



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

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MEMORANDUM

Subject: **Lactofen:** Preliminary Human Health Risk Assessment for Tolerance
Reassessment incorporating Revised Cancer Unit Risks; PC Code: 128888; DP
Barcode: D269621

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Attached is the Revised Preliminary Human Health Risk Assessment for the herbicide lactofen. The toxicology assessment was prepared by Elizabeth Mendez, the dietary risk analysis was conducted by Felicia Fort, and EFED contributed the information on exposure to lactofen in water.

In response to the Preliminary Assessment dated 4/26/00, the registrant noted that inappropriate scaling factors were used to calculate the cancer unit risk. This revision incorporates the modified cancer assessment.

The acute, chronic, and cancer dietary risk considering food and water exposure to lactofen *per se* is below our level of concern. In ground and surface water, lactofen is converted to acifluorfen, which is also registered as a herbicide. The preliminary cancer risk assessment for acifluorfen exceeds our level of concern when considering only residues in water from application of lactofen. Cancer risk for acifluorfen also exceeds the level of concern from residential applications of acifluorfen as well (Farwell, 5/31/00).

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1.0 EXECUTIVE SUMMARY

This document describes the human health risk assessment conducted for the herbicide lactofen in association with the reassessment of lactofen tolerances. Although lactofen was registered for use after 1984, the date after which re-registration is not currently required, the Food Quality Protection Act of 1996 (FQPA) required reassessment of all tolerances within ten years. This assessment therefore only discusses the human health risk assessment required for reassessment of tolerances, and does not include an occupational risk assessment required for reregistration of products.

Lactofen is currently registered for use on snap beans, soybeans, and cottonseed, and a use on peanuts is pending. Tolerances are established in 40 CFR 180.432 for snap beans and soybeans only; a tolerance for cottonseed expired 12/31/96, and was not renewed. The registrant has not removed the cotton registration from product labels. 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. Use information indicates that in a typical year, no more than 5% of any of the registered crops are treated with lactofen.

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 the parameters of clinical chemistry associated with liver toxicity. More severe effects were noted at higher dose levels. Lactofen has been classified as a B2 carcinogen (Probable Human Carcinogen) and assigned a Q_1^* of $1.19 \times 10^{-1} \text{ (mg/kg/day)}^{-1}$. This determination 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 a rat developmental toxicity study, the dose level that causes adverse effects to the developing fetus also elicits signs of toxicity in the parental 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 abnormalities (increased incidence of bent ribs, bent limb bones and a reduction in the ossification of the vertebral arches).

Based on these studies, 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, an endpoint for females of child-bearing age for acute exposure, and a cancer endpoint for the general population. The FQPA required the Agency to consider any special sensitivity to children. The FQPA Safety Factor committee did not find any evidence indicating increased sensitivity for the chronic effects and removed the factor for the chronic assessment, but retained a factor of three for the acute risk assessment because there is uncertainty associated with the data gap for a developmental toxicity study in rabbits with lactofen (doses used in the existing study are insufficient).

HED has selected reference doses (RfDs) for acute and chronic exposure for risk assessments. The Population Adjusted Dose (PAD), used for comparison to the exposure values, is the RfD divided by the FQPA safety factor. The PAD for acute effects (females 13+ only) is 0.13 mg/kg

bw/day). The PAD for chronic effects (general population) is equal to the reference dose of 0.008 mg/kg bw/day.

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. Sodium acifluorfen was classified as a Group B2, probable human carcinogen, and the unit risk [q^*_1] was calculated to be 5.3×10^{-2} (mg/kg/day)⁻¹.

The Health Effects Division (HED) has selected an endpoint for sodium acifluorfen based on kidney lesions for chronic exposure to the general population, an endpoint for females of child-bearing age based on fetal effects for acute exposure, and a cancer endpoint for the general population. 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.

Adequate residue data are available for the reassessment of the tolerances for soybeans and snap beans, and establishment of cottonseed and peanut tolerances. New plant metabolism data have recently been submitted, and the HED Metabolism Assessment Review Committee has also recommended including only the parent compound in the tolerance expression and risk assessment for lactofen in/on plant commodities. The tolerance expression formerly included acifluorfen as well as other metabolites with the diphenyl ether linkage. Residues in plant commodities are generally non-detectable or below the limit of quantitation, even when lactofen is applied at exaggerated rates. Therefore HED recommends a revised tolerance level of 0.01 ppm for the parent only in plant commodities. Several metabolites of concern were found in livestock metabolism studies. However, tolerances for meat, milk, poultry, and eggs are not required based on the livestock metabolism and magnitude of residue studies.

A dietary risk analysis was conducted for lactofen. The analysis, incorporating percent of crop treated information for those commodities for which there is a registration, and assuming all of the crop is treated for peanuts (a pending use), showed that all populations are exposed to less than 0.1% of the population adjusted dose (PAD) for acute and chronic risk. HED is generally not concerned if less than 100% of the PAD is consumed. The estimated cancer risk is 8×10^{-8} . A risk of 1×10^{-6} or lower is generally considered to be negligible.

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 registered for use as a herbicide 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 persistent in the environment and mobile. 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 estimated environmental concentrations (EECs) of lactofen and acifluorfen in ground and surface water using models. The EECs for lactofen are considerably below the concentrations in water that would result in a risk exceeding the level of concern, when considering the food exposure as well, for acute, chronic, and cancer effects. Therefore, there are no concerns for residues of lactofen *per se* in drinking water. HED has estimated the maximum acifluorfen concentration (drinking water level of comparison or DWLOC) in water for the various endpoints in water that would result in risks below our level of concern, and assuming no exposure from food or residential use. The DWLOCs for acute and chronic effects are greater than the EECs for acifluorfen (when lactofen is applied); therefore, there are no drinking water concerns for acifluorfen related to these endpoints. However, the modeled concentration for acifluorfen in ground water is greater than the maximum concentration in water that would result in cancer risk below 1×10^{-6} . Therefore there is a potential cancer concern for acifluorfen in drinking water. There will be a greater concern when the dietary and residential exposure to acifluorfen is considered.

