



# UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF  
PREVENTION, PESTICIDES  
AND TOXIC SUBSTANCES

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## MEMORANDUM

**SUBJECT:** **Lactofen:** Revised Human Health Risk Assessment for Proposed Uses on Fruiting Vegetables and Okra. PC Code: 128888, Petition No: PP#5E6930, DP Barcode: D339011.

Risk Assessment Type: Single Chemical Aggregate

**FROM:** Christine L. Olinger, Chemist/Risk Assessor  
Reregistration Branch 1  
Health Effects Division (7509P)

AND

Whang Phang, Ph.D., Toxicologist  
Timothy Dole, ORE Assessor  
Reregistration Branch 1  
Health Effects Division (7509P)

**THROUGH:** Michael S. Metzger, Chief  
Elizabeth Méndez, Ph.D., Senior Scientist  
Reregistration Branch 1  
Health Effects Division (7509P)

AND

Paula Deschamp, Chief  
Registration Branch 3  
Health Effects Division (7509P)

**TO:** Dan Rosenblatt, Chief  
Minor Use and Emergency Response Branch  
Registration Division (7505P)

And

Dan Kenny/Joanne Miller  
Herbicide Branch  
Registration Division (7505P)

And

Amaris Johnson/Susan Lewis  
Reregistration Branch 1  
Special Review and Reregistration Division (7508P)

Valent, USA, has proposed new uses of the herbicide lactofen on fruiting vegetables and okra. The RD of OPP has requested that HED evaluate hazard and exposure data and conduct dietary, occupational, residential, and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from all registered and proposed uses of the herbicide lactofen. A summary of these findings is provided in this document. The risk assessment, residue chemistry review, and dietary exposure assessment were provided by Christine Olinger of RRB1; support for the hazard characterization was provided by Whang Phang of RRB1; the occupational exposure and risk assessment was provided by Timothy Dole of RRB1; and the drinking water assessment was provided by James Wolf of the Environmental Fate and Effects Division (EFED). Although the proposed new use had been previously assessed (C. Olinger, 1/8/07, DP Barcode: D319593), this document incorporates additional information on the cancer classification.

#### ***Recommendation for Tolerances and Registration***

Provided revised Sections B and F are submitted, the toxicological and residue chemistry databases, as well as the aggregate risk assessments, support tolerances with regional registration for fruiting vegetables and okra. The recommended revisions are listed below:

- The label must be amended to specify that the applications may not include two post-transplant applications. . The label must also be amended to reflect either a 30-day RTI or a minimum post-transplant interval of 18 days for tomatoes.
- The label should specify examples of fruiting vegetables in the use directions to avoid confusion.
- The proposed tolerance for the fruiting vegetables crop group should be revised to reflect the recommended tolerance definition (lactofen *per se*), the correct commodity definition, “Vegetable, fruiting, group 8,” and the recommended level of 0.02 ppm.
- The proposed tolerance for okra should be revised to reflect the recommended tolerance definition (lactofen *per se*) and the recommended level of 0.02 ppm.

Should the registrant request tolerances with a national registration in the future, then additional crop field trials would be required.

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## 1.0 Executive Summary

This document describes the human health risk assessment conducted for the herbicide lactofen in association with proposed new uses on fruiting vegetables and okra.

Lactofen is currently registered for use on snap beans, peanuts, soybeans, and cottonseed and tolerances are established in 40 CFR 180.432 for these commodities. Lactofen is typically used early in the growing season, before or shortly after the crop has emerged. The minimum interval between the last application and harvest is 45 days, although for some crops it can be as long as 90 days. The registrant is proposing new uses on fruiting vegetables and okra and restricting the use to AL, AR, FL, GA, MS, NC, SC, TN, and VA. The proposed use on fruiting vegetables and okra would include two applications, one prior to planting and one after planting, with a minimum pre-harvest interval of 30 days.

The toxicity database for lactofen is relatively complete. Lactofen has a low acute toxicity, generally categories III and IV. The chronic toxicity profile for lactofen clearly indicates that the liver and kidneys are the target organs for this chemical. The effects seen at the lowest dose levels in the chronic toxicity study included changes in clinical chemistry associated with liver toxicity. More severe effects were noted at higher dose levels. The registrant has submitted information on the mechanism of liver toxicity that indicates that the mode of action is quantitatively implausible and unlikely to take place in humans. Lactofen has been classified as not likely to be carcinogenic to humans.

In a rat developmental toxicity study, the dose level that causes adverse effects to the developing fetus also elicits signs of toxicity in the maternal group (e.g., excess salivation, lethargy, and decreased body weight gain). Effects seen in the fetus consisted of decreases in fetal weight as well as skeletal variations (increased incidence of bent ribs, bent limb bones and a reduction in the ossification of the vertebral arches). Two rabbit developmental studies have been submitted. Although conducted in similar strains of rabbits according to acceptable protocols, the results of the two studies are somewhat inconsistent. In the first study, post-implantation loss was observed, but not in the second study. In the second study animals were not dosed high enough to observe developmental affects in the pups; however, maternal toxicity was observed. When the results of the two studies are considered together, there is sufficient information to set a no-effect level for the post-implantation loss.

The Health Effects Division (HED) has selected an endpoint based on changes in clinical chemistry that relate to liver effects for chronic exposure to the general population and an endpoint for females of child-bearing age for acute exposure based on the post-implantation loss. The chronic endpoint is protective of the carcinogenic effects. No endpoint has been identified for the general population based on a single exposure to lactofen. The Food Quality Protection Act (FQPA) requires the Agency to consider special sensitivities of the young to chemical exposure. The lactofen risk assessment team has reviewed the entire database for lactofen and determined there is no residual uncertainty regarding exposure to children at any developmental stage and recommends that the factor be reduced to 1X.

**Sodium acifluorfen is a degradate of lactofen found in water and is also registered as a herbicide.** Sodium acifluorfen is similar to lactofen in that the liver and kidneys are the target

organs for sodium acifluorfen as well. Sodium acifluorfen produced developmental toxicity (decreased fetal body weight and the increase in anatomical variations) in rats but did not affect the reproductive parameters in rats. The carcinogenicity data showed that sodium acifluorfen produced a statistically significant increase in the incidence of liver and stomach tumors in mice but not in rats. The registrant has submitted information on the mechanism of liver toxicity that indicates that the mode of action is quantitatively implausible and unlikely to take place in humans. Acifluorfen has been classified as not likely to be carcinogenic to humans.

The Health Effects Division (HED) has selected an endpoint for sodium acifluorfen based on kidney lesions for chronic exposure to the general population and an endpoint for females of child-bearing age based on fetal effects for acute exposure. The FQPA Safety Factor committee retained a factor of three for the chronic dietary risk assessment and retained a factor of ten for the acute risk assessment because of the qualitative increase in susceptibility in the developmental study with sodium acifluorfen and the developmental neurotoxicity data gap.

Crop field trials conducted in FL for tomatoes and peppers were submitted in support of this petition. Typically trials in additional states would be conducted but considering the number of trials submitted and that no residues were detected, no additional data are required in support of this use with a regional registration. Should the registrant seek a national registration then additional studies would be required.

A dietary risk analysis was conducted for lactofen. The analysis, assuming all of the crops are treated and residues are tolerance level, showed that all populations are exposed to less than 0.1% of the population adjusted dose (PAD) for acute and chronic risk. This is below the Agency's level of concern (i.e., when dietary exposure exceeds 100% of the PAD. The margin of exposure (MOE) for estimated cancer risk greatly exceeds the target MOE, so is not of concern.

HED has also considered the exposure to lactofen and its degradates in water. Lactofen degrades very quickly in the environment, with some studies suggesting a half-life of three days. The primary degradate is acifluorfen, which is also a degradate of sodium acifluorfen, a herbicide registered for use in agricultural and residential settings. A minor degradate is des-ethyl lactofen. Environmental fate data suggest that while lactofen is not likely to reach water resources in any significant quantities, acifluorfen is both mobile and persistent in the environment. Acifluorfen has been found in monitoring studies of ground and surface water, but insufficient monitoring data are available for quantitation of the risk from lactofen and acifluorfen in drinking water. The Environmental Fate and Effects Division (EFED) has provided estimated drinking water concentrations (EDWCs) of lactofen and acifluorfen (from lactofen applications) in ground and surface water using models.

There are no residential uses of lactofen; therefore, HED has prepared aggregate risk assessments that include food and drinking water estimates only. The aggregate estimates for acute and chronic exposures are well below the level of concern.

HED also conducted aggregate risk assessments for acifluorfen including food exposure from acifluorfen applications, residential handler exposure from spot treatments of acifluorfen, and

drinking water exposure to acifluorfen as a result of environmental degradation of lactofen. The aggregate assessments for all exposure durations were below the Agency's level of concern.

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to lactofen and any other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that lactofen has a common mechanism of toxicity with other substances.

Two occupational scenarios were identified and assessed for the proposed new uses of lactofen: mixing/loading liquids for groundboom application and applying liquids using groundboom applications. Mixing/loading liquids for groundboom application) exceeds HED's level of concern if no personal protective equipment (PPE) is used. However, the risk of concern can be mitigated with a single layer of dermal personal protective equipment (PPE). The margin of exposure (MOE) for applying liquids using groundboom equipment at the baseline level (no PPE) does not exceed HED's level of concern.

The proposed label indicates that lactofen should be applied to row middles in a directed, shielded spray; therefore, post application exposures are not expected and were not assessed.

