

skin sensitizer but is a very slight dermal irritant.

2. *Genotoxicity.* Lactofen has very little mutagenic or genotoxic activity. While a positive mutagenic response was reported in one trial of a *Salmonella typhimurium*/mammalian microsome mutagenicity assay, this response was not repeated in the second assay conducted. In addition, lactofen did not appear to induce chromosomal aberrations, unscheduled deoxyribonucleic acid (DNA) synthesis or inhibit DNA repair.

3. *Reproductive and developmental toxicity.* Reproduction and teratology studies indicate that adverse effects, including embryotoxicity, occur only at doses that are also maternally toxic. Since lactofen causes effects only at levels which also produce systemic toxicity, the compound is not a reproductive hazard.

In a 2-generation reproduction study in rats, decreased pup weight and decreased absolute and relative weights of the spleen were first reported at approximately 26.2 milligrams/kilogram/day (mg/kg/day) (based on dose administered to the parental group). The same dose level elicited mortality and decreased male fertility in the parental groups. The no observed adverse effect level (NOAEL) for both systemic and reproductive toxicity in this study was 2.6 mg/kg/day.

In the developmental toxicity study in rats, effects were observed at the 150 mg/kg/day dose level consisting of decreases in fetal weight as well as skeletal abnormalities. This dose level also elicited signs of toxicity in the parental group. The NOAEL for this study was 50 mg/kg/day. Based on this NOAEL and an uncertainty factor (UF) of 100, the acute reference dose (RfD) for lactofen has been set at 0.50 mg/kg/day.

Two developmental toxicity studies were conducted in rabbits. In the first study, pregnant rabbits were administered oral doses of 0, 5, 15, or 50 mg/kg bwt/day lactofen technical on days 6–18 of gestation. Maternal toxicity (clinical signs and reduced weight gain) and developmental effects (increased embryonic death, decreased litter size and increased post-implantation loss) were reported at 15 and 50 mg/kg. The Agency concluded that the data were insufficient to establish a clear NOAEL. In the second rabbit developmental toxicity study, pregnant rabbits were exposed to 0, 1, 4, or 20 mg/kg bwt/day oral doses on days 6–18 of gestation. Maternal toxicity (reduced food consumption) was observed at 20 mg/kg bwt/day, but no developmental effects were observed at any dose. Therefore, the maternal NOAEL was 4 mg/kg bwt/

day and the developmental NOAEL was greater than 20 mg/kg bwt/day.

4. *Subchronic toxicity*—i. *Rats 4-week.* Male and female rats were fed diets containing lactofen technical at concentrations of 0, 200, 1,000, 5,000, and 10,000 ppm, for 4 weeks. A slight increase in spleen weight was the basis for a lowest observed adverse effect level (LOAEL) of 200 ppm, lowest dose tested (LDT). At doses of 1,000 ppm, or higher, the following findings were reported: clinical signs of toxicity; decreased red blood cell (RBC), hemoglobin, hematocrit, and increased white blood cell (WBC); increased relative liver and spleen weights; and necrosis and pigmentation of hepatocytes. At 10,000 ppm, severe toxic signs were observed by day 7 and all animals were dead or killed *in extremis* by day 11. Hypocellularity of the spleen, thymus, and bone marrow was also observed in animals exposed to 10,000 ppm.

ii. *Rats 3-month.* Lactofen technical was fed to male and female rats at dietary concentrations of 0, 40, 200, and 1,000 ppm, for 13 weeks. Histopathological changes in the liver and significant changes in clinical chemistry associated with the liver were observed in rats exposed to 1,000 ppm, dosage. Decreased RBC, hemoglobin and hematocrit values were also observed at 1,000 ppm. The NOAEL in this study was 200 ppm, 14.1 mg/kg/day.

iii. *Dogs 4-week.* In a range finding study lactofen technical was fed in the diet of dogs at 0, 1,000, 3,000, and 10,000 ppm, for 4 weeks. Toxic effects noted in dogs fed 10,000 ppm, included decreased RBC count and hemocrit, and increased blood urea nitrogen (BUN) and serum glutamic-pyruvic transaminase (SGPT). Food palatability problems led to greatly decreased feed consumption at higher dosages. The NOAEL appeared to be 1,000 ppm.

iv. *Mice 3-month.* Groups of male and female mice were fed diets containing lactofen technical at concentrations of 0, 40, 200, 1,000, 5,000, and 10,000 for 13 weeks. At week 5, the dosage of the 40 ppm, groups was increased to 2,000 ppm. Treatment related mortality occurred at dosages above 1,000 ppm. The LOAEL was 200 ppm, 28.6 mg/kg/day based on:

- Increased WBC; decreased hematocrit, hemoglobin and RBC.
- Increased alkaline phosphatase, serum glutamic-oxaloacetic transaminase (SGOT), SGPT, cholesterol and total serum protein levels.
- Increased weights or enlargement of the spleen, liver, adrenals, heart, and kidney; histopathological changes of the

liver, kidney, thymus, spleen, ovaries, and testes.

In general, effects were slight in the 200 ppm groups, and moderate to severe in the 1,000 ppm groups.

v. *Peroxisome proliferation.* Butler *et al* (1988) studied the effects of lactofen on peroxisome proliferation in mice exposed for 7 weeks to dietary concentrations of 2, 10, 50, and 250 ppm. Liver-weight to body-weight ratio, liver catalase, liver acyl-CoA oxidase, liver cell cytoplasmic eosinophilia, nuclear, and cellular size, and peroxisomal staining were increased by the tumorigenic dose of lactofen, i.e. 250 ppm. Lower doses of lactofen had little to no effect on these parameters. This study indicates that lactofen induces peroxisome proliferation and further, that 50 ppm, 7 mg/kg/day, a dose which is not tumorigenic, would be considered a threshold dose in mice for peroxisome proliferation produced by lactofen. A subchronic study conducted in chimpanzees (Couch and Erickson 1986), indicated no effect on clinical chemistry or histological endpoints that would suggest liver toxicity or peroxisome proliferation at doses up to 75 mg/kg bwt/day administered for 93 days. Therefore, Valent believes that 75 mg/kg bwt/day is a clear NOAEL for peroxisome proliferation observed in a species closely related to man. On January 17, 2001, the Mechanism of Toxicity Assessment Review Committee (MTARC) reviewed the merits of the toxicological data supporting peroxisome proliferation as the proposed mode of action for lactofen. Based on the weight-of-evidence from guideline, as well as mechanistic studies, the MTARC concluded that there are sufficient data to classify lactofen as a non-genotoxic hepatocarcinogen in rodents with peroxisome proliferation being a plausible mode of action.

5. *Chronic toxicity.* Lactofen causes adverse health effects when administered to animals for extended periods of time. These effects include proliferative changes in the liver, spleen, and kidney; hematological changes; and blood biochemistry changes.

i. *Mouse 18-month.* In a dietary 18-month oncogenicity study in mice at dosages of 10, 50, and 250 ppm, lactofen technical, an increase in liver adenomas and carcinomas, cataracts, and liver pigmentation was observed at 250 ppm, a dose that clearly exceeded the maximum tolerance dose (MTD). The lowest dose, 10 ppm, 1.4 mg/kg/day, was the LOAEL based on increased liver weight and hepatocytomegaly.