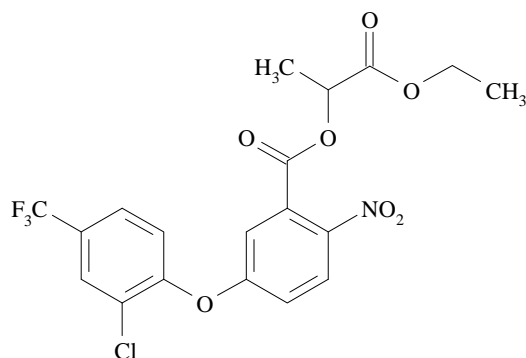
No uses are registered for lactofen in a residential setting. Therefore the aggregate risk considers only exposures from food and water. However, the Agency has concerns about possible residential risks from lactofen spray drift. The Agency is currently developing methods to assess residential risks from spray drift, and these will be assessed in the future when new methods are available. **HED has no concern for the aggregate exposure to lactofen *per se*. However, HED does have a concern for cancer risk from acifluorfen in water resulting from lactofen applications to crops and subsequent degradation to acifluorfen in the environment.** The aggregate risk from acifluorfen will be discussed in the forthcoming reregistration eligibility document for sodium acifluorfen.

Lactofen is a member of the diphenyl ether group of herbicides, as are sodium acifluorfen and oxyfluorfen. EPA has some evidence that these compounds induce similar toxic effects but has not yet determined whether or not these compounds exhibit a common mechanism. In addition, the Agency is in the process of developing methodology to conduct a cumulative risk assessment. For this assessment of lactofen, therefore, EPA will not conduct a cumulative risk assessment.

The Agency will, however, consider the relative contribution of each of these related pesticides to the multichemical and multiroute aggregated risks due to acifluorfen from use of sodium acifluorfen as a herbicide or environmental degradation of lactofen. This discussion will be included in the sodium acifluorfen risk assessment.

2.0 PHYSICAL CHEMICAL PROPERTIES CHARACTERIZATION

The chemical name for lactofen is 1-(carboethoxy)ethyl 5-[2-chloro-4-(trifluoromethyl)-phenoxy]-2-nitrobenzoate. The chemical structure is:



Other identifying characteristics and codes are:

Empirical Formula:	C ₁₉ H ₁₅ ClF ₃ NO ₇
Molecular Weight:	461.8
CAS Registry No.:	77501-63-4
PC Code No.:	128888
Common Name:	lactofen
Solubility in Water:	0.97 ppm at 25 C
Soil Half Life:	3 days (silt loam)

3.0 HAZARD CHARACTERIZATION

3.1 Hazard Profile

Lactofen. Lactofen has a very low acute toxicity profile: the acute oral LD₅₀ = 5.96 g/kg b.w. (Tox Category IV), the acute dermal LD₅₀ > 2.0 g/kg b.w. (Tox Category III) and the acute inhalation LC₅₀ > 6.3 mg/L (Tox Category (IV)). Furthermore, lactofen is not a skin sensitizer but it is a very slight dermal irritant. The manufacture's use product (MUP), however, is classified as a moderate eye irritant. A summary of the hazard profile may be found in Table 4 at the end of Section 3.0 of this document.

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 (lactofen's major 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, and fomesafen produces hepatocellular adenomas and carcinomas in mice.¹ The relevant data on the carcinogenic potential of lactofen were evaluated by the Cancer Peer Review Committee (CPRC) in 1987. Lactofen has been classified by the CPRC as a B2 carcinogen (Probable Human Carcinogen) and assigned a Q₁* of 1.19 x 10⁻¹ (mg/kg/day)⁻¹. This

¹ Health Effects Division Evaluation of Lactofen Memo (2/5/87).

determination 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.

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. In a carcinogenicity study in mice, effects were seen at doses as low as 1.4 mg/kg/day. Toxicity at this dose level was manifested by increases in liver weight, increases in the incidence of hepatocytomegaly, and increases in sinusoidal cell pigmentation. 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, 19.78 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 a developmental toxicity study 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 abnormalities (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). While a developmental toxicity study in rabbits has been submitted to the Agency, HIARC considered this study unacceptable since it failed to elicit signs of toxicity in the maternal group at the highest-dose tested (20 mg/kg/day). The committee considers the doses used in this study to be inadequate to evaluate the potential developmental toxicity of this compound in the rabbits and has recommended that another developmental toxicity in rabbits be conducted and submitted to the Agency for evaluation.

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.

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.”

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 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. Sodium acifluorfen was classified as a Group B2, probable human carcinogen, and the unit risk [q*₁] was calculated to be 5.3 x 10⁻² (mg/kg/day)⁻¹.

Sodium acifluorfen produced developmental toxicity (decreased fetal body weight and the increase in anatomical variations) in rats and 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 **reduced to 3x** for lactofen.

The Committee recommended that the FQPA safety factor be **reduced to 3x** because: 1) the available data provide no indication of quantitative or qualitative increased susceptibility from *in utero* and/or postnatal exposure to lactofen in rats; 2) adequate actual data, surrogate data, and/or modeling outputs are available to satisfactorily assess food exposure and to provide a screening level drinking water exposure assessment (there are currently no residential uses); and 3) a satisfactory rabbit developmental study is outstanding.