## **2.0 Ingredient Profile**

### **2.1 Summary of Proposed Uses**

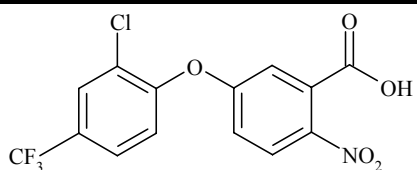
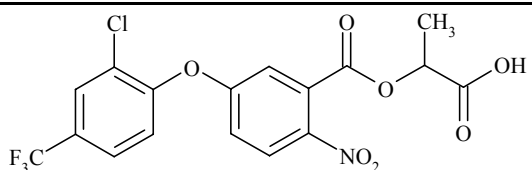
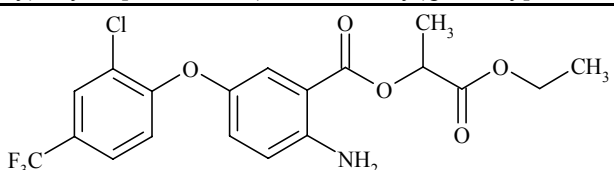
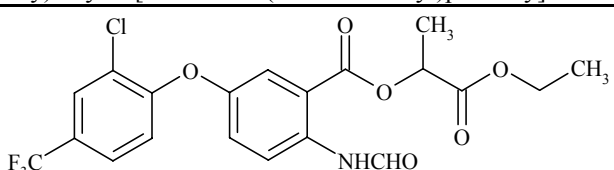
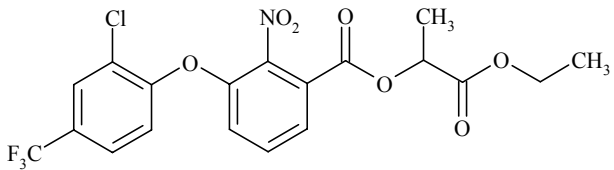
Valent has included the proposed use directions under Section B of the petition and a supplemental label for the 2 lb/gal EC formulation of lactofen (Cobra® Herbicide; EPA Reg. No. 59639-34). The proposed uses are presented in Table 2.1.

HED recommends minor changes to the labels to clarify the use directions including: 1) specify that the applications may not include two post-transplant applications; 2) specify a retreatment interval of 30-days or a minimum post-transplant interval of 18 days for tomatoes; and 3) include examples of fruiting vegetables in the use directions to avoid confusion.

Table 2.1. Summary of Directions for Use of Lactofen.						
Applic. Timing; Type; and Equip.	Formulation [EPA Reg. No.]	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Fruiting vegetables and okra						
Pre-transplant Post-transplant; Directed to row middles; Ground, shielded	2 lb/gal EC [59639-34]	0.3-0.5	2	1.0 (implied)	30	Use is restricted to AL, AR, FL, GA, MS, NC, SC, TN, and VA. Applications are to be made in 20-50 gal/A. <u>Pre-transplant</u> : Applications are to be made a minimum of 10 days prior to transplanting. <u>Post-transplant</u> : Applications are to be made using an adjuvant such as crop oil concentrate at 1% v:v or a nonionic surfactant at 0.25% v:v. Tomato plants must be at least 16" in height prior to post-transplant application. Peppers must have been transplanted at least 45 days before making a post-transplant application.

## 2.2 Structure and Nomenclature

Table 2.2. Lactofen Nomenclature.	
Chemical structure	
Common name	Lactofen
Company experimental name	PPG-844
IUPAC name	ethyl O-[5-(2-chloro- $\alpha,\alpha,\alpha$ -trifluoro- <i>p</i> -tolylloxy)-2-nitrobenzoyl]-DL-lactate
CAS name	2-ethoxy-1-methyl-2-oxoethyl 5-[2-chloro-4-(trifluoromethyl)phenoxy]-2-nitrobenzoate
CAS registry number	77501-63-4
End-use product (EP)	2 lb/gal EC (Cobra <sup>®</sup> Herbicide; EPA Reg. No. 59639-34)

<b>Table 2.2. Lactofen Nomenclature.</b>	
Chemical structure of acifluorfen (PPG-847)	 <p>5-[2-chloro-4-(trifluoromethyl)phenoxy]-2-nitrobenzoic acid</p>
Chemical structure of desethyl lactofen (PPG-947)	 <p>1-(carboxy)ethyl 5-[2-chloro-4-(trifluoromethyl)phenoxy]-2-nitrobenzoate</p>
Chemical structure of amino lactofen (PPG-1576)	 <p>1-(carboethoxy)ethyl 5-[2-chloro-4-(trifluoromethyl)phenoxy]-2-aminobenzoate</p>
Chemical structure of N-formyl lactofen (PPG-2597)	 <p>1-(carboethoxy)ethyl 5-[2-chloro-4-(trifluoromethyl)phenoxy]-2-formamidobenzoate</p>
Chemical structure of PPG-1530; Isomer A (internal standard)	 <p>1-(carboethoxy)ethyl 5-[2-chloro-4-(trifluoromethyl)phenoxy]-6-nitrobenzoate</p>

## 2.3 Physical and Chemical Properties

<b>Table 2.3 Physicochemical Properties of Lactofen.</b>		
Parameter	Value	Reference
Melting point/range	>250°C	44447003 <sup>1</sup>
pH	7.2 (on Pure Active Ingredient, 1% solution) at 25°C	44447003 <sup>1</sup>
Density (specific gravity)	1.34 at 24°C	44447003 <sup>1</sup>
Water solubility	0.97 ppm at 25°C 0.945 ± 0.131 ppm (column elution method at 20 ± 1 °C)	44447003 <sup>1</sup> 44460902 <sup>2</sup>

<b>Table 2.3 Physicochemical Properties of Lactofen.</b>		
Parameter	Value	Reference
Solvent solubility	_____ g/100 g at 23 °C	44447003 <sup>1</sup>
	kerosene 15.6 2-ethyl-1-hexanol 18.4 N-decanol 10.1 lactic acid 0.9  Lactofen is miscible at all proportions with the following solvents at -18°C or higher: DMSO, monochlorotoluene, dipropylene glycol dibenzoate, isophorone, cyclohexanone, mixed xylene, ethylene dichloride, acetone, DMF, amyl acetate, methyl isobutyl ketone.	
Vapor pressure	3.69 ± 1.73 x 10 <sup>-5</sup> Pa (2.8 x 10 <sup>-7</sup> mm Hg)	44460901 <sup>2</sup>
Dissociation constant, pK <sub>a</sub>	Not required	D241826, 1/16/98, H. Podall
Octanol/water partition coefficient, Log(K <sub>OW</sub> )	1 x 10 <sup>5</sup> at ambient temperature, estimated value	44460903 <sup>2</sup>
UV/visible absorption spectrum	In Review <sup>3</sup>	44447003 <sup>3</sup>

<sup>1</sup> RD Memorandum, D241826, 1/16/98, H. Podall.

<sup>2</sup> RD Memorandum D242241, 2/5/98, S. Mathur.

<sup>3</sup> D332587, C. Olinger, In Review.

### 3.0 Hazard Characterization/Assessment

#### 3.1 Hazard and Dose-Response Characterization

##### Lactofen

Lactofen has a low acute toxicity profile: the acute oral LD<sub>50</sub> = 5.96 g/kg b.w. (Tox Category IV), the acute dermal LD<sub>50</sub> > 2.0 g/kg b.w. (Tox Category III) and the acute inhalation LC<sub>50</sub> > 6.3 mg/L (Tox Category (IV)). Furthermore, lactofen is not a skin sensitizer but it is a very slight dermal irritant. The manufacturing use product (MUP), however, is classified as a moderate eye irritant. A summary of the hazard profile may be found in Appendix 1 of this document.

The chronic toxicity profile for lactofen clearly indicates that the liver and kidneys are the target organs for this chemical. In a combined chronic/oncogenicity study in rats, no effects were seen at a dose of 2 mg/kg/day. The lowest dose at which effects were reported was 19 mg/kg/day. The effects described at this dose level included: 1) an increased incidence of mottled or diffusely dark livers and kidneys; 2) increased aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase; and 3) decreases in cholesterol, total protein, globulin, and blood urea nitrogen. Many of these changes in the clinical chemistry are indicative of liver toxicity. At higher doses in this study, the severity of the toxicity described above was increased, and other toxicity included dark discoloration of the testes. Similar effects were also reported in the subchronic oral toxicity study in rats. At the lowest dose level in a carcinogenicity study in mice, adaptive effects such as increases in liver weight, increases in the incidence of hepatocytomegally, and increases in sinusoidal cell pigmentation were observed,

and are considered minor. At higher dose levels, these signs of toxicity were more severe, and neoplastic as well as non-neoplastic lesions in the liver were also reported. In the chronic oral toxicity study in dogs, animals treated at a dose level of 3.96 mg/kg/day had increased incidence of proteinaceous casts in the kidneys and statistically significant decreases in the absolute weight of thyroid and adrenal glands in males. At the highest dose tested, 19.8 mg/kg/day, test animals had slight anemia, increased absolute kidney weights, increased relative kidney weight (kidney/body weight ratio) as well as an increase in the incidence of proteinaceous casts in the kidneys.

Reproductive and developmental parameters that may be affected by exposure to lactofen were studied in a 2-generation reproduction study, a developmental toxicity study in rats, and two developmental toxicity studies in rabbits. In the two-generation reproduction study in rats, decreased pup weight and decreased absolute and relative weights of the spleen were first reported at approximately 26.2 mg/kg/day (based on dose administered to the parental group). It is noteworthy that these effects are seen at the same dose level that elicits mortality and decreased male fertility in the parental groups. In the developmental toxicity study in rats, developmental effects were observed at the 150 mg/kg/day dose level and consisted of decreases in fetal weight as well as skeletal variations (increased incidence of bent ribs, bent limb bones and a reduction in the ossification of the vertebral arches). Once again, the dose level that causes adverse effects to the developing conceptus also elicits signs of toxicity in the parental group (e.g. excess salivation, lethargy, and decreased body weight gain). Two rabbit developmental studies have been submitted. Although conducted in similar strains of rabbits according to acceptable protocols, the results of the two studies are somewhat inconsistent. In the first study post-implantation loss was observed, but not in the second study. In the second study animals were not dosed high enough to observe developmental affects in the pups; however, toxicity was observed in the maternal animals. Maternal effects were noted in the first study as well.

The mutagenicity database for lactofen suggests that this chemical 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 reported in the second assay conducted. In addition, lactofen did not appear to induce chromosomal aberrations, unscheduled DNA synthesis or inhibit DNA repair.

