

CHEMICALS UNDER CONSIDERATION FOR POSSIBLE LISTING 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 may 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 appear to have been identified or labeled to communicate a risk of cancer or reproductive or developmental harm, in accordance with formal requirements by the US Food and Drug Administration (FDA). Following the table, language taken directly from the FDA-approved product labels which appears to meet the requirements outlined in Title 22 CCR Section 12902 is quoted for each of the substances listed.

Chemical	CAS No.	Toxicological Endpoints	References
<i>Carcinogens</i> Cidofovir	113852-37-2	Cancer	FDA (1996a)
<i>Developmental and Reproductive Toxicants</i> Auranofin	34031-32-8	Developmental toxicity	FDA (1989a)
Carbamazepine	298-46-4	Developmental toxicity	FDA (1998)
Cidofovir	113852-37-2	Developmental toxicity Female reproductive toxicity	FDA (1996a)

		Male reproductive toxicity	
Dacarbazine	4342-03-4	Developmental toxicity	FDA (1989b)
Diflunisal	22494-42-4	Developmental toxicity Female reproductive toxicity	FDA (1994a)
Doxorubicin hydrochloride	23214-92-8	Developmental toxicity Male reproductive toxicity	FDA (1994b)
Haloperidol	52-86-8	Developmental toxicity Female reproductive toxicity	FDA (1988a)
Levodopa	59-92-7	Developmental toxicity	FDA (1986)
Nifedipine	21829-25-4	Developmental toxicity Female reproductive toxicity Male reproductive toxicity	FDA (1996b)
Pyrimethamine	58-14-0	Developmental toxicity	FDA (1988b)
Sulfasalazine	599-79-1	Male reproductive toxicity	FDA (1996)
Sulindac	38194-50-2	Developmental toxicity Female reproductive toxicity	FDA (1995)

CARCINOGENS

Cidofovir (Under WARNINGS and PRECAUTIONS)

Under boxed WARNINGS in bold type: "In animal studies cidofovir was carcinogenic..."

Under PRECAUTIONS: Carcinogenesis, Mutagenesis and Impairment of Fertility: "Chronic, two-year carcinogenicity studies in rats and mice have not been carried out to evaluate the carcinogenic potential of cidofovir. However, a 26-week toxicology study evaluating once weekly subscapular subcutaneous injections of cidofovir in rats was terminated at 19 weeks because of the induction in females, of palpable masses, the first of which was detected after six doses. The masses were diagnosed as mammary adenocarcinomas which developed at doses as low as 0.6 mg/kg/week, equivalent to 0.04 times the human systemic exposure at the recommended intravenous Vistide [cidofovir] dose based on AUC comparisons."

"In a 26-week intravenous toxicology study in which rats received 0.6, 3, or 15 mg/kg cidofovir once weekly, a significant increase in mammary adenocarcinomas in female rats as well as a significant incidence of Zymbal's gland carcinomas in male and

female rats were seen at the high dose but not at the lower two doses. The high dose was equivalent to 1.1 times the human systemic exposure at the recommended dose of Vistide [cidofovir], based on comparisons of AUC measurements. In light of the results of these studies, cidofovir should be considered to be a carcinogen in rats as well as a potential carcinogen in humans."

DEVELOPMENTAL AND REPRODUCTIVE TOXICANTS

Auranofin (under PRECAUTIONS)

Pregnancy: Teratogenic Effects - Pregnancy Category C. "Use of Ridaura (auranofin, SK&F) by pregnant women is not recommended. Furthermore, women of childbearing potential should be warned of the potential risks of 'Ridaura' therapy during pregnancy."

"Pregnant rabbits given auranofin at doses of 0.5, 3 or 6 mg/kg/day (4.2 to 50 times the human dose) had impaired food intake, decreased maternal weights, decreased fetal weights and an increase above controls in the incidence of resorptions, abortions and congenital abnormalities, mainly abdominal defects such as gastroschisis and umbilical hernia."

Carbamazepine (Under WARNINGS)

Usage in Pregnancy. "Carbamazepine can cause fetal harm when administered to a pregnant woman."

"Epidemiological data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital malformations, including spina bifida. The prescribing physician will wish to weigh the benefits of therapy against the risks in treating or counseling women of childbearing potential. 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."

Cidofovir (Under WARNINGS and PRECAUTIONS)

Under boxed WARNING in bold type: "In animal studies cidofovir was carcinogenic, teratogenic and caused hypospermia..."

Under PRECAUTIONS: Carcinogenesis, Mutagenesis and Impairment of Fertility: "Studies showed that cidofovir caused inhibition of spermatogenesis in rats and monkeys. ... Female rats dosed intravenously once weekly at 1.2 mg/kg/week (equivalent to 0.09 times the recommended human dose based on AUC) or higher, for up to 6 weeks prior to mating and for 2 weeks post-mating had decreased litter sizes and live births per litter and increased early resorptions per litter."

Pregnancy Category C. "There are no adequate and well-controlled studies in pregnant women. Vistide (cidofovir) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus."

Dacarbazine (under WARNINGS and PRECAUTIONS)

Under boxed WARNING: "Studies have demonstrated this agent to have a carcinogenic and teratogenic effect when used in animals."

Under PRECAUTIONS: Pregnancy Category C: "DTIC Dome [dacarbazine] has been shown to be teratogenic in rats when given in doses 20 times the human daily dose on day 12 of gestation....There are no adequate and well controlled studies in pregnant women. DTIC Dome should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus."

