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

PACKAGE 6a
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Reproductive and Cancer Hazard Assessment Section
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

The chemicals in the table below meet the requirements outlined in Title 22, California Code of Regulations, Section 12902 for the listing under Proposition 65 of a chemical that a state or federal agency has formally required to be labeled or identified as causing reproductive toxicity.

According to Title 22 CCR Section 12902,

- " 'labeled' means that a warning message about the … 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 … 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 reproductive toxicity" means "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 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 meet the requirements outlined in Title 22 CCR Section 12902 is quoted for each of the substances listed.

Chemical	CAS No.	Toxicological Endpoints	References
Acetazolamide	59-66-5	developmental toxicity	FDA (1990a)
Altretamine	645-05-6	developmental toxicity male reproductive toxicity	FDA (1993a)

Chemical	CAS No.	Toxicological Endpoints	References
Etodolac	41340-25-4	developmental toxicity female reproductive toxicity	FDA (1996)
Flurbiprofen	5104-49-4	developmental toxicity female reproductive toxicity	FDA (1989a)
Gemfibrozil	25812-30-0	male reproductive toxicity female reproductive toxicity	FDA (1995a)
Halobetasol propionate	66852-54-8	developmental toxicity	FDA (1990b)
Idarubicin hydrochloride	---	developmental toxicity male reproductive toxicity	FDA (1995b)
Mebendazole	31431-39-7	developmental toxicity	FDA (1989b)
Pimozide	2062-78-4	developmental toxicity female reproductive toxicity	FDA (1994)
Prednisolone sodium phosphate	125-02-0	developmental toxicity	FDA (1993b)
Sermorelin acetate	---	developmental toxicity	FDA (1991)
Streptozocin	18883-66-4	developmental toxicity male reproductive toxicity female reproductive toxicity	FDA (1986)

Acetazolamide (under PRECAUTIONS)
Pregnancy: Pregnancy Category C.

"Acetazolamide, administered orally or parenterally, has been shown to be teratogenic (defects of the limbs) in mice, rats, hamsters and rabbits. There are no adequate and well-controlled studies in pregnant women. Acetazolamide should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus."

Altretamine (under WARNINGS and PRECAUTIONS)
Under WARNINGS: Pregnancy Category D.

"Hexalen [altretamine] has been shown to be embryotoxic and teratogenic in rats and rabbits when given at doses 2 and 10 times the human dose. Hexalen may cause fetal damage when administered to a pregnant woman. If Hexalen is used during pregnancy, or if the patient becomes pregnant while taking the 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: Carcinogenesis, Mutagenesis and Impairment of Fertility.
"Hexalen administered to female rats 14 days prior to breeding through the gestation period had no adverse effect on fertility, but decreased post-natal survival at 120 mg/m^2/day and was embryocidal at 240 mg/m^2/day. Administration of 120 mg/m2/day Hexalen to male rats for 60 days prior to mating resulted in testicular atrophy, reduced fertility and a possible dominant lethal mutagenic effect. Male rats treated with

Hexalen at 450 mg/m^2/day for 10 days had decreased spermatogenesis, atrophy of testes, seminal vesicles and ventral prostate."

Etodolac (under WARNINGS and PRECAUTIONS)
Under WARNINGS: "Pregnancy: In late pregnancy, as with other NSAIDs, LODINE [etodolac] should be avoided because it may cause premature closure of the ductus arteriosus."

Under PRECAUTIONS: Pregnancy: Teratogenic Effects: Pregnancy Category C: "In teratology studies, isolated occurrences of alterations in limb development were found and included polydactyly, oligodactyly, syndactyly, and unossified phalanges in rats and oligodactyly and synostosis of metatarsals in rabbits. These were observed at dose levels (2 to 14 mg/kg/day) close to human clinical doses However, the frequency and the dosage group distribution of these findings in initial or repeated studies did not establish a clear drug or dose response relationship.

There are no adequate or well-controlled studies in pregnant women. Lodine should be used during pregnancy only if the potential benefits justify the potential risk to the fetus. Because of the known effects of NSAIDs on parturition and on the human fetal cardiovascular system with respect to closure of the ductus arteriosus, use during pregnancy should be avoided."

Labor and Delivery: "In rat studies with etodolac, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. The effects of Lodine on labor and delivery in pregnant women are unknown."

Flurbiprofen (under PRECAUTIONS)

"Labor and Delivery: Ansaid's effects on labor and delivery in women are not known. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats treated throughout pregnancy. Because of the known effects of prostaglandin-inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus), use of Ansaid during late pregnancy is not recommended."

Gemfibrozil (under PRECAUTIONS)
Carcinogenesis, Mutagenesis and Impairment of Fertility: Administration of approximately 0.6 to 2 times the human dose (based on surface area) to male rats for 10 weeks resulted in a dose-related decrease of fertility."

Pregnancy Category C: "Lopid [gemfibrozil] has been shown to produce adverse effects in rats and rabbits at doses between 0.5 and 3 times the human dose (based on surface area) but no developmental toxicity or teratogenicity among offspring of either species. There are no adequate and well-controlled studies in pregnant women. Lopid should be used during pregnancy only if the potential benefit justifies the risk to the fetus."

"Administration of Lopid to female rats at 0.6 and 2 times the human dose (based on surface area) before and throughout gestation caused a dose-related decrease in conception rate and, at the high dose, an increase in stillborns and a slight reduction in pup weight during lactation. There were also dose-related increased skeletal variations. Anophthalmia occurred, but rarely."