As a member of the diphenyl ether chemical family, lactofen is structurally related to four other chemicals that are oncogenic in rodents namely sodium acifluorfen (a metabolite and environmental degradate of lactofen), 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, and fomesafen produces hepatocellular adenomas and carcinomas in mice. The registrant proposed a mechanism of toxicity for lactofen based on PPAR $\alpha$  activation (Fricke, 2002) which was accepted by the HED Mechanism of Toxicity Assessment Review Committee (MTARC). The Cancer Assessment Review Committee (CARC) concurred with the MTARC's conclusion and classified lactofen as not likely to be carcinogenic to humans at doses that do not cause biochemical and histopathological changes in the liver of rodents.

Since the 2002 CARC report, significant research information has accumulated on the human relevance of rodent liver tumors that are induced through the activation of the peroxisome proliferator-activated receptor (PPAR $\alpha$ ). Although the precise mechanism for the formation of rodent liver tumors by a PPAR $\alpha$  agonist has not been established, it is accepted that the key events for the mode of action leading to rodent hepatocarcinogenesis are well established. Further, more recent information has established that chemicals that are PPAR $\alpha$  agonists can induce liver rodent tumors, but the potential for PPAR $\alpha$  agonists to induce liver tumors in other species, including humans, appears to be unlikely. This is because evidence shows that quantitatively these other species are less sensitive to the effects of PPAR $\alpha$  agonism due to toxicodynamic differences between human and rodent nuclear PPAR receptor (e.g., Klaunig et al, 2003; Cheung et al., 2004; Cariello et al., 2005; Hoivik et al., 2004). Overall, the majority of the 2003 FIFRA Scientific Advisory Panel agreed that there are relevant data indicating that humans are less sensitive than rodents to the hepatic effects of PPAR- $\alpha$  agonists (add website). To incorporate the current state of the science, the CARC has recently revised its approach to the hazard characterization for pesticides that are hepatic carcinogens via PPAR $\alpha$  agonism to reflect this quantitative species difference. Thus, the more appropriate characterization for lactofen is: “Not Likely to be Carcinogenic to Humans” because of available data on lactofen supports activation of the peroxisome proliferator activated receptor alpha (PPAR $\alpha$ ) as the mode of action for induced hepatocarcinogenesis in rodents. Additionally, the available data on lactofen do not support mutagenesis as an alternative mode of action. While the proposed mode of action for liver tumors in rodent is qualitatively possible in humans, it is quantitatively implausible and unlikely to take place in humans based on quantitative species toxicodynamic differences in PPAR $\alpha$  activation. The quantification of risk is not required.

Currently the lactofen database does not contain acute neurotoxicity, subchronic neurotoxicity, developmental neurotoxicity or acute delayed neurotoxicity studies. The absence of these studies is not considered a data gap since according to the Code of Federal Regulations §158.340, these tests are not required “unless test material, is an organophosphate, or a metabolite or degradation product thereof which causes acetylcholinesterase depression or is structurally related to a substance that causes delayed neurotoxicity” or unless “the acute oral, dermal, or inhalation studies showed neuropathy or neurotoxicity.” It is noted that neurotoxicity was NOT observed in any of the submitted toxicity studies.

The rat metabolism study showed that lactofen was metabolized to acifluorfen, and it 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).

### **Sodium Acifluorfen**

Toxicity information is included here for sodium acifluorfen, a registered herbicide, because acifluorfen is the major lactofen degradate found in surface and ground water. Since hazard data are available for sodium acifluorfen, the Agency is able to do a separate risk assessment for sodium acifluorfen. A more complete hazard discussion is available in the sodium acifluorfen human health risk assessment (Farwell, 5/31/2000).

The acute toxicity data indicated that sodium acifluorfen had low acute oral, dermal and inhalation toxicity. It was not a skin sensitizer. However, it caused severe eye and moderate skin irritation.

The subchronic feeding study in rats and mice for sodium acifluorfen showed a decrease in body weight and signs of liver toxicity (characterized by increased liver weight and increased incidence of cellular hypertrophy).

The chronic feeding toxicity studies in rats, mice, and dogs demonstrated that sodium acifluorfen induced liver toxicity (acidophilic cells in the liver and increased liver weight) and kidney toxicity (nephritis/pyelonephritis and increased kidney weight). An increase in the incidence of stomach ulcers was also seen in chronic feeding study in rats.

The registrant has also proposed a mechanism of toxicity for sodium acifluorfen based on PPAR $\alpha$  activation (Farwell, 2003) which was accepted by the HED Mechanism of Toxicity Assessment Review Committee (MTARC). The Cancer Assessment Review Committee (CARC) concurred with the MTARC's conclusion and classified sodium acifluorfen as not likely to be carcinogenic to humans at doses that do not cause the biochemical and histopathological changes in the liver of rodents. Similar to lactofen, HED has reconsidered the mechanism of toxicity and now believes the cancer classification should be characterized as "not likely to be carcinogenic in humans".

Sodium acifluorfen produced developmental toxicity (decreased fetal body weight and the increase in anatomical variations) in rats but it did not affect the reproductive parameters in rats.

The acceptable genetic toxicology studies indicate that sodium acifluorfen was weakly mutagenic in *Salmonella typhimurium* TA100 at high S9-activated concentrations and weakly recombinogenic in *Saccharomyces cerevisiae* at high nonactivated concentrations but was negative for gene mutations in Chinese hamster ovary (CHO) cells. The test material was also negative for clastogenic effects *in vivo* and did not induce unscheduled DNA synthesis in primary rat hepatocytes. Although sodium acifluorfen induced Y chromosome loss and dominant lethal mutations in *Drosophila melanogaster*, the concern for possible heritable effects is lessened by the negative results of the rat dominant lethal assay. The acceptable studies satisfy the pre-1991 mutagenicity guideline requirements.

In a rat metabolism study, sodium acifluorfen was rapidly absorbed orally and eliminated mainly in the urine (46-58% of the dose) and feces (21-41% of the dose). The major component present in urine and feces was unchanged acifluorfen and amine metabolite, respectively. No tissue accumulation was observed.

## 3.2 FQPA Considerations

### Lactofen

The FQPA Safety Factor Committee met on March 13, 2000 to evaluate the hazard and exposure data for lactofen and recommended that the FQPA Safety Factor (as required by Food Quality Protection Act of August 3, 1996) for protection of infants and children should be 3x for lactofen, based on a datagap of a rabbit developmental study. Although two rabbit developmental studies were submitted, the results of these studies were inconsistent, so a new study had been required.

The registrant submitted a request to waive the rabbit developmental study in 2005, including additional background information on the two prior studies. HED has reviewed their request (Phang, 2006) and concurred with their position that sufficient information has been submitted on developmental effects in rabbits and no further studies are needed, so a database uncertainty factor is no longer required. However, a LOAEL to NOAEL FQPA factor is needed as there was no NOAEL identified in the study the Agency is now using for acute dietary endpoint selection (for females of reproductive age), a Prenatal Developmental Toxicity Study in Rabbits (TXR No. 003724). The endpoints of concern identified in this study are: decreased live young/litter, increased embryonic death/litter, and increased incidence of post-implantation loss. These effects were noted at all dose levels (5, 15, 50 mg/kg/day) thus a NOAEL was not established. Though a second Prenatal Developmental Toxicity Study in Rabbits (MRIDs: 00264577 and 00264847) failed to reproduce these effects at doses comparable to those used in the first study, the effects in the first study are still considered valid given the fact that the two studies were conducted in different facilities (Huntington for the first study and Wil Labs for the second study) and the different colonies used by these facilities may account for the different results. It should be noted that the incidence for the effects observed in the first study at the lowest dose tested were only marginally higher than the historical control data submitted by the testing facility as well as the historical control data available through the Middle Atlantic Reproduction and Teratology Association (MARTA). Consequently, an FQPA uncertainty factor of 3X is expected to be protective of infants and children and will be used for the LOAEL to NOAEL extrapolation.

The following considerations were used by the Agency when selecting an appropriate FQPA Safety Factor:

- there are no residual uncertainties regarding the exposure of infants and children to lactofen;
- there are no outstanding datagaps for developmental toxicity or reproductive toxicity studies;
- developmental effects were observed in the presence of maternal toxicity; and
- the acute dietary exposure endpoints are based on the developmental effects found in the rabbit developmental study.

Accordingly, the Agency has reduced the FQPA safety factor for 3X for acute exposures and 1X for chronic exposures. At this time there are no other exposure intervals that require evaluation as there are no residential uses of lactofen.

### **Sodium acifluorfen**

The toxicology database provides sufficient information for selecting various toxicity endpoints and doses for assessing the risks for sodium acifluorfen. The Health Effects Division (HED) FQPA Safety Factor Committee (SFC) met on September 13, 1999 to evaluate the hazard and exposure data for sodium acifluorfen and recommended retaining the safety factor at 10X due to the data gap for the developmental neurotoxicity study in rats. The developmental neurotoxicity study is designed to evaluate neurotoxic effects on the mother and fetus from the time of implantation of the fertilized egg into the wall of the uterus through post-natal day 21. This study may provide additional information that could be used to further characterize the effects of sodium acifluorfen on the developing organism. In accordance with the current policy within the Health Effects Division, the 10x factor will be applied to all exposure durations. A more detailed discussion of the safety factor selection may be found in the human health assessment for acifluorfen (Farwell, 2003).

### **3.3 Dose Response Assessment and Hazard Endpoint Selection**

#### **Lactofen**

On February 22, 2000 the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology database for lactofen, re-assessed the existing reference dose, and selected the doses and toxicological endpoints for dietary and non-dietary exposure risk assessments. Additional data and information have been submitted since then, including mechanistic data on the carcinogenicity of lactofen (Fricke 2002) and a request to waive the rabbit developmental study (Phang 2006). As previously discussed in section 3.1 the cancer classification of lactofen should be characterized as “not likely to be carcinogenic in humans”.

The selected endpoints and doses for the lactofen assessments may be found in Tables 3.1 and 3.2.

