

ii. *Rat 24-month.* In a 2-year chronic feeding/oncogenicity study of lactofen technical in rats at dosages of 0, 500, 1,000 ppm; and 2,000 ppm, in the diet, an increase in liver neoplastic nodules and foci of cellular alteration was observed in both sexes at 2,000 ppm. The NOAEL for systemic toxicity is 500 ppm, 2 mg/kg/day based on kidney and liver pigmentation.

iii. *Dog 12-month.* In a 1-year study in dogs exposed to 40, 200, and 1,000 ppm; week 1–17 or 3,000 ppm; week 18–52 lactofen technical in their diet, the NOAEL was determined to be 200 ppm, (0.79 mg/kg/day) based on renal dysfunction and decreased RBC, hemoglobin hematocrit and cholesterol observed at 1,000/3,000 ppm. Based on this NOAEL and an uncertainty factor (UF) of 100, the chronic RfD for lactofen has been set at 0.008 mg/kg/day.

iv. *Carcinogenicity.* As a member of the diphenyl ether chemical family, lactofen is structurally related to four other chemicals that are oncogenic in rodents:

- Sodium acifluorfen (acifluorfen is a lactofen metabolite), nitrofen, oxyfluorfen, and fomesafen.
- Sodium acifluorfen produces hepatocellular adenomas and carcinomas in mice but is negative in rats.
- Nitrofen produces hepatocellular carcinomas in mice and pancreatic carcinomas in rats.
- Oxyfluorfen produces marginally positive liver tumors in mice but is negative in rats.
- Fomesafen produces hepatocellular adenomas and carcinomas in mice.

The Cancer Peer Review Committee (CPRC) evaluated the relevant data on the carcinogenic potential of lactofen in 1987 and classified lactofen as a B2 carcinogen Probable Human Carcinogen and assigned a Cancer Potency Factor ( $Q_1^*$ ) of  $1.7 \times 10^{-1}$  mg/kg/day<sup>-1</sup>, based on a interspecies scaling factor of 0.67. This  $Q_1^*$  has since been reduced to  $1.19 \times 10^{-1}$  mg/kg/day<sup>-1</sup> based on recent EPA guidance indicating that 0.75 is a more appropriate interspecies scaling factor. The B2 classification is based on an increase in the combined incidence of liver adenomas and carcinomas in mice and increases in liver neoplastic nodules and foci of cellular alteration (possible precursor of tumors) in rats. In 1996, and 1999, EPA proposed new cancer risk assessment guidelines which

state that nonmutagenic carcinogens known to cause cancer via a threshold mechanism, such as peroxisome proliferation, could be assessed using a nonlinear margin of exposure (MOE) approach rather than the  $Q_1^*$  method. EPA has recently determined that lactofen acts via a peroxisome proliferation mechanism and is currently reevaluating its approach to the quantification of the cancer risk for lactofen.

6. *Animal metabolism.* In a rat metabolism study, lactofen was shown to metabolize to acifluorfen, 5-[2-chloro-4-(trifluoromethyl)phenoxy]-2-nitrobenzoate, which was eliminated via both urine and feces. While lactofen was the primary compound found in the feces, acifluorfen accounted for >90% of the radioactivity in the urine. Negligible amounts of the administered radioactivity were found in any tissue with less than 0.8% of the administered radioactivity being found in the liver one of the main target organs.

7. *Metabolite toxicology.* Acifluorfen is also a hydrolytic metabolite of lactofen. The sodium salt of this benzoic acid is the registered herbicide, sodium acifluorfen. This product has a complete data base supporting registration with a RfD of 0.013 mg/kg/day and a  $Q_1^*$  of  $5.30 \times 10^{-2}$  mg/kg/day<sup>-1</sup>. Because lactofen and its metabolites are not retained in the body, the potential for acute toxicity from *in situ* formed metabolites is low. The potential for chronic toxicity of lactofen metabolites has been adequately addressed by an extensive battery of lactofen chronic toxicity testing.

8. *Endocrine disruption.* No special studies to investigate the potential for estrogenic or other endocrine effects of lactofen have been performed. However, a large and detailed toxicology data base exists for the compound including studies acceptable to the Agency in all required categories. These studies include evaluations of reproduction and reproductive toxicity and detailed pathology and histology of endocrine organs following repeated or long-term exposure. These studies are considered capable of revealing endocrine effects and no such effects were observed.

#### C. Aggregate Exposure

1. *Dietary exposure.* A full battery of toxicology testing, including studies of acute, chronic, oncogenicity, developmental, mutagenicity, and

reproductive effects is available for lactofen. For the following risk assessments, the NOAEL from the chronic oral toxicity study in dogs, 0.79 mg/kg/day, was selected as the chronic oral toxicity endpoint. Based on this NOAEL, and an UF of 100, the chronic RfD and the chronic population adjusted dose (cPAD) for lactofen has been set at 0.008 mg/kg/day. The NOAEL from the rat developmental study, 50 mg/kg/day, was selected as the acute oral toxicity endpoint. Based on this NOAEL and an UF of 100, the acute RfD for lactofen has been set at 0.50 mg/kg/day. An acute adjusted dose (aPAD) of 0.17 mg/kg/day was calculated using this endpoint and an additional Food Quality Protection Act (FQPA) safety factor of 3. This aPAD will only be used to assess acute exposures to the females 13 to 50 year old population subgroup since it is derived from a developmental toxicity endpoint. No other acute endpoints were identified to assess acute exposures to other populations.

i. *Food.* Dietary risk was considered for the currently registered uses of lactofen on soybeans, snap beans, and cotton and for the pending use on peanuts. Dietary risk assessments were done using the Dietary Exposure Evaluation Model (DEEM™), which incorporates consumption data generated in U. S. Department of Agriculture (USDA) Continuing Surveys of Food Intakes by Individuals (CSFII), 1989–1992. For chronic dietary risk assessments, the 3-day average of consumption for each subpopulation is combined with residues in commodities to determine average exposure in mg/kg/day. For refined acute dietary risk assessments, the entire distribution of consumption events for individuals is multiplied by a distribution of residues to obtain a distribution of exposures in mg/kg/day. This is a probabilistic analysis, referred to as “Monte Carlo,” and the risk is reported at the 99.9th percentile of exposure. Food monitoring data are not available from Food and Drug Administration (FDA) or USDA for residues of lactofen. Therefore, only field trial data were used. A value of one-half the LOQ, 0.005 ppm, was used to represent the residues in all treated commodities. Percent crop treated (PCT) were incorporated for soybeans and snap beans, as reliable usage information was available for these commodities. The estimated risk from food is presented in the following table: