infant for which treatment with Vitamin K may be indicated."

Trientine hydrochloride (Under PRECAUTIONS)
Pregnancy Category C. Trientine hydrochloride was teratogenic in rats at doses similar to the human dose. The frequencies of both resorptions and fetal abnormalities, including hemorrhage and edema, increased while fetal copper levels decreased when trientine hydrochloride was given in maternal diets of rats. There are no adequate and well-controlled studies in pregnant women. Syprine [trientine hydrochloride] should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus."

References

Food and Drug Administration (FDA, 1993a). Final printed labeling for the drug amantadine hydrochloride. FDA approved 1993.

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

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

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

Food and Drug Administration (FDA, 1992). Final printed labeling for the drug filgrastim. FDA approved 1992.

Food and Drug Administration (FDA, 1993b). Final printed labeling for the drug ribavirin. FDA approved 1993.

Food and Drug Administration (FDA, 1997b). Final printed labeling for the drug rifampin. FDA approved 1997.

Food and Drug Administration (FDA, 1988). Final printed labeling for the drug trientine hydrochloride. FDA approved 1988.