The FQPA safety factor for lactofen is applicable to the **Females 13-50 Population Subgroup** for **Acute Dietary Risk Assessment** (there are currently no residential scenarios) since the developmental toxicity study in rabbits (considered a data gap) will only provide information relevant to *in utero* exposures (which could potentially occur after a single dose).

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 made the following

When assessing **Acute Dietary Exposures to sodium acifluorfen**, the safety factor should be **retained at 10x** for the **Females 13-50** since a qualitative increase in susceptibility was observed following *in utero* exposure to rats in the developmental study (which could potentially occur after a single dose) and since there is a 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.

When assessing the **Chronic Dietary and Long-Term Residential Exposures to sodium acifluorfen**, the safety factor can be **reduced to 3x** for the **Females 13-50**; and the **Infants and Children Subgroups** since there is a data gap for the developmental neurotoxicity study. (The qualitative increase in susceptibility seen after *in utero* exposure in the developmental study has no bearing on chronic exposure scenarios).

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. Table 1 contains the acute toxicity categories. Table 2 contains a summary of the doses and toxicity endpoints selected for use in the various human health risk assessments for lactofen.

The population adjusted dose (PAD) is equivalent to the Reference Dose (RfD) adjusted for the FQPA safety factor. The acute PAD is equal to the RfD divided by the FQPA factor of 3. However, since the factor was removed for the chronic endpoint of concern, the chronic PAD is equal to the chronic RfD.

Table 1. Acute Toxicity of Lactofen

Guideline No.	Study Type	Accession #(S).	Results	Toxicity Category
81-1	Acute Oral	73859	LD ₅₀ > 5.96 g/kg	IV
81-2	Acute Dermal	73859	LD ₅₀ > 2.0 g/kg	III
81-3	Acute Inhalation	73859	LC ₅₀ > 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 2. Summary of Dietary Endpoints and Doses for **Lactofen**

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary Females 13+	NOAEL = 50 LOAEL = 150 UF = 100 FQPA SF = 3	Decreased fetal weight and skeletal abnormalities.	Developmental Toxicity Study - RAT
	Acute RfD = 0.5 mg/kg b.w. Acute Population Adjusted Dose = 0.17 mg/kg b.w.		
Chronic Dietary	NOAEL = 0.79 LOAEL = 3.96 UF = 100 FQPA SF = 1	Increased incidence of proteinaceous casts in the kidneys and statistically significant decreases in the absolute weight of thyroid and adrenal glands in males.	Chronic Oral Toxicity Study - DOG
	Chronic RfD = 0.008 mg/kg/day Chronic Population Adjusted Dose = 0.008 mg/kg/day		
Carcinogenic Effects	$Q^*_1 = 1.19 \times 10^{-1}$ (mg/kg/day) ⁻¹	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	

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. The selected toxicological endpoints and the doses for risk assessment are summarized in Table 3.

Table 3. Summary of Dietary Endpoints and Doses for **Sodium acifluorfen**

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary (Female 13+)	NOAEL=20 LOAEL = 90 UF=100 FQPA SF = 10	Decreased fetal weight and increased incidences of dilated lateral ventricles of the brain	Developmental–rat
		Acute RfD = 0.2 mg/kg/day Acute PAD = 0.02 mg/kg/day (applies to females 13+)	
Chronic Dietary non-carcinogenic effects	NOAEL=1.25 LOAEL = 25 UF=100 FQPA SF = 3	based on kidney lesions, characterized predominantly by dilatation of tubules in the outer medulla, in females of both generations	2-generation reproduction–rat
		Chronic RfD = 0.013 mg/kg/day Chronic PAD = 0.004 mg/kg/day (children and females 13+)	
Carcinogenic effects	$Q^*_1 = 5.3 \times 10^{-2}$ (mg/kg/day) ⁻¹	Liver tumors (adenomas, carcinomas, and adenomas/carcinomas combined) and stomach tumors (papillomas) in both sexes of mice	

3.4 Endocrine Disruption

EPA is required under the FFDCA, 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 was 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, FFDCA 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).

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.

Table 4. 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 ₅₀ Males = 6.7 g/kg b.w. Females = 5.25 g/kg b.w. Combined - 5.96 g/kg b.w.	Symptoms seen in all dose groups: decreased activity, ataxia, diarrhea, excessive lacrimation and salivation, wet abdomen. Significant mortality: 12 g/kg dose (4/5 ♂ and all ♀ died on or before 3 rd day of study); 6.93 g/kg (3/5♂ and 4/5♀ died within first 3 days of study). ² Toxicity Category IV
Acute Dermal Toxicity/Rabbit: 2.0 g/kg/ b.w. for 24 hrs. Accession No. 073859		LD ₅₀ > 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). Toxicity Category III
Primary Eye Irritation/Rabbit: 0.1 ml of Manufacturing Use Product (MUP) Accession No. 073859. (Original study was unreadable therefore exact % a.i. could not be determined)		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. Toxicity Category II
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. Toxicity Category IV
Acute Inhalation Toxicity/Rat: Nominal Concentration of 52 mg/L (analytical concentration of 6.3 mg/L) for 4 hrs. Accession No. 073859		LC ₅₀ 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. Toxicity Category IV

² Symbols key: ♀ = Female; ♂ = Male

Table 4. Toxicology Profile for **Lactofen** (Continued)

Study Type	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Additional Relevant Data
Dermal Sensitization - Guinea Pig 50% MUP. Accession No. 073859			Not a dermal sensitizer
Dermal Penetration Study - RAT: 3.6, 18.1, and 72.3 $\mu\text{g}/\text{cm}^2$. 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. ^{14}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 $\mu\text{g}/\text{cm}^2$ (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 $\geq 97\%$ 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.

Table 4. Toxicology Profile for **Lactofen** (Continued)

Study Type	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Additional Relevant Data
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 MRID No.41967901	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 glands in males.	Effects seen at the highest-dose tested (19.78/59.3 mg/kg/day) 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 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 ♂, 1/6 ♀).
Carcinogenicity/Mouse: 0, 1.4, 7.1, and 35.7 mg/kg/day. 18 months Accession No. 073848	Could not be established	1.4 (LDT) based on hepatocytomegaly, increased liver weight, and increased sinusoidal cell pigmentation.	Effects seen at the 7.1 mg/kg/day dose level included: 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. 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: 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.

Table 4. Toxicology Profile for **Lactofen** (Continued)

Study Type	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Additional Relevant Data
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.	Effects seen at 38 mg/kg/day included: 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. Effects seen at the 76 mg/kg/day dose level (HDT)³ were similar to those seen at the 38 mg/kg/day but more severe. In addition other effects seen at this dose level were: 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.	

³ Abbreviations: HDT = Highest-dose tested; GD = Gestation day; LDT = Lowest-dose tested; UDS = Unscheduled DNA Synthesis

Table 4. Toxicology Profile for *Lactofen* (Continued)

Study Type	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Additional Relevant Data
Developmental Toxicity/ Rabbit: 0, 1, 4, 20 mg/kg/day. GD 6 - 18.	Could not be established	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. The HIARC considers this study as unacceptable/non-upgradable based on the fact that the dosing was inadequate.
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	Parental: 2.6 Offspring: 2.6 Reproductive . 2.6	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.	For parental groups at the high-dose level , 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 litterings]; 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. For offspring groups at the high-dose level , 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].
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.	14.1	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.	

Table 4. Toxicology Profile for *Lactofen* (Continued)

Study Type	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Additional Relevant Data
Subchronic Oral Toxicity Study/MOUSE: 0, 5.7, 28.6, 142.9, 714.3, or 1,428.6 mg/kg/day. 90 days. MRID No. 00132882	Could not be established	28.6 mg/kg/day based on changes clinical chemistry parameters, increases in organ weight and histopathological findings.	All animals at the two highest-doses tested died within the first 3 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. 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.
<i>Salmonella typhirium</i> /mammalian microsome mutagenicity assay. Doses 50 - 5000 $\mu\text{g}/\text{plate}$ \pm S9 activation. MRID 00150346.			No cytotoxicity evident at $\geq 50 \mu\text{g}/\text{plate}$ in the absence or presence of metabolic activation. 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).
<i>Salmonella typhirium</i> /mammalian microsome mutagenicity assay. Doses 50 - 5000 $\mu\text{g}/\text{plate}$ \pm S9 activation. MRID 00150347			Cytotoxicity was not evident for any strain up to the limit dose (5000 $\mu\text{g}/\text{plate}$). No evidence of PPG-844 induced mutagenic effect.
<i>In vitro</i> cytogenetic assay with Chinese Hamster Ovary (CHO) cells. Doses: 31.25 - 500 $\mu\text{g}/\text{ml}$ + S9 activation and 15.63 - 250 $\mu\text{g}/\text{ml}$ - 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 $\mu\text{g}/\text{ml}$. MRID No. 00150348			No evidence of cytotoxicity at any dose tested. No clear indication of mutagenic effect in the presence or absence of S9 activation.
Unscheduled DNA Synthesis/ ³ H mouse hepatocytes: 5 x 10 ⁻⁶ to 5 mg/ml for 19 hrs. MRID No. 00156064		Cytotoxicity at $\geq 5 \times 10^{-2}$ mg/ml	No UDS

Table 4. Toxicology Profile for **Lactofen** (Continued)

Study Type	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Additional Relevant Data
<i>In vivo</i> DNA covalent binding in mouse liver Dose: ¹⁴ C-PPG-844 at 3.8 mCi/mole			A covalent binding index of 1.4 ± 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.

4.0 EXPOSURE ASSESSMENT

4.1 Summary of Registered Uses

A search of the Agency's Reference Files System (REFS) on 2/11/00 indicates that there are two lactofen end-use products (EPs) registered to Valent U.S.A. Corporation that have uses on food and/or feed crops: Cobra® (EPA Reg. No. 59639-34) and Stellar® (EPA Reg. No. 59639-92). The 2.4 lb/gal EC formulation of lactofen (EPA Reg. No. 59639-92) is a multiple active ingredient (MAI) product, which contains 0.7 lb/gal of flumiclorac pentyl ester in addition to lactofen.

Currently lactofen is registered for use on soybeans, snap beans, and cottonseed and a use is pending on peanuts. Lactofen may be applied pre- or post-emergence at rates ranging from 0.1 to 0.4 lb ai/A. Pre-harvest intervals range from 45 days for soybeans to 90 days for cotton. The maximum seasonal application rate for any crop is 0.8 lb ai/A for cottonseed.

4.2 Dietary Exposure and Risk Assessment

4.2.1 Dietary Exposure from Food Sources

Adequate studies are available depicting the metabolism of [¹⁴C]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. The chemical names and structure of the lactofen residues of concern in plants and animals are presented in Figure 1 (page 20).

Adequate studies are available depicting the metabolism of [¹⁴C]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 in the edible commodities (40 CFR 180.6 (a)(3)). However, should

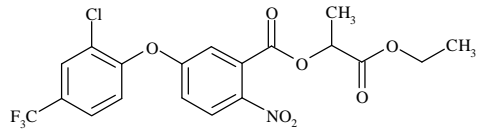
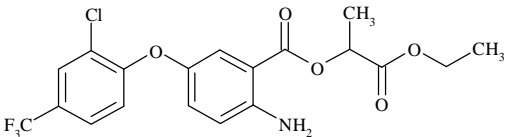
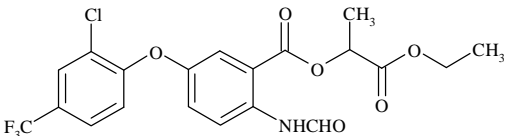
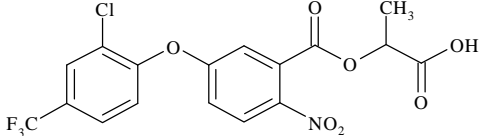
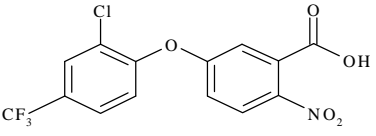
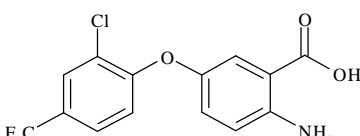
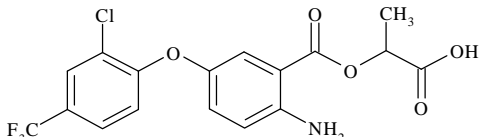
additional feed commodities be registered in the future that would necessitate consideration of livestock commodities, all metabolites containing the diphenyl ether linkage should be included in the tolerance expression and risk assessment for livestock commodities. The individual metabolites to be included in the tolerance expression, should tolerances be necessary, are acifluorfen, des-ethyl lactofen, amino lactofen, N-formyl lactofen, amino acifluorfen, and amino des-ethyl lactofen.

Analytical methods are available for the determination of lactofen and the individual metabolites of concern in plant and livestock commodities. Adequate data are available on the recovery of lactofen and its metabolites through Multiresidue Method Testing Protocols.

Adequate lactofen residue data are available for cotton, peanuts, snap beans, and soybeans. An adequate number of field trials have been conducted on these crops depicting lactofen residues resulting from the application of lactofen at the maximum labeled or proposed use rate. Residues are below the limit of quantitation of 0.01 ppm for lactofen in all commodities. Residues do not concentrate in the processed commodities of soybeans, cottonseed, and peanuts.

An adequate feeding study has been conducted for lactofen at feeding levels up to 500x the maximum dietary burden. Finite residues are not expected in meat, milk, poultry, and eggs, and there is no need for meat and milk tolerances.

Figure 1. Chemical name and structure of lactofen residues of concern in plants and animals.

Common names/(Codes) Chemical name	Chemical Structure
<p>Lactofen^a (PPG-844, PG-1)</p> <p>1-(Carboethoxy)ethyl-5-[2-chloro-4-(trifluoromethyl)phenoxy]-2-nitrobenzoate</p>	
<p>Amino lactofen; amino CTBL^a (PPG-1576, PG-74)</p> <p>1-(Carboethoxy)ethyl 5-[2-chloro-4-(trifluoromethyl)phenoxy]-2-aminobenzoate</p>	
<p>N-formyl lactofen^a (PPG-2597, PG-73)</p> <p>1-(Carboethoxy)ethyl 5-[2-chloro-4-(trifluoromethyl)phenoxy]-2-formamidobenzoate</p>	
<p>Desethyl lactofen^a (PPG-947, PG-11)</p> <p>1-(Carboxy)ethyl 5-[2-chloro-4-(trifluoromethyl)phenoxy]-2-nitrobenzoate</p>	
<p>Acifluorfen (PPG-847, PG-5)^a</p> <p>5-[2-chloro-4-(trifluoromethyl)phenoxy]-2-nitrobenzoic acid</p>	
<p>Amino acifluorfen^b; amino NCTBA (PPG-2053, PG-75)</p> <p>2-amino-5-[2-chloro-4-(trifluoromethyl)phenoxy]-benzoic acid</p>	
<p>PPG-2828^b (PPG-A947)</p> <p>1-(carboxy)ethyl-5-[2-chloro-4-(trifluoromethyl)phenoxy]-2-aminobenzoate</p>	

^a Metabolite residues formerly regulated in plants include: desethyl lactofen, amino lactofen, N-formyl lactofen, and acifluorfen. ^bPPG-2053 and PPG-2828 are residues of concern in animal commodities, along with lactofen and the four plant metabolites.

4.2.2 Dietary Risk from Food Sources

Dietary risk was considered for the currently registered uses of lactofen on cotton, soybeans, and snap beans, and from the pending use on peanuts.

HED conducts dietary risk assessments using the Dietary Exposure Evaluation Model (DEEM™), which incorporates consumption data generated in USDA’s Continuing Surveys of Food Intakes by Individuals (CSFII), 1989-1992. For chronic dietary risk assessments, the three-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 FDA or USDA for residues of lactofen. Therefore only field trial data were used. A value of one-half the limit of quantitation (0.005 ppm) was used to represent the residues in all treated commodities. Percent crop treated were incorporated for soybeans and snap beans, as reliable usage information was available for these commodities. The estimated risk from food is presented in Table 5.

Table 5. Dietary Exposure and Risk to Lactofen from Food Sources

Population	Acute Endpoint		Chronic Endpoint		Cancer Endpoint ²	
	Exposure mg/kg BW/day	%aPAD	Exposure mg/kg BW/day	%cPAD	Exposure mg/kg BW/day	Risk
US Population	N/A ¹	N/A	1×10^{-6}	<0.1	1×10^{-6}	8×10^{-8}
Females 13-50	2×10^{-6}	<0.1	$< 1 \times 10^{-6}$	<0.1	N/A ²	N/A
Children 1-6	N/A ¹	N/A	2×10^{-6}	<0.1	N/A ²	N/A

¹ Acute endpoint applies only to females of childbearing age.