#### **Sodium Acifluorfen**

On January 19 and February 11, 1999, the Hazard Identification Assessment Review Committee (HIARC) evaluated the entire toxicological database on sodium acifluorfen and selected the relevant toxicity endpoints, taking into consideration the use patterns and exposure information on this chemical. Additional data and information have been submitted since then, including mechanistic data on the carcinogenicity of acifluorfen (Farwell, 2003). As previously discussed in section 3.1, the cancer classification of acifluorfen should be characterized as “not likely to be carcinogenic in humans”. The selected endpoints and doses for the acifluorfen assessments may be found in Table 3.3.

<b>Table 3.1 Toxicological Doses and Endpoints for <u>Lactofen</u> for Use in Dietary and Non-Occupational Human Health Risk Assessments<sup>1</sup></b>				
<b>Exposure/ Scenario</b>	<b>Point of Departure</b>	<b>Uncertainty/FQPA Safety Factors</b>	<b>RfD, PAD, Level of Concern for Risk Assessment</b>	<b>Study and Toxicological Effects</b>
Acute Dietary <i>General Population</i>	No endpoint has been identified for the general population based on a single exposure to lactofen.			
Acute Dietary <i>Females 13-49 years of age</i>	LOAEL = 5 mg/kg/day	UF <sub>A</sub> = 10x UF <sub>H</sub> = 10x FQPA SF = 3x (UF <sub>L</sub> )	Acute RfD = 0.017 mg/kg/day  aPAD = 0.017 mg/kg/day	Developmental Toxicity Study – Rabbit  LOAEL was 5 mg/kg based on decrease in live young per litter accompanied by increases in post implantation loss and in early embryonic death/litter.
Chronic Dietary <i>All Populations</i>	NOAEL = 0.79 mg/kg/day	UF <sub>A</sub> = 10x UF <sub>H</sub> = 10x FQPA SF = 1x	Chronic RfD = 0.008 mg/kg/day  cPAD = 0.008 mg/kg/day	Chronic Oral Toxicity Study - Dog LOAEL = 3.96 mg/kg/day based on increased incidence of proteinaceous casts in the kidneys and statistically significant decreases in the absolute weight of thyroid and adrenal glands in males.
Cancer (oral, dermal, inhalation)	Classification: Not likely to be carcinogenic to humans.			
Incidental Oral Short-Term (1-30 days)	Endpoints and doses have not been selected for these scenarios as there are no residential exposures to lactofen.			
Incidental Oral Intermediate-Term (1-6 months)				
Dermal Short-Term (1-30 days)				
Dermal Intermediate-Term (1-6 months)				

<sup>1</sup>**Explanation of Abbreviations:** Point of Departure (PoD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF<sub>A</sub> = extrapolation from animal to human (intraspecies). UF<sub>H</sub> = potential variation in sensitivity among members of the human population (interspecies). UF<sub>L</sub> = use of a LOAEL to extrapolate a NOAEL. UF<sub>S</sub> = use of a short-term study for long-term risk assessment. UF<sub>DB</sub> = to account for the absence of key data (i.e., lack of a critical study). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

<b>Table 3.2 Summary of Toxicological Doses and Endpoints for <u>Lactofen</u> for Use in Occupational Human Health Risk Assessments</b>				
<b>Exposure/ Scenario</b>	<b>Point of Departure</b>	<b>Uncertainty Factors</b>	<b>Level of Concern for Risk Assessment</b>	<b>Study and Toxicological Effects</b>
Dermal Short-Term (1-30 days)	NOAEL = 5 mg/kg/day	UF <sub>A</sub> =10x UF <sub>H</sub> =10x UF <sub>L</sub> =3X	Occupational LOC for MOE = 300	Developmental Toxicity Study – Rabbit LOAEL was 5 mg/kg based on decrease in live young per litter accompanied by increases in post implantation loss and in early embryonic death/litter.
Dermal Intermediate-Term (1-6 months)				
Inhalation Short-Term (1-30 days)	NOAEL = 5 mg/kg/day	UF <sub>A</sub> =10x UF <sub>H</sub> =10x UF <sub>L</sub> =3X	Occupational LOC for MOE = 300	Developmental Toxicity Study – Rabbit LOAEL was 5 mg/kg based on decrease in live young per liver accompanied by increases in post implantation loss and in early embryonic death/litter.
Inhalation Intermediate-term (1-6 months)				
Cancer (oral, dermal, inhalation)	Classification: Not likely to be carcinogenic to humans.			

<sup>1</sup>**Explanation of Abbreviations:** Point of Departure (PoD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF<sub>A</sub> = extrapolation from animal to human (intraspecies). UF<sub>H</sub> = potential variation in sensitivity among members of the human population (interspecies). UF<sub>L</sub> = use of a LOAEL to extrapolate a NOAEL. FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

<b>Table 3.3 Toxicological Doses and Endpoints for <u>Acifluorfen</u> for Use in Dietary and Non-Occupational Human Health Risk Assessments</b>				
<b>Exposure/ Scenario</b>	<b>Point of Departure</b>	<b>Uncertainty/FQPA Safety Factors</b>	<b>RfD, PAD, Level of Concern for Risk Assessment</b>	<b>Study and Toxicological Effects</b>
Acute Dietary <i>General Population</i>	No endpoint has been identified for the general population based on a single exposure to acifluorfen.			
Acute Dietary <i>Females 13-49 years of age</i>	NOAEL = 20 mg/kg/day	UF <sub>A</sub> = 10x UF <sub>H</sub> = 10x FQPA SF = 10x Database Uncertainty Factor due to the lack of a developmental neurotoxicity study	Acute RfD = 0.02 mg/kg/day  aPAD = 0.02 mg/kg/day	Developmental Toxicity Study – Rat LOAEL = 90 mg/kg/day based on decreased fetal weight and increased incidences of dilated lateral ventricles of the brain
Chronic Dietary <i>All Populations</i>	NOAEL = 1.25 mg/kg/day	UF <sub>A</sub> = 10x UF <sub>H</sub> = 10x FQPA SF = 10x	Chronic RfD = 0.013 mg/kg/day cPAD = 0.0013 mg/kg/day	2- Generation Reproduction Study - Rat LOAEL = 25 mg/kg/day based on kidney lesions (dilatation of tubules in outer medulla)
Dermal Short-Term (1-30 days)	NOAEL = 20 mg/kg/day	UF <sub>A</sub> = 10x UF <sub>H</sub> = 10x FQPA SF = 10x Database uncertainty factor for Females ages 13-49	Residential LOC for MOE = 1000	Developmental Toxicity Study – Rat LOAEL = 90 mg/kg/day based on decreased fetal weight and increased incidences of dilated lateral ventricles of the brain
Dermal Intermediate-Term (1-6 months)				
Inhalation Short-Term (1-30 days)	NOAEL = 20 mg/kg/day	UF <sub>A</sub> = 10x UF <sub>H</sub> = 10x FQPA SF = 10x Database uncertainty factor for Females ages 13-49	Residential LOC for MOE = 1000	Developmental Toxicity Study – Rat LOAEL = 90 mg/kg/day based on decreased fetal weight and increased incidences of dilated lateral ventricles of the brain
Inhalation Intermediate-Term (1-6 months)				
Cancer (oral, dermal, inhalation)	Classification: Not likely to be carcinogenic to humans.			

<sup>1</sup> **Explanation of Abbreviations:** Point of Departure (PoD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF<sub>A</sub> = extrapolation from animal to human (intraspecies). UF<sub>H</sub> = potential variation in sensitivity among members of the human population (interspecies). UF<sub>L</sub> FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

### **3.4 Endocrine Disruption**

EPA is required under the FFDCFA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there were scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCFA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP). In the available animal toxicity studies on lactofen, there was no evidence of estrogen, androgen, and/or thyroid mediated toxicity.

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, lactofen may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

### **4.0 Public Health and Pesticide Epidemiology Data**

HED recently reviewed the poisoning incident data on lactofen in the following databases: OPP Incident Data System (IDS), Poison Control Centers, California Department of Pesticide Regulation, National Pesticide Information Center (NPIC), and National Institute of Occupational Safety and Health's Sentinel Event Notification System for Occupational Risks (NIOSH SENSOR). There were few reports of ill effects from exposure to lactofen in the available data bases. No recommendations can be made based on the limited information available for this pesticide (Hawkins and Allender, 2006).

### **5.0 Dietary Exposure/Risk Characterization**

#### **5.1 Food Residue Profile**

Adequate studies are available depicting the metabolism of [<sup>14</sup>C]lactofen in soybeans, peanuts, and tomatoes. Although the quantities of individual metabolites vary between crops, the data indicate that the metabolic pathway is similar between crops. The metabolism of lactofen initially involves reduction of the nitro group to an amino group, with or without loss of the ethyl ester side chains to form the preliminary diphenyl ether metabolites: amino lactofen (PPG-1576), N-formyl lactofen (PPG-2597), desethyl lactofen (PPG-947), acifluorfen (PPG-947), and

amino acifluorfen (PPG-2053). Subsequent conjugation of these primary metabolites through their carboxyl and amino groups results in the formation of complex soluble and insoluble polar components.

Adequate studies are available depicting the metabolism of [<sup>14</sup>C]lactofen in ruminants and poultry. Lactofen was not detected in ruminant tissues or milk; only minor amounts of lactofen were detected in poultry tissues. Major residues found in edible ruminant and poultry commodities include acifluorfen, desethyl lactofen, and amino desethyl lactofen.

The Health Effects Division Metabolism Assessment Review Committee (MARC) met on April 4, 2000 to discuss the residues of concern in food and water. The MARC concluded that only lactofen is of concern in plants. Newer metabolism studies indicated that metabolites containing the diphenyl ether linkage are not likely to be present at significant levels under the current use conditions and there is no need to include them in the tolerance expression and risk assessment. At this time tolerances are not required for livestock commodities, since there is no reasonable expectation of finite residues (40 CFR 180.6 (a)(3)). However, should additional feed commodities be registered in the future that would necessitate consideration of livestock commodities, all metabolites containing the diphenyl ether linkage should be included in the tolerance expression and risk assessment for livestock commodities. The individual metabolites to be included in the tolerance expression, should tolerances be necessary, are acifluorfen, desethyl lactofen, amino lactofen, N-formyl lactofen, amino acifluorfen, and amino des-ethyl lactofen.