"Administration of 0.6 and 2 times the human dose (based on surface area) of Lopid to female rats from gestation day 15 through weaning caused dose-related decreases in birth weight and suppressions of pup growth during lactation."

"Administration of 1 and 3 times the human dose (based on surface area) of Lopid to female rabbits during organogenesis caused a dose-related decrease in litter size and, at the high dose, an increased incidence of parietal bone variation."

Halobetasol propionate (under PRECAUTIONS)
Pregnancy: Teratogenic effects: Pregnancy Category C.

"Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application to laboratory animals. Halobetasol propionate has been shown to be teratogenic in SPF rats and chinchilla-type rabbits when given systemically during gestation at doses of 0.04 to 0.1 mg/kg in rats and 0.01 mg/kg in rabbits. These doses are approximately 13, 33 and 3 times, respectively, the human topical dose of Ultravate (halobetasol propionate) Cream. Halobetasol propionate was embryotoxic in rabbits but not in rats."

"Cleft palate was observed in both rats and rabbits. Omphalocele was seen in rats but not in rabbits."

"There are no adequate and well-controlled studies of the teratogenic potential of halobetasol propionate in pregnant women. Therefore, ULTRAVATE (halobetasol propionate) Cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus."

Idarubicin hydrochloride (under WARNINGS and PRECAUTIONS)
Under WARNINGS: Pregnancy Category D.

"Idarubicin was embryotoxic and teratogenic in the rat at a dose of 1.2 mg/m^2/day or one tenth the human dose, which was nontoxic to dams. Idarubicin was embryotoxic but not teratogenic in the rabbit even at a dose of 2.4 mg/m^2/day or two tenths the human dose, which was toxic to dams."

"If IDAMYCIN is to be used during pregnancy, or if the patient becomes pregnant during therapy, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid pregnancy."

Under PRECAUTIONS: "In male dogs given 1.8 mg/m^2/day or more idarubicin (3 times/week for 13 weeks), testicular atrophy was observed with inhibition of spermiogenesis and sperm maturation, and few or no mature sperm. Effects were not readily reversible after an eight week recovery period."

Mebendazole (under PRECAUTIONS)
"Information for Patients: Patients should be informed of the potential risk to the fetus in women taking Vermox [mebendazole] during pregnancy, especially during the first trimester."

Use in Pregnancy: Pregnancy Category C: "Vermox has shown embryotoxic and teratogenic activity in pregnant rats at single oral doses as low as 10 mg/kg. In view of these findings the use of Vermox is not recommended in pregnant women. … During pregnancy, especially during the first trimester, VERMOX® should be used only if the potential benefit justifies the potential risk to the fetus."

Pimozide (under PRECAUTIONS)
"Reproduction studies in animals were not adequate to assess all aspects of fertility. Nevertheless, female rats administered pimozide had prolonged estrous cycles, an effect also produced by other antipsychotic drugs."

"Pregnancy: Category C. Reproduction studies performed in rats and rabbits at oral doses up to 8 times the maximum human dose did not reveal evidence of teratogenicity. In the rat, however, this multiple of the human dose resulted in decreased pregnancies and in the retarded development of fetuses. These effects are thought to be due to an inhibition or delay in implantation which is also observed in rodents administered other antipsychotic drugs. In the rabbit, maternal toxicity, mortality, decreased weight gain, and embryotoxicity including increased resorptions were dose related. Because animal reproduction studies are not always predictive of human response, pimozide should be given to a pregnant woman only if the potential benefits of treatment clearly outweigh the potential risks."

Prednisolone sodium phosphate (under PRECAUTIONS)
Pregnancy: Pregnancy Category C.
"Prednisolone has been shown to be teratogenic in many species when given in doses equivalent to human dose. There are no adequate and well controlled studies in pregnant women. Pediapred should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Animal studies in which prednisolone has been given to pregnant mice, rats, and rabbits have yielded an increased incidence of cleft palate in the offspring."

Sermorelin acetate (under PRECAUTIONS)
Pregnancy Category C.
"Sermorelin acetate has been shown to produce minor variations in fetuses of rats and rabbits when given in subcutaneous doses of 50, 150, 500 mcg/kg. In the rat teratology study, external malformations (thin tail) were observed in the higher dose groups, and there was an increase in minor skeletal variants at the high dose. Some visceral malformations (hydroureter) were observed in all treatment groups with the incidence greatest in the high-dose group. In rabbits, minor skeletal anomalies were significantly greater in the treated animals than in the controls. There are no adequate and well-

controlled studies in pregnant women. Geref [sermorelin acetate] should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus."

Streptozocin (under PRECAUTIONS)
"Mutagenesis, Carcinogenesis, Impairment of Fertility: Streptozocin adversely affected fertility when administered to male and female rats."

Pregnancy Category C: "Reproduction studies revealed that streptozocin is teratogenic in the rat and has abortifacient effects in rabbits. When administered intravenously to pregnant monkeys, it appears rapidly in the fetal circulation. There are no studies in pregnant women. ZANOSAR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus."

References

Food and Drug Administration (FDA, 1986). Final printed labeling for the drug streptozocin sterile powder. FDA approved 1986.

Food and Drug Administration (FDA, 1989a). Final printed labeling for the drug flurbiprofen. FDA approved 1989.

Food and Drug Administration (FDA, 1989b). Final printed labeling for the drug mebendazole. FDA approved 1989.

Food and Drug Administration (FDA, 1990a). Final printed labeling for the drug acetazolamide. FDA approved 1990.

Food and Drug Administration (FDA, 1990b). Final printed labeling for the drug halobetasol propionate. FDA approved 1990.

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

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

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

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

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

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

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