² Cancer risk is generally reported for the US population.

4.2.3. Dietary Exposure from Water Sources

Environmental fate properties indicate that lactofen is not very persistent or mobile. Hydrolysis half-lives (rates) were reported to be 10.7, 4.6, and <1.0 days at pH 5,7, and 9 at 40°C, respectively. This temperature (e.g., 40°C) most likely exceeds temperatures that lactofen would be expected to be exposed to under normal condition, thus the hydrolysis rates are probably slower (i.e., longer half-lives). Aerobic soil metabolism half-lives ranged from one to three days. Lactofen appears to have a low probability to contaminate drinking water because it has a short half-life (three days or less) and high binding potential ($K_{oc} > 1000$). Limited data suggest that the lactofen conversion to acifluorfen in water is approximately 52 percent. Lactofen is not routinely included in water monitoring studies due to its short half-life and low mobility. The registrant sponsored a small-scale, prospective ground-water monitoring study for lactofen in Ohio. The study was inconclusive because the study did not provide confirmation that leaching actually occurred at the site.

Acifluorfen has been detected in surface water and ground water. Acifluorfen is extremely mobile as the binding potential is quite low. At pHs greater than 3.5 (all agriculture soils have pH greater than this), acifluorfen is predominately an anion and would be expected to have little sorption in many soils. Acifluorfen binding is positively correlated with soil organic carbon content. The aerobic soil metabolism half-life for acifluorfen ranges from six days to six months or more. It is stable to hydrolysis. Environmental factors such as soil temperature and soil water content influences soil microbial activity and thus, acifluorfen's degradation rate. The decarboxy derivative of acifluorfen was the primary degradate found in solution. An amino analog of acifluorfen is the major degradate under anaerobic soil conditions.

The HED MARC has concluded that the residues of concern in drinking water are acifluorfen and amino acifluorfen. Insufficient information is available to estimate the amino acifluorfen concentration in water, but it is likely to be less than that of acifluorfen.

Monitoring Data. Acifluorfen has been detected in surface water and ground water. Degradates of acifluorfen have not been included in monitoring studies. Lactofen is also not routinely included in water monitoring studies due to its short half-life and low mobility. There have been no reported detections of lactofen in surface or ground water.

Acifluorfen has been detected in both surface and ground water samples collected in the USGS National Water Quality Assessment (NAWQA) program. The USGS NAWQA study reports 0.12 percent of samples collected from major aquifers had detectable levels of acifluorfen, the maximum detection of 0.19 µg/L. For all ground water samples collected by NAWQA, 0.04 percent of samples had detectable levels of acifluorfen ranging between 0.035 to 0.19 µg/L. The NAWQA study goal was to assess water quality in general and not specifically lactofen and acifluorfen. The only surface water monitoring data available is that which has been collected by NAWQA. The maximum detection of acifluorfen reported in surface water is 2.2 µg/L.

Acifluorfen residues in ground water were reported in the Pesticides in Ground Water Data Base, PGWDB (USEPA, 1992), a summary of other ground-water monitoring studies. The PGWDB (USEPA, 1992) reports four of 1185 wells sampled had detectable levels of acifluorfen with concentrations ranging from 0.003 to 0.025 µg/L. Because the studies summarized in the PGWDB were conducted with many objectives and study designs, the results may reflect conditions where no lactofen or acifluorfen had been used or where there is a low susceptibility to ground water contamination. Therefore, the Environmental Fate and Effects Division (EFED) has low confidence that the monitoring reflects the potential contamination of ground water from acifluorfen.

Because of the uncertainty noted with the surface water and ground water monitoring studies, monitoring data cannot be used in a quantitative risk assessment. The monitoring data do indicate that acifluorfen is detected in ground and surface waters. It is not known whether the detected acifluorfen is from application of acifluorfen or lactofen.

Ground Water. The SCI-GROW (Screening Concentration in Ground Water) screening model developed in EFED (Barrett, 1997) was used to estimate potential ground water concentrations for lactofen and the degradate acifluorfen under hydrologically vulnerable conditions. The maximum lactofen ground water concentration predicted by the SCI-GROW using the maximum application rates (and seasonal amounts) for cotton (one application) of 0.32 lb. a.i./A and for soybeans of 0.50 lb. a.i./A (one application) was 0.006 µg/L (low default value). There is much more uncertainty associated with the ground water acifluorfen concentrations, because of the uncertainty of some model input values and the rate of degradation of lactofen to form acifluorfen. The maximum acifluorfen concentration predicted by SCI-GROW was 10.3 µg/L.

Surface Water. The Tier II estimated environmental concentration (EEC) assessment in surface water uses a single site, or multiple single sites, which represents a high-end exposure scenario from pesticide use on a particular crop or non-crop use site. The EECs for lactofen and acifluorfen were generated for the standard Mississippi cotton scenario. The Agency has recently implemented the concept of index reservoirs (IR) and the percent crop treated area (PCA) to better estimate potential residues levels in drinking water sources. The scenarios used with PRZM and EXAMS to estimate of lactofen and acifluorfen in the "standard pond" were rerun with the IR for the cotton and soybean scenarios. The Agency has estimated that the percent crop treated area (PCA) for the Mississippi Cotton scenario is 0.20 (20 %)

The highest estimated peak concentrations for acifluorfen and lactofen for cotton in the index reservoir adjusted for PCA were 10.36 and 0.52 µg/L, respectively. The highest long term averages for acifluorfen and lactofen for cotton in the IR adjusted for PCA were 0.72 and 0.012 µg/L, respectively.