Acceptable gas chromatography with electron capture detection (GC/ECD) methods are available in the Pesticide Analytical Manual (PAM) Vol. II for the enforcement of tolerances of lactofen and metabolites in plant commodities. A modified version of Method B is listed in the U.S. EPA Index of Pesticide Analytical Methods under lactofen. Samples from the pepper and tomato field trials were analyzed using established GC/ECD enforcement methods or modified versions of established enforcement methods. The validated limits of quantitation (LOQs) were 0.01 ppm for peppers from the 1991 trial, and 0.02 ppm for samples from all other trials. The methods are adequate for data collection based on acceptable method validation and concurrent recovery data.

There are no livestock feedstuffs associated with the proposed uses on fruiting vegetables and okra. Therefore, feeding studies are not required to support this petition.

The submitted crop field trial data for pepper and tomato do not meet the recommendations in the guidance for guideline no. 860.1500 because of inadequate geographic representation. However, due to the very low residues, and the available data are in a region to that similar to those requested in this petition for a tolerance with a regional registration, HED will not request any additional data for the proposed use. The data indicate that residues of lactofen were below the LOQ (<0.01 - <0.02 ppm) in/on samples following application of lactofen according to the proposed use pattern.

No crop field trial data were submitted to support the proposed use on okra. Okra will be added to the fruiting vegetable crop group (Personal communication, B. Schneider 10/13/06), so the tomato and pepper data may be translated to okra.

Additional data/information are required to support the available confined rotational and limited rotational crop data; however, the available data suggest that the nature of the residue in rotational crops is adequately understood and that plantback intervals are not needed for the proposed use on fruiting vegetables and okra.

There are no established or proposed Codex, Canadian, or Mexican MRLs for residues of lactofen in any crop. Therefore, there are no harmonization issues with respect to U.S. tolerances.

Tolerance levels were used in the acute, chronic, and cancer assessments for lactofen and are listed in Table 5.1 below.

Table 5.1. Tolerance Levels Used in Lactofen Dietary Assessment	
Crop	Tolerance Level, ppm
<b>Existing Tolerances</b>	
Beans, Snap	0.01
Cotton, Gin Byproducts	0.02
Cotton, undelinted seed	0.01
Peanut	0.01
Soybean, seed	0.01
<b>Proposed Tolerances</b>	
Fruiting Vegetables	0.02
Okra	0.02

An aggregate assessment for acifluorfen was also conducted because acifluorfen is an environmental degradate of lactofen. Tolerance values for acifluorfen were used and may be found in Table 5.2.

Table 5.2. Tolerance Levels Used in Acifluorfen Dietary Assessment	
Crop	Tolerance Level, ppm
Peanut	0.1
Rice, grain	0.1
Soybean	0.1
Strawberry	0.05

No concentration, reduction, or processing factors were used in this assessment, as concentration of residues was not observed in processing studies.

## 5.2 Drinking Water Residue Profile

The drinking water residues used in the dietary risk assessment were provided by the Environmental Fate and Effects Division (EFED) (J. Wolf, D319594, 10/13/06) and incorporated directly into this dietary assessment. Acifluorfen is an environmental degradate of lactofen and another registered herbicide, sodium acifluorfen. Therefore, EFED estimated drinking water concentrations for both lactofen and acifluorfen from lactofen applications. Water residues were incorporated in the DEEM-FCID into the food categories “water, direct, all sources” and “water, indirect, all sources.”

The Tier 2 surface water EDWCs (estimated drinking water concentrations) for lactofen and acifluorfen were generated with standard Florida pepper and Florida tomato cropping scenarios using PRZM3 and EXAMS, and may be found in Table 5.3. PRZM simulates pesticide fate and transport as a result of leaching, direct spray drift, runoff and erosion from an agricultural field and EXAMS estimates environmental fate and transport of pesticides in surface water body for a 30-year period (1961-1990). PRZM and EXAMS were linked by the program PE4-PL (version 01). The EDWC assessment for surface water uses single or multiple sites which typically represent a high-end exposure scenario from pesticide use on a particular cropped or non-cropped site. Ground-water concentrations were estimated using the Tier 1 screening model SCI-GROW and may be found in Table 5.4. The models and its description are available at the EPA internet site: <http://www.epa.gov/oppefed1/models/water/>.

For comparison purposes the EDWCs of acifluorfen from sodium acifluorfen applications are included as well. The EDWC values are higher for lactofen derived acifluorfen as compared to sodium acifluorfen derived acifluorfen is likely due to the following considerations: 1) slightly higher amount of acifluorfen applied as compared to sodium acifluorfen; 2) the PCA is lower for soybeans (0.41) compared to the default value of 0.87 when there is no PCA available; and 3) different scenarios (crops) may also have different runoff potentials.

Table 5.3.a. Estimated Drinking Water Concentrations (EDWC) In Surface Water Lactofen And The Acifluorfen Derived From Lactofen <sup>1</sup>				
Crop	Chemical Species	1-in-10 year Maximum/mean (µg/L)		Long term average Mean (30 yrs.) (µg/L)
		Acute	Chronic	Cancer
Pepper	Lactofen	<b>1.48</b>	0.040	0.033
	Acifluorfen	<b>22.5</b>	3.5	2.0
Tomato	Lactofen	1.13	<b>0.044</b>	0.039
	Acifluorfen	20.9	<b>3.9</b>	1.7
Table 5.3.b. Estimated Drinking Water Concentrations (EDWC) In Surface Water of Acifluorfen Derived From Sodium Acifluorfen <sup>2</sup>				
Soybeans	Acifluorfen	14	<b>3</b>	1.4

<sup>1</sup>Bolded values were used in the dietary exposure assessment.

<sup>2</sup>Addendum to EFED RED Chapter for Sodium Acifluorfen and TRED for Lactofen (DP Barcode D291747, 09-15-03).

Table 5.4.a. SCI-GROW Estimates Of Lactofen And Acifluorfen EDWCs In Ground Water From Application of Lactofen	
Chemical	Acute and Chronic (µg/L)
Lactofen	0.006
Acifluorfen	2.00
Table 5.4.b. SCI-GROW Estimates Acifluorfen EDWCs In Ground Water From Application of Sodium Acifluorfen <sup>1</sup>	
Acifluorfen	3.67

<sup>1</sup> Addendum to EFED RED Chapter for Sodium Acifluorfen and TRED for Lactofen (DP Barcode D291747, 09-15-03).

### 5.3 Dietary Exposure and Risk

Lactofen acute, chronic, and cancer dietary exposure assessments were conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 2.03), which incorporates consumption data from USDA’s Continuing Surveys of Food Intakes by Individuals (CSFII), 1994-1996 and 1998. The 1994-96, 98 data are based on the reported consumption of more than 20,000 individuals over two non-consecutive survey days. Foods “as consumed” (e.g., apple pie) are linked to EPA-defined food commodities (e.g. apples, peeled fruit - cooked; fresh or N/S; baked; or wheat flour - cooked; fresh or N/S, baked) using publicly available recipe translation files developed jointly by USDA/ARS and EPA. For chronic exposure assessment, consumption data are averaged for the entire U.S. population and within population subgroups, but for acute exposure assessment are retained as individual consumption events. Based on analysis of the 1994-96, 98 CSFII consumption data, which took into account dietary patterns and survey respondents, HED concluded that it is most appropriate to report risk for the following population subgroups: the general U.S. population, all infants (<1 year old), children 1-2, children 3-5, children 6-12, youth 13-19, adults 20-49, females 13-49, and adults 50+ years old.

For chronic dietary exposure assessment, an estimate of the residue level in each food or food-form (e.g., orange or orange juice) on the food commodity residue list is multiplied by the average daily consumption estimate for that food/food form to produce a residue intake estimate. The resulting residue intake estimate for each food/food form is summed with the residue intake estimates for all other food/food forms on the commodity residue list to arrive at the total average estimated exposure. Exposure is expressed in mg/kg body weight/day and as a percent of the cPAD. This procedure is performed for each population subgroup.

For acute exposure assessments, individual one-day food consumption data are used on an individual-by-individual basis. The reported consumption amounts of each food item can be multiplied by a residue point estimate and summed to obtain a total daily pesticide exposure for a deterministic exposure assessment, or “matched” in multiple random pairings with residue values and then summed in a probabilistic assessment. The resulting distribution of exposures is

expressed as a percentage of the aPAD on both a user (i.e., only those who reported eating relevant commodities/food forms) and a per-capita (i.e., those who reported eating the relevant commodities as well as those who did not) basis. In accordance with HED policy, per capita exposure and risk are reported for all tiers of analysis. However, for tiers 1 and 2, any significant differences in user vs. per capita exposure and risk are specifically identified and noted in the risk assessment.

### 5.2.1 Acute Dietary Exposure/Risk

No endpoints were identified for the general population so the only assessment was conducted for Females ages 13-49. The results of the acute dietary exposure analysis for lactofen from food alone are reported in Table 5.5. All exposures are below the level of concern, with the lactofen assessments at less than 1% of the aPAD.

### 5.2.2 Chronic Dietary Exposure/Risk

The results of the chronic dietary exposure analyses for lactofen are reported in Table 5.5 for food alone. All exposures are below the level of concern, at less than 1% of the cPAD.

### 5.2.3 Cancer Dietary Risk

A cancer assessment is not required.

Population Subgroup	Acute Dietary (95 <sup>th</sup> Percentile)		Chronic Dietary	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD
General U.S. Population	N/A	N/A	0.000024	<1
All Infants (< 1 year old)			0.000024	<1
Children 1-2 years old			0.000051	<1
Children 3-5 years old			0.000047	<1
Children 6-12 years old			0.000032	<1
Youth 13-19 years old			0.000022	<1
Adults 20-49 years old			0.000021	<1
Adults 50+ years old			0.000019	<1

<b>Table 5.5. Summary of Dietary Exposure and Risk for Lactofen – Food Only</b>				
Population Subgroup	Acute Dietary (95 <sup>th</sup> Percentile)		Chronic Dietary	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD
Females 13-49 years old	<b>0.000066</b>	<1	0.000020	<1

## 6.0 Residential (Non-Occupational) Exposure/Risk Characterization

There are no products containing lactofen as an active ingredient that are registered for use in a residential or other non-occupational setting. Therefore there is no need to conduct a residential exposure and risk assessment. Residential exposures to the environmental degradate acifluorfen, which does have registered residential spot treatment uses, is discussed in the HED Chapter to the Reregistration Eligibility Decision Document (Farwell, 2002).