Diffunisal (under PRECAUTIONS)

Pregnancy: Pregnancy Category C. "A dose of 60 mg/kg/day of diflunisal (equivalent to two times the maximum human dose) was maternotoxic, embryotoxic and teratogenic in rabbits.... There are no adequate and well controlled studies with diflunisal in pregnant women. Diflunisal should be used during the first two trimesters of pregnancy only if the potential benefit justifies the potential risk to the fetus. Because of the known effect of drugs of this class on the human fetus (closure of the ductus arteriosus, platelet dysfunction with resulting bleeding, renal dysfunction or failure with oligohydramnios, gastrointestinal bleeding or perforation, and myocardial degenerative changes), use during the third trimester of pregnancy is not recommended."

"In rats at a dose of one and one-half times the maximum human dose, there was an increase in the average length of gestation. Similar increases in the length of gestation have been observed with aspirin, indomethacin, and phenylbutazone and may be related to inhibition of prostaglandin synthetase. Drugs of this class may cause dystocia and delayed parturition in pregnant animals."

Doxorubicin hydrochloride (under WARNINGS and PRECAUTIONS)

Under WARNINGS: Pregnancy Category D. "Safe use of doxorubicin in pregnancy has not been established. Doxorubicin is embryotoxic and teratogenic in rats and embryotoxic and abortifacient in rabbits. There are no adequate and well-controlled studies in pregnant women. If doxorubicin 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 age should be advised to avoid becoming pregnant."

Under PRECAUTIONS: "Testicular atrophy was observed in rats and dogs."

Haloperidol (under WARNINGS)

Usage in Pregnancy: "Rodents given 2 to 20 times the usual maximum human dose of haloperidol by oral or parenteral routes showed an increase in incidence of resorption, reduced fertility, delayed delivery and pup mortality."

"There are no well controlled studies with HALDOL (haloperidol) in pregnant women. There are reports, however, of cases of limb malformation observed following maternal use of HALDOL along with other drugs which have suspected teratogenic potential during the first trimester of pregnancy. Causal relationships were not established in these cases. Since such experience does not exclude the possibility of fetal damage due

to HALDOL, this drug should be used during pregnancy or in women likely to become pregnant only if the benefit clearly justifies a potential risk to the fetus."

Levodopa (under WARNINGS)

Usage in Pregnancy: "The safety of Larodopa (levodopa) in women who are or who may become pregnant has not been established: hence, it should be given only when the potential benefits have been weighed against possible hazards to mother and child. Studies in rodents have shown that levodopa at dosages in excess of 200 mg/kg/day has an adverse effect on fetal and postnatal growth and viability."

Nifedipine (under PRECAUTIONS)

Carcinogenesis, Mutagenesis, Impairment of Fertility: "When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose."

Pregnancy: Pregnancy Category C. "In rodents, rabbits, and monkeys, nifedipine has been shown to have a variety of embryotoxic, placentotoxic, and fetotoxic effects, including stunted fetuses (rats, mice, and rabbits), digital anomalies (rats and rabbits), rib deformities (mice), cleft palate (mice), small placentas and underdeveloped chorionic villi (monkeys), embryonic and fetal deaths (rats, mice, and rabbits), prolonged pregnancy (rats; not evaluated in other species), and decreased neonatal survival (rats; not evaluated in other species). On a mg/kg or mg/m² basis, some of the doses associated with these various effects are higher than the maximum recommended human dose and some are lower, but all are within one order of magnitude of it."

"The digital anomalies seen in nifedipine-exposed rabbit pups are strikingly similar to those seen in pups exposed to phenytoin, and these are in turn similar to the phalangeal deformities that are the most common malformation seen in human children with *in utero* exposure to phenytoin."

"There are no adequate and well-controlled studies in pregnant women. ADALAT [nifedipine] should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus."

Pyrimethamine (under WARNINGS)

Use in Pregnancy: "Pyrimethamine, like other folic acid antagonists, may, in large doses, produce teratogenic effects in laboratory animals. The large doses required to treat toxoplasmosis should be used only after a definitive diagnosis of acute toxoplasmosis has been made, and the possibility of teratogenic effects from the drug has been carefully weighed against the possible risks of permanent damage to the fetus from the infection."

Sulfasalazine (under WARNINGS)

"Oligospermia and infertility have been observed in men treated with Azulfidine [sulfasalazine]. Withdrawal of the drug appears to reverse these effects."

Sulindac (under PRECAUTIONS)

Use in Pregnancy: "Sulindac is not recommended for use in pregnant women, since safety for use has not been established, and because of the known effect of drugs of this class on the human fetus (closure of the ductus arteriosus, platelet dysfunction with resultant bleeding, renal dysfunction or failure with oligohydramnios, gastrointestinal bleeding or perforation, and myocardial degenerative changes) during the third trimester of pregnancy. In reproduction studies in the rat, a decrease in average fetal weight and an increase in numbers of dead pups were observed on the first day of the postpartum period at dosage levels of 20 and 40 mg/kg/day (2.5 and 5 times the usual maximum daily dose in humans), although there was no adverse effect on survival and growth during the remainder of the postpartum period. Sulindac prolongs the duration of gestation in rats, as do other compounds of this class which may also cause dystocia and delayed parturition in pregnant animals."

References

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

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

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

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

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

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

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

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

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

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

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

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

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