4.2.4. Dietary Risk from Water Sources

OPP has calculated drinking water levels of comparison (DWLOCs) for acute and chronic exposure to lactofen and acifluorfen in surface and groundwater which are presented in Tables 6 and 7. The $DWLOC_{acute}$ is the concentration in drinking water as a part of the aggregate acute exposure that occupies no more than 100% of the acute PAD. Typically, to calculate the DWLOC for acute exposure relative to an acute toxicity endpoint, the acute dietary food exposure (from the DEEMTM analysis) was subtracted from the acute PAD. However, since the dietary component for acifluorfen has not yet been determined, the $DWLOC_{acute}$ assumes that all of the exposure is from drinking water.

The $DWLOC_{chronic}$ is the concentration in drinking water as a part of the aggregate chronic exposure that occupies no more than 100% of the chronic PAD. To calculate the DWLOC for chronic (non-cancer) exposure relative to a chronic toxicity endpoint, the chronic dietary food exposure (from DEEMTM) was subtracted from the chronic PAD to obtain the acceptable chronic (non-cancer) exposure to lactofen and acifluorfen in drinking water. DWLOCs were then calculated using default body weights and drinking water consumption figures. A $DWLOC_{cancer}$ was calculated in a similar manner, assuming a negligible risk of 1×10^{-6} . Since the dietary component for acifluorfen has not yet been determined, the DWLOCs for chronic and cancer risk assume that all of the exposure is from drinking water. Assumptions used in calculating the DWLOCs include 70 kg body weight for the US population, 60 kg body weight for adult females, 10 kg body weight for children, two liters of water consumption per day for adults, and one liter consumption for children.

Table 6a. DWLOCs for Chronic Exposure to Lactofen						
Population Subgroup	Chronic Scenario					
	Chronic PAD (mg/kg/day)	Food Exposure (mg/kg/day)	Maximum Water Exposure (mg/kg/day)	EEC SCI-GROW $\mu\text{g/L}$	EEC - PRZM/ EXAMS (IR) $\mu\text{g/L}$	DWLOC (CHRONIC) ($\mu\text{g/L}$)
U.S. Population	8.00e-03	1 x 10 ⁻⁶	8.00e-03	0.006	0.022	280.0
Children 1-6	8.00e-03	2 x 10 ⁻⁶	8.00e-03	0.006	0.022	80.0

Table 6b. DWLOCs for Acute Exposure to Lactofen						
Population Subgroup	Acute Scenario					
	Acute PAD (mg/kg/day)	Food Exposure (mg/kg/day)	Maximum Water Exposure (mg/kg/day)	EEC SCI-GROW $\mu\text{g/L}$	EEC - PRZM/ EXAMS (IR) $\mu\text{g/L}$	DWLOC (Acute) ($\mu\text{g/L}$)
Females 13+	1.30e-01	2.00e-06	1.30e-01	0.006	0.62	5100.0

Table 6c. DWLOCs for Cancer Risk for Lactofen						
Population Subgroup	Cancer Scenario					
	Q ₁ *	Food Exposure (mg/kg/day)	Maximum Water Exposure (mg/kg/day)	EEC SCI-GROW $\mu\text{g/L}$	EEC - PRZM/ EXAMS $\mu\text{g/L}$	DWLOC (Cancer) ($\mu\text{g/L}$)
U.S. Population	1.19e-01	7.00e-07	5.00e-06	0.006	0.012	0.3

Table 7a. DWLOCs for Chronic Exposure to Acifluorfen from Applied Lactofen						
Population Subgroup	Chronic Scenario					
	Chronic PAD (mg/kg/day)	Food and Residential Exposure (mg/kg/day)	Maximum Water Exposure (mg/kg/day)	EEC SCI-GROW $\mu\text{g/L}$	EEC PRZM/ EXAMS (IR) $\mu\text{g/L}$	DWLOC (Chronic) ($\mu\text{g/L}$)
U.S. Population	4.00e-03	0 ¹	4.00e-03	10.3	0.99	140.0
Children 1-6	4.00e-03	0 ¹	4.00e-03	10.3	0.99	40.0

Table 7b. DWLOCs for Acute Exposure to Acifluorfen from Applied Lactofen						
Population Subgroup	Acute Scenario					
	Acute PAD (mg/kg/day)	Food and Residential Exposure (mg/kg/day)	Maximum Water Exposure (mg/kg/day)	EEC SCI-GROW $\mu\text{g/L}$	EEC PRZM/ EXAMS (IR) $\mu\text{g/L}$	DWLOC (Acute) ($\mu\text{g/L}$)
Females 13+	2.00e-02	0 ¹	2.00e-02	10.3	4.9	600.0

Table 7c. DWLOCs for Cancer Risk for Acifluorfen from Applied Lactofen						
Population Subgroup	Cancer Scenario					
	Q ₁ *	Food and Residential Exposure (mg/kg/day)	Maximum Water Exposure (mg/kg/day)	EEC SCI-GROW $\mu\text{g/L}$	EEC PRZM/ EXAMS (IR) $\mu\text{g/L}$	DWLOC (Cancer) ($\mu\text{g/L}$)
U.S. Population	5.30e-02	0 ¹	2.80e-05	10.3	0.34	0.7

¹ Food and residential exposure are assumed to be zero; actual values are described in the preliminary chapter for acifluorfen (Farwell, 1999). Therefore the aggregate DWLOCs when food exposure is considered will be lower.