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from groundboom application methods. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new data base submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off target drift and risks associated with aerial as well as other application types where appropriate.

## 7.0 Aggregate Risk Assessments and Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure. There are no residential uses of lactofen, so the aggregate assessments consider exposure from food and drinking water.

Acifluorfen is an environmental degradate of two registered herbicides, lactofen and sodium acifluorfen. Therefore, an aggregate assessment is required for acifluorfen considering exposures from uses of both active ingredients. Dietary exposures included in the acifluorfen aggregate assessment included tolerance level residues of acifluorfen (from sodium acifluorfen uses) and modeled estimates of acifluorfen in drinking water as a result of application of lactofen. Only the estimates in drinking water from lactofen applications were included in the aggregate assessments because it is unlikely that both acifluorfen and lactofen will be used in the same area such that the exposures would be additive and that the acifluorfen drinking water exposures have already been assessed in the acifluorfen RED (Farwell, 2002). Also, the modeled estimates for the new uses of lactofen are higher than the estimates from sodium acifluorfen uses. The aggregate for acifluorfen also includes residential exposures as sodium acifluorfen may be used as a spot treatment in residential settings.

### 7.1 Acute Aggregate Risk

Acute (one day) exposures to **lactofen** may result from consuming treated food and drinking water. No endpoints were identified for the general population so the only assessment was conducted for Females ages 13-49. The results of the acute aggregate assessment for lactofen are reported in Table 7.1 for food and drinking water. All exposures are below the level of concern, with the lactofen assessments at less than 1% of the aPAD.

The acute aggregate assessment for **acifluorfen** includes food exposure from tolerance level residues (from sodium acifluorfen applications) and water exposures of acifluorfen as an environmental degradate of lactofen. No acute endpoints were identified for the general population so the only assessment was conducted for Females ages 13-49. All exposures are below the level of concern, with the acifluorfen assessments at 6% of the aPAD.

Both the lactofen and acifluorfen assessments are likely to be overestimates of risk because they assume all of the crops (for which there are registered uses) consumed in the US are treated and bear tolerance-level residues.

### 7.2 Short-Term Aggregate Risk

A short-term assessment is not required for **lactofen** as there are no residential uses of lactofen.

Registered residential uses of sodium acifluorfen include spot treatments only. The short term endpoint selected applies to females ages 13-49, but is protective of all populations. The **acifluorfen** aggregate assessment for this exposure duration includes the average food exposure assuming tolerance level residues, average water exposure (acifluorfen as an environmental degradate of lactofen), and residential handler exposures (Dole, 2003). The MOE for the aggregate assessment, found in Table 7.3, is 16000, which exceeds the target MOE of 1000. Therefore, short term aggregate risks are not of concern.

### **7.3 Intermediate-Term Aggregate Risk**

An intermediate-term assessment is not required for **lactofen** as there are no residential uses of lactofen.

Intermediate-term exposure is not expected for **acifluorfen** because residential uses are limited to spot treatments that do not include broadcast application to lawns.

### **7.4 Long-Term Aggregate Risk**

The results of the long-term aggregate assessment for **lactofen** are reported in Table 7.1 for food and drinking water. All exposures are below the level of concern, with the lactofen assessments at less than 1% of the cPAD.

The results of the long-term aggregate assessment for **acifluorfen** are reported in Table 7.2 for food and drinking water. All exposures are below the level of concern. The most highly exposed subgroup in the acifluorfen assessment at 37% of the cPAD was infants, less than one year old.

### **7.5 Cancer Risk**

A cancer assessment is not required.

<b>Table 7.1. Summary of Dietary Exposure and Risk for Lactofen – Food and Drinking Water</b>				
Population Subgroup	Acute Dietary (95 <sup>th</sup> Percentile)		Chronic Dietary	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD
General U.S. Population	N/A	N/A	0.000025	<1
All Infants (< 1 year old)			0.000027	<1
Children 1-2 years old			<b>0.000052</b>	<b>&lt;1</b>
Children 3-5 years old			0.000048	<1
Children 6-12 years old			0.000033	<1
Youth 13-19 years old			0.000023	<1
Adults 20-49 years old			0.000022	<1
Adults 50+ years old			0.000020	<1
Females 13-49 years old			<b>0.000066</b>	<b>&lt;1</b>

<b>Table 7.2. Summary of Dietary Exposure and Risk for Acifluorfen – Food and Drinking Water (Acifluorfen in Drinking Water From Lactofen Applications)</b>				
Population Subgroup	Acute Dietary (95 <sup>th</sup> Percentile)		Chronic Dietary	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD
General U.S. Population	N/A	N/A	0.00017	13
All Infants (< 1 year old)			<b>0.000478</b>	<b>37</b>
Children 1-2 years old			0.000324	25
Children 3-5 years old			0.00031	24
Children 6-12 years old			0.00021	16
Youth 13-19 years old			0.000142	11
Adults 20-49 years old			0.000151	12
Adults 50+ years old			0.000135	10
Females 13-49 years old			<b>0.00119</b>	<b>6.0</b>

Table 7.3. Short-Term Aggregate Risk Calculations for Acifluorfen						
Population	Short-Term Scenario					
	NOAEL mg/kg/day	LOC <sup>1</sup>	Target Maximum Exposure <sup>2</sup> mg/kg/day	Average Food & Water Exposure mg/kg/day	Residential Exposure <sup>3</sup> mg/kg/day	Aggregate MOE (food and residential) <sup>4</sup>
Adult Female	20	1000	0.02	0.000143	0.0011	16000

<sup>1</sup> The LOC includes the standard inter- and intra- species uncertainty factors totaling 100.

<sup>2</sup> Target Maximum Exposure (mg/kg/day) = NOAEL/LOC

<sup>3</sup> Residential Exposure was obtained from the risk assessment for acifluorfen (Farwell, 2002).

<sup>4</sup> Aggregate MOE = NOAEL/(Average Food & Water Exposure + Residential Exposure)

## 8.0 Cumulative Risk Characterization/Assessment

Lactofen is a member of the diphenyl ether chemical family. The common toxicity that these compounds share is induction of liver effects (liver hypertrophy, increase in liver weight, tumors). Members of this class have been shown to induce rodent liver effects /tumors through the activation of the peroxisome proliferator-activated receptor (PPAR $\alpha$ ). It should be noted that liver hypertrophy and increases in liver weight are part of the range of morphological changes that result from chemically-mediated effects on the PPAR $\alpha$  receptor and hepatocarcinogenesis. Although PPAR $\alpha$  agonists can induce liver rodent tumors, the potential for PPAR $\alpha$  agonists to induce liver tumors in other species, including humans, appears to be unlikely. This is because evidence shows that these other species are quantitatively less sensitive to the effects of PPAR $\alpha$  agonism due to toxicodynamic differences between the human and rodent nuclear PPAR receptor. Thus, while this mode of action for liver tumors in rodent is qualitatively possible in humans, it is quantitatively implausible and unlikely to take place in humans. **Accordingly, although members of the diphenyl ether family as well as other classes of compounds may share a common hepatocarcinogenic mode of action, cumulative exposure to PPAR $\alpha$  agonists is unlikely to induce liver carcinogenesis in humans.**

For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at <http://www.epa.gov/pesticides/cumulative>.

## 9.0 Occupational Exposure/Risk Pathway

### 9.1 Short-/Intermediate-Term Handler Risk

HED has determined that occupational handlers are likely to be exposed during lactofen use and that these uses would result in short/intermediate term exposures. Because the lactofen products are typically applied only one or two times per year, long-term or chronic exposures (i.e., daily exposures which occur for a minimum of several months) are not expected. The anticipated use patterns and current labeling indicate that there two exposure scenarios that are associated with this new use. These scenarios include mix/load liquids and groundboom application.

The handler's exposure assessments were performed using unit exposure values from the PHED Surrogate Exposure Guide (8/98) along with the following assumptions:

- \* 80 acres are treated per day based upon the ExpoSAC Policy 9 "Standard Values for Daily Acres Treated in Agriculture". This is the value for groundboom application to typical crops.
- \* The application rate is 0.5 lbs ai per acre based upon the proposed label.
- \* The handler body weight is 70 kg based upon the fact that the endpoint is not gender specific.

A summary of the risk estimates (i.e. MOEs) is included in Table 9.1. The MOE for the mix/load scenario is below 100 at the baseline PPE level and exceeds the Agency level of concern. The risk can be mitigated with the addition of chemical resistant gloves, which is currently required on the lactofen product label. The MOE for groundboom application is above 100 at the baseline level and does not exceed the Agency level of concern.

The PHED unit exposure values generally range from the geometric mean to the median of the selected data set, and therefore tend to be central tendency values. The daily acreage value is based upon PHED application data normalized to an 8 hour day and cultural use patterns and is considered to be a high end estimate. Therefore, the potential risk is characterized as mid to high end.

## **9.2 Postapplication Risk**

The proposed label indicates that lactofen should be applied to row middles in a directed, shielded spray; therefore, post application exposures are not expected.

<b>Table 9.1 Short- and Intermediate-Term Occupational Exposure and Risk Estimates for Proposed New Uses of Lactofen</b>								
<b>Exposure Scenario</b>	<b>Application Rate Lb ai/Acre</b>	<b>Acres Treated per day</b>	<b>Mitigation Level</b>	<b>Daily Dermal Dose<sup>3</sup>, mg/kg/day</b>	<b>Daily Inhalation<sup>4</sup> Dose, mg/kg/day</b>	<b>Dermal MOE<sup>5</sup></b>	<b>Inhalation MOE<sup>6</sup></b>	<b>Combined MOE<sup>7</sup></b>
Mixer/Loader (Baseline Dermal Unit Exposure = 2.9 mg/lb ai handled, Baseline Inhalation Unit Exposure = 0.012 mg/lb ai handled) (Single Layer Dermal Unit Exposure = 0.023 mg/lb ai handled)								
Mix/Load Liquids for Groundboom Application to Fruiting Vegetables and Okra	0.5	80	Baseline <sup>1</sup>	0.33	0.00069	15 <sup>8</sup>	7200 <sup>8</sup>	15 <sup>8</sup>
	0.5	80	Single layer Dermal PPE <sup>2</sup>	0.0026	0.00069	1900 <sup>8</sup>	7200 <sup>8</sup>	1500 <sup>8</sup>
Applicator (Baseline Dermal Unit Exposure = 0.014 mg/lb ai handled, Baseline Inhalation Unit Exposure = 0.00074 mg/lb ai handled)								
Groundboom Application to Fruiting Vegetables and Okra	0.5	80	Baseline	0.0016	0.00042	2500 <sup>8</sup>	12000 <sup>8</sup>	2500 <sup>8</sup>

1. Baseline dermal PPE includes long sleeved shirt, long pants, shoes and socks. Baseline inhalation PPE includes no respiratory protection.
2. Single Layer PPE included Baseline PPE and chemical resistant gloves.
3. Dermal dose = (Application rate \* Acres Treated per Day \* Unit Exposure \* Dermal Absorption Factor of 20 Percent)/Body Weight (70 kg).
4. Inhalation dose = (Application rate \* Acres Treated per Day \* Unit Exposure \* Inhalation Absorption Factor of 100 Percent)/Body Weight (70 kg).
5. Dermal MOE = NOAEL/Dermal Dose where the NOAEL is 5 mg/kg/day from a developmental toxicity study in rabbits.
6. Inhalation MOE = NOAEL/Inhalation Dose where the NOAEL is 5 mg/kg/day the same study as above.
7. Combined MOE = NOAEL/(Dermal Dose + Inhalation Dose) where the NOAEL is 5 mg/kg/day.
8. HED is generally not concerned if the MOE exceeds 300.

## **10.0 Environmental Justice Considerations**

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (<http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf>).

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Survey of Food Intakes by Individuals (CSFII) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Whenever appropriate, nondietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas postapplication are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

## **11.0 Review of Human Research**

This risk assessment does not rely on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical.

## **12.0 Data Needs and Label Recommendations**

### **12.1 Label Recommendations**

- The label must be amended to specify that the applications may not include two post-transplant applications. Finally, the label must be amended to reflect either a 30-day RTI or a minimum post-transplant interval of 18 days for tomatoes.
- The label should specify examples of fruiting vegetables in the use directions to avoid confusion.

### **12.2 Proposed Tolerances**

- The proposed tolerance for the fruiting vegetables crop group should be revised to reflect the recommended tolerance expression and the correct commodity definition, "Vegetable, fruiting, group 8," and the recommended level of 0.02 ppm.

- The proposed tolerance for okra should be revised to reflect the recommended tolerance expression and the recommended level of 0.02 ppm.

### 13.0 References

The documents listed in Table 13.1 were considered in this risk assessment.

Table 13.1 References			
Author	Barcode	Date	Title
C. Olinger	D333149	1/2007	Lactofen Acute, Chronic, and Cancer Aggregate Dietary and Drinking Water Exposure and Risk Assessments for the Section 3 Registration Action
C. Olinger	D333151	1/2007	Lactofen. Addition of New Uses: Fruiting Vegetables (Crop Group 8) and Okra. PRIA R17. Summary of Analytical Chemistry and Residue Data.
M. Hawkins and H. Allender	D323214	11/7/2006	Review of Lactofen Incident Reports
W. Phang	D320512	10/18/2006	Lactofen: Response to a waiver request for a developmental toxicity in rabbits
S. Diwan	N/A	10/17/2006	Lactofen - Report of the Cancer Assessment Review Committee
J. Wolf	D319594	10/13/2006	Drinking water and aquatic exposure water assessments for IR4 Tolerance petition for the new use (R17) of lactofen on the fruiting vegetable group and okra
S. Winfield	D296972	7/22/2004	Occupational and Residential Risk Assessment for Lactofen on Cotton and Peanuts
M. Metzger	D292794	8/12/2003	Lactofen. Revisions to HED Tolerance Reassessment Risk Assessment
C. Olinger	D278406	1/9/2002	Tolerance Reassessment of Lactofen: Registrant Response to Preliminary Human Health Risk Assessment
T. Dole	D279482	11/13/2001	Sodium Acifluorfen: Second Revised Occupational and Residential Exposure and Risk Assessment for the Reregistration Eligibility Decision (RED) Document
R. Fricke	D267472	3/12/2001	LACTOFEN: Report of the Mechanism of Toxicity Assessment Review Committee
C. Olinger	D269621	10/12/2000	Lactofen: Preliminary Human Health Risk Assessment for Tolerance Reassessment incorporating Revised Cancer Unit Risks
C. Olinger	D265477	4/26/2000	Lactofen: Preliminary Human Health Risk Assessment for Tolerance Reassessment
K. Farwell	D279497	1/15/2002	SODIUM ACIFLUORFEN. HED Chapter for the Reregistration Eligibility Decision Document
K. Farwell	D291742	7/14/2003	SODIUM ACIFLUORFEN. Revision to HED Chapter for the Reregistration Eligibility Decision Document

## Appendix A: Toxicity Profile

Table A1. Acute Toxicity of Lactofen

Guideline No.	Study Type	Accession #(S).	Results	Toxicity Category
81-1	Acute Oral	73859	LD <sub>50</sub> > 5.96 g/kg	IV
81-2	Acute Dermal	73859	LD <sub>50</sub> > 2.0 g/kg	III
81-3	Acute Inhalation	73859	LC <sub>50</sub> > 6.3 m/L	IV
81-4	Primary Eye Irritation (MUP)	73859	Moderate eye irritant	III
81-5	Primary Skin Irritation (MUP)	73859	Very slight dermal irritant	IV
81-6	Dermal Sensitization	73859	Not a dermal sensitizer	

Table A2. Toxicology Profile for **Lactofen**

Study Type	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Additional Relevant Data
Acute Oral Toxicity/Rat: 4.0, 5.06, 6.93, 9.12, 12 g/kg/day a.i. Accession No. 073859		LD <sub>50</sub> Males = 6.7 g/kg b.w. Females = 5.25 g/kg b.w. Combined - 5.96 g/kg b.w.	<b>Symptoms seen in all dose groups:</b> decreased activity, ataxia, diarrhea, excessive lacrimation and salivation, wet abdomen. Significant mortality: 12 g/kg dose [4/5(M) and all F died on or before 3 <sup>rd</sup> day of study]; 6.93 g/kg (3/5 M and 4/5 F died within first 3 days of study). <b>Toxicity Category IV</b>
Acute Dermal Toxicity/Rabbit: 2.0 g/kg/ b.w. for 24 hrs. Accession No. 073859		LD <sub>50</sub> > 2.0 g/kg/ b.w.	Symptoms: nasal discharge, soft stools, diarrhea, anorexia, decreased activity, paleness, mucus, and lacrimation. One animal died on day 15 of the study (this death was deemed incidental). <b>Toxicity Category III</b>
Primary Eye Irritation/Rabbit: 0.1 ml of Manufacturing Use Product (MUP). Accession No. 073859. <b>(Original study was unreadable therefore exact % a.i. could not be determined)</b>		Moderate eye irritant	Conjunctivae involvement (moderate redness, slight chemosis, and minimal discharge) seen in all animals 1 hr. post-dose but cleared after 72 hrs. Irridial irritation in 8/9 animals; cleared by 48 hrs No corneal injury. <b>Toxicity Category II</b>
Primary Dermal Irritation/Rabbit: 0.5 ml for 4 hrs. Accession No. 073859		Very slight dermal irritant	Very slight erythema and eschar formation in 5/6 animals which persisted for 48 hrs. <b>Toxicity Category IV</b>
Acute Inhalation Toxicity/Rat: Nominal Concentration of 52 mg/L (analytical concentration of 6.3 mg/L) for 4 hrs. Accession No.		LC <sub>50</sub> Combined > 6.3 mg/L	Nasal discharge, ataxia, decreased activity and labored breathing seen within the first few hours post-dosing. All clinical signs had resolved by day 5 of the study. One animal died on day 3 of the study; this death was classified as incidental. <b>Toxicity Category</b>

Table A2. Toxicology Profile for **Lactofen**

Study Type	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Additional Relevant Data
073859			<b>IV</b>
Dermal Sensitization - Guinea Pig 50% MUP. Accession No. 073859			Not a dermal sensitizer
Dermal Penetration Study - RAT: 3.6, 18.1, and 72.3 µg/cm <sup>2</sup> . Extent of absorption was determined at 0.5, 1, 2, 4, 10, and 72 hrs. after exposure to the test article. Accession No. 073843		1-4% dermal absorption at the 4 and 10 hr. time points	No systemic toxicity was reported. <sup>14</sup> C-PPG-844 (lactofen) was observed in the blood 2 hrs. post-application. Levels of compound continued to rise over the next 24 hrs. Plateaued and remained constant up to 72 hrs. (terminal sacrifice). After 72 hrs. ~ 8-10% of test article is absorbed through the skin.
Dermal Penetration Study - MONKEY 100 µg/cm <sup>2</sup> (exposure time 10 hrs.)		4.6% dermal absorption throughout the duration of the study.	No systemic toxicity reported.
Metabolism and Pharmacokinetics Study - RAT. Doses: 125 or 1250 mg/kg (gavage). Accession No. 071222			Seventy two hours after administration ≥ 97% of the radiolabel was recovered in the excreta (urine and feces). Urinary excretion comprised 39 - 56% of the dose while the fecal output totaled ~ 43 - 67% of the dose. While the parent compound, lactofen, was the major metabolite in the feces, the major metabolite in urine was acifluorfen which accounted for > 90% of the radioactivity recovered in this fraction. The maximum percentage of administered radioactivity that accumulated in a tissue sample was 0.55 - 0.75% in the liver.
Chronic Feeding Study/Dog: 0, 40, 200, and 1000/3000 ppm (0, 0.79, 3.96, 19.78/59.33 mg/kg/day) 1 year	0.79	3.96 based on proteinaceous casts in the kidneys (1/6 _), and statistically significant increases in the absolute weights of the thyroid and adrenal	<b>Effects seen at the highest-dose tested (19.78/59.3 mg/kg/day)</b> included: 1) decreases in body weight, body weight gain, and food consumption in males only; 2) decreases in the red blood cell count (RBC), hematocrit and hemoglobin levels as well as