HED has a concern if the DWLOC for any scenario is below the estimated environmental concentration from the models. The only scenario for which there is a concern is cancer risk from acifluorfen when lactofen is applied (Table 7c). The DWLOC_{cancer} for acifluorfen is an estimate assuming all the risk is from water. This DWLOC will be even lower once the contribution from food is incorporated in the acifluorfen risk assessment.

4.3 Residential Exposure

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.

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.

5.0 AGGREGATE RISK ASSESSMENT AND RISK CHARACTERIZATION

5.1 Aggregate Risk Assessment

FQPA requires an aggregate risk assessment to be conducted considering all non-occupational sources, including exposure from water, food, and residential use. Lactofen is not used in a residential setting so only food and water need be considered.

Water is not expected to be a significant source of exposure for lactofen, as it degrades quickly in the environment to acifluorfen. Estimated environmental concentrations (EECs) for lactofen *per se* are well below the Drinking Water Levels of Comparison for chronic, acute, and cancer risk. Therefore, the only significant source of human exposure to lactofen *per se* is in food. Residues

are generally non-detectable at a limit of quantitation of 0.005 ppm in all food forms. The exposure is <0.1% of the acute and chronic population adjusted doses (PAD) for all population groups. Exposure is generally not of concern if it is less than 100% of the PAD. The estimated cancer risk for the US population is 8×10^{-8} , which is more than order of magnitude less than the risk that is generally considered negligible (1×10^{-6}). HED does not have a concern for exposure to lactofen from food, nor does it have an aggregate concern for lactofen *per se*.

In the environment, lactofen degrades quickly to acifluorfen, which is also registered as an herbicide. Acifluorfen is both persistent and mobile, and has been found in water monitoring studies. The human health risk assessment has not yet been completed for acifluorfen so an aggregate risk assessment cannot be conducted. However, preliminary considerations suggest that while conversion of lactofen to acifluorfen in water may not be of concern for acute and chronic endpoints, the preliminary Drinking Water Level of Comparison (DWLOC) for cancer risk that considers acifluorfen water risk from lactofen applications only is below the Estimated Environmental Concentrations (EEC) for both surface water and groundwater. Accordingly, it will be of concern when the food and residential risk from sodium acifluorfen is aggregated in the forthcoming risk assessment for the reregistration eligibility document.

Some environmental studies suggest that lactofen may alternatively degrade to des-ethyl lactofen (PPG-947) instead of acifluorfen. OPP does not have sufficient information to model the concentrations of des-ethyl lactofen in ground and surface water. In all likelihood, the EECs would be less than those for acifluorfen since PPG-947 is less persistent and mobile than acifluorfen. Therefore, the risk from exposure to acifluorfen in the water is likely to be greater than that of des-ethyl lactofen.

5.2 Cumulative Risk Assessment

Lactofen is a member of the diphenyl ether group of herbicides, as are sodium acifluorfen and oxyfluorfen. EPA has some evidence that these compounds induce similar toxic effects but has not yet determined whether or not these compounds exhibit a common mechanism. In addition, the Agency is in the process of developing methodology to conduct a cumulative risk assessment. For this preliminary assessment of lactofen, therefore, EPA is not conducting a cumulative risk assessment.

The Agency will, however, consider the relative contribution of each of these related pesticides to the multichemical and multiroute aggregated risks due to acifluorfen from use of sodium acifluorfen as a herbicide or environmental degradation of lactofen. This discussion will be included in the sodium acifluorfen risk assessment.

6.0 TOLERANCE REASSESSMENT RECOMMENDATIONS

6.1 Tolerance Reassessment Recommendation

HED has sufficient residue data for reassessing the tolerances in/on snap beans and soybeans, and setting tolerances in/on cottonseed and peanuts. A summary of the recommended tolerance levels is presented in Table 8.

Table 8. Tolerance Reassessment Summary for Lactofen.

Commodity	Current Tolerance (ppm) ^a	Range of residues (ppm)	Tolerance Reassessment ^b (ppm)	Comment/Correct Commodity Definition
Tolerances listed under 40 CFR §180.432(a):				
Beans, snap	0.05	<0.01	0.01	<i>Beans, snap, succulent (excluding Limas)</i>
Cottonseed	0.05 ^c	<0.01	0.01	<i>Cotton, undelinted seed</i>
Soybean	0.05	<0.005-0.007	0.01	<i>Soybean, seed</i>
Tolerances needed under 40 CFR §180.432(a):				
Cotton, gin byproducts	None	<0.01-0.03	0.02	
Peanut	None	<0.01	0.01	

^a Currently expressed in terms of lactofen and metabolites containing the diphenyl ether linkage.

^b Expressed in terms of lactofen.

^c Time limited tolerance for cottonseed expired on 12/31/96.

6.2 Codex/International Harmonization

No maximum residue limits (MRLs) for lactofen have been established or proposed by Codex for any agricultural commodity. Therefore, no compatibility questions exist with respect to U.S. tolerances.

7.0 DATA NEEDS

- Developmental Toxicity Study in Rabbits.
- The following physical/chemical properties studies are required for the for the 76%T (EPA Reg. No. 59639-94): 830.6317, 830.6320, 830.7050, and 830.7100.
- The following physical/chemical properties studies are required for the for the 60%FI (EPA Reg. No. 59639-70): 830.6302, 830.6303, 830.6304, 830.6313, 830.6314, 830.6315, 830.6316, 830.6317, 830.6319, 830.6320, 830.7000, 830.7050, 830.7100, 830.7200, 830.7220, and 830.7300. These data are required because the product composition has changed significantly as a result of a change in the manufacturing process.
- Confined Rotational Crop Study (860.1850)