Table A2. Toxicology Profile for **Lactofen**

Study Type	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Additional Relevant Data
MRID No.41967901		glands in males.	increases in the leukocyte and lymphocyte counts (males and females) [these changes in hematology and clinical chemistry parameters were first noted during the month 5 evaluation and persisted until the end of the study period]; 3) statistically significant decreases in the absolute weights of the heart, spleen, adrenals, thyroid, and kidneys; 4) statistically significant increases in the relative weights of the liver and kidneys (organ/body weight); and 5) increase in the incidence of proteinaceous casts in the kidneys (2/6 M, 1/6 F).
Carcinogenicity/Mouse: 0, 1.4, 7.1, and 35.7 mg/kg/day. 18 months Accession No. 073848	<b>Could not be established</b>	1.4 (LDT) based on hepatocytomegaly, increased liver weight, and increased sinusoidal cell pigmentation.	<b>Effects seen at the 7.1 mg/kg/day dose level included:</b> 1) increases in liver weight; 2) increased incidence of dark colored and/or enlarged livers; 3) hepatocytomegaly; 4) increased incidences of focal cell alteration and sinusoidal cell pigmentation in the liver; and 5) hepatocellular adenomas. <b>At the highest-dose tested (35.7 mg/kg/day), the severity of these signs of toxicity was increased. Other effects noted at the 35.7 mg/kg/day dose level were:</b> 1) increase in the incidence of non-neoplastic and neoplastic liver masses; 2) increase in kidney pigmentation and 3) increase in the incidence of cataracts.
Combined Chronic/Oncogenicity Study/RAT: 0, 2, 19, 38, and 76 mg/kg/day for 104 wks. MRID No. 150329	2	19 based on statistically significant increases in the incidence of mottled or discolored livers and changes in clinical chemistry.	<b>Effects seen at 38 mg/kg/day included:</b> 1) decreased food consumption, 2) increased incidence of mottled diffusely dark livers and kidneys, 3) increased incidence of dark discoloration of the testes, 4) decreases in hematocrit and hemoglobin levels, 5) increases in aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase levels, 6) decreases in cholesterol, blood urea nitrogen, and total protein globulin levels, and 7) increased incidence in the pigmentation of hepatocytes, Kupffer cells and renal cortical tubule cells. <b>Effects seen at the 76 mg/kg/day dose</b>

Table A2. Toxicology Profile for **Lactofen**

Study Type	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Additional Relevant Data
			<b>level (HDT)<sup>1</sup> were similar to those seen at the 38 mg/kg/day but more severe. In addition other effects seen at this dose level were:</b> 1) decreased body weight; 2) mortality; and 3) increased incidence in basophilic or eosinophilic foci of cellular alteration; and 4) increased incidence of neoplastic liver. nodules.
Prenatal Developmental Study/Rat: 0, 15, 50, or 150 mg/kg b.w. in GD 6-19. Accession No. 071226	Maternal: 50 Developmental: 50	Maternal: 150 based on signs of toxicity (excessive salivation, lethargy, dried red material around the nares and inguinal regions) and statistically significant decreases in body weight gain. Developmental: 150 based on decreased fetal weight and skeletal abnormalities (increased incidence of bent ribs and/or limb bones) and reduced ossification of vertebral arches.	
Developmental Toxicity/ Rabbit: 0, 1, 4, 20 mg/kg/day. GD 6 - 18.		Maternal > 20 (HDT) Developmental > 20 (HDT)	The only effect seen in this study was a decrease in food consumption by the does. This was not accompanied by decreases in body weight or body weight gain. <b>The HIARC considers this study as unacceptable/non-upgradable based on the fact that the dosing was inadequate.</b>

<sup>1</sup> Abbreviations: HDT = Highest-dose tested; GD = Gestation day; LDT = Lowest-dose tested; UDS = Unscheduled DNA Synthesis

Table A2. Toxicology Profile for **Lactofen**

Study Type	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Additional Relevant Data
Developmental Toxicity/ Rabbit: 0, 5, 15, 50 mg/kg/day.	Maternal and Developmental: <b>Could Not Be Established</b>	Maternal: 5 Developmental: 5	
<p>Multigeneration Reproduction Study/Rat: 0, 50, 500, or 2000 ppm ( 0, F0 males 2.6 /F0 females 3.1 mg/kg/day; F1 males 2.7/F1 females 3.3 mg/kg/day, F0 males 26.2/F0 females 31.8 mg/kg/day; F1 males 26.7/F1 females 32.9 mg/kg/day, and F0 males 103.5/F0 females 121.3 mg/kg/day; F1 males 115.4/F1 females 138.9 mg/kg/day. Accession Nos. 072201, 072202, 072203</p>	<p>Parental: 2.6 Offspring: 2.6 Reproductive 2.6</p>	<p>Parental: 26.2 based on mortality and decreased male fertility. Offspring: 26.2 based on reduced pup body weigh and decreases in the absolute and relative spleen weight Reproductive: 26.2 based on decreased male fertility.</p>	<p><b>For parental groups at the high-dose level</b>, in addition to death, there was: 1) decrease in body weight/gain; 2) increases in spleen and liver weights; 3) increase in the number of litters with dead pups at birth [both litters]; 4) increased incidence of liver [hepatocytic centrolobular degeneration and necrosis] and spleen [extramedullary hematopoiesis] microscopic lesions; 5) increases in testis weight; 6) increased incidence of bilateral degeneration or maturation arrest of germinal epithelium in the testes, hepatocytic centrolobular degeneration, necrosis in the liver, and extramedullary hematopoiesis in the spleen.</p> <p><b>For offspring groups at the high-dose level</b>, in addition to decreased pup body weight, there was: 1) decreased pup survival; and 2) decreased testes [F1 and F2], brain [F1, both sexes], spleen [F1 and F2, both sexes], and liver weights [F1 males].</p>
<p>Subchronic Oral Toxicity Study/RAT: 0, 2.9, 14.1, or 73.7 mg/kg/day for _; 0, 3.5, 17.0, and 84.5 mg/kg/day for _. 13 weeks. Accession No. 071224.</p>	<p>14.1</p>	<p>73.7 based on decreased body weight, increased incidence of anemia, increased levels of serum enzymes and bilirubin, decreased levels of glucose, increased liver weights, and increased incidence of microscopic liver lesions.</p>	
<p>Subchronic Oral Toxicity</p>	<p><b>Could not be</b></p>	<p><b>28.6 mg/kg/day based on changes</b></p>	<p>All animals at the two highest-doses tested died within the first 3</p>

Table A2. Toxicology Profile for **Lactofen**

Study Type	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Additional Relevant Data
Study/MOUSE: 0, 5.7, 28.6, 142.9, 714.3, or 1,428.6 mg/kg/day. 90 days. MRID No. 00132882	<b>established</b>	<b>clinical chemistry parameters, increases in organ weight and histopathological findings.</b>	weeks of the study. A myriad of effects including changes in hematology, clinical chemistry, and organ weight parameters were noted at the 142.9 mg/kg/day dose level. <b>During week 7 of the study period, the 5.7 mg/kg/day dose level was increased to 285.7 mg/kg/day to assess the maximum tolerated dose level (MTD). As a result, no NOAEL could be determined.</b>
<i>Salmonella typhirium</i> /mammalian microsome mutagenicity assay. Doses 50 - 5000 µg/plate ± S9 activation. MRID 00150346.			No cytotoxicity evident at ≥50 µg/plate in the absence or presence of metabolic activation. <b>PPG-844 induced a dose-related increase in revertant colonies of strain TA1538 in the absence of S9 activation; however, no effect seen in strain TA98 (derived from TA1538).</b>
<i>Salmonella typhirium</i> /mammalian microsome mutagenicity assay. Doses 50 - 5000 µg/plate ± S9 activation. MRID 00150347			Cytotoxicity was not evident for any strain up to the limit dose (5000µg/plate). <b>No evidence of PPG-844 induced mutagenic effect.</b>
<i>In vitro</i> cytogenetic assay with Chinese Hamster Ovary (CHO) cells. Doses: 31.25 - 500 µg/ml + S9 activation and 15.63 - 250 µg/ml - S9 activation. MRID No. 00150626			No evidence of clastogenic effect in the presence or absence of S9 activation.
Mammalian Cells in Culture Gene Mutation in Chinese Hamster Ovary (CHO) cells. Doses: 25-150 µg/ml. MRID No. 00150348			No evidence of cytotoxicity at any dose tested. <b>No clear indication of mutagenic effect in the presence or absence of S9 activation.</b>
Unscheduled DNA Synthesis/ <sup>1</sup> ary		Cytotoxicity at ≥ 5 x 10 <sup>-2</sup> mg/ml	No UDS

Table A2. Toxicology Profile for **Lactofen**

Study Type	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Additional Relevant Data
mouse hepatocytes: $5 \times 10^{-6}$ to 5 mg/ml for 19 hrs. MRID No. 00156064			
<i>In vivo</i> DNA covalent binding in mouse liver Dose: $^{14}\text{C}$ -PPG-844 at 3.8 mCi/mmol			A covalent binding index of $1.4 \pm 0.6$ was determined for lactofen. This suggests a low binding to mouse hepatic DNA may occur. This finding could not be attributed solely to DNA binding since some protein-binding of the parent compound and/or metabolite could be occurring.