Lactofen Summary Document: Registration Review

January 2007

Lactofen Summary Document
Registration Review: Initial Docket
January 2007

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I. Preliminary Work Plan

Introduction:

The Food Quality Protection Act of 1996 mandated a new program: **registration review**. All pesticides distributed and sold in the United States must be **registered** by EPA, based on scientific data showing that they will not cause unreasonable risks to human health, workers, or the environment when used as directed on product labeling. The new registration review program is intended to make sure that, as the ability to assess risk evolves and as policies and practices change, all registered pesticides continue to meet the statutory standard of no unreasonable adverse effects. Changes in science, public policy, and pesticide use practices will occur over time. Through the new registration review program, the Agency periodically reevaluates pesticides to make sure that as change occurs, products in the marketplace can be used safely. Information on this program is provided at: http://www.epa.gov/oppsrrd1/registration_review/.

The Agency has begun to implement the new Registration Review program, and will review each registered pesticide approximately every 15 years to determine whether it continues to meet the FIFRA standard for registration. The public phase of registration review begins when the initial docket is opened for each case. The docket is the Agency's opportunity to state clearly what it knows about the pesticide and what additional risk analyses and data or information it believes are needed to make a registration review decision. Lactofen is one of the first chemicals going through the registration review process.

Anticipated Risk Assessment and Data Needs:

The Agency anticipates conducting a comprehensive ecological risk assessment, including an endangered species assessment for all uses. The Agency also anticipates that occupational risk assessments may be needed for some uses.

Ecological Risk:

- Ecological risk assessments for most lactofen uses were completed several years ago, and the Agency has not conducted a risk assessment that supports a complete endangered species determination. Please refer to Section III, Ecological Risk Assessment Problem Formulation, for a detailed discussion of the anticipated risk assessment needs.

- The Agency anticipates needing the following data in order to conduct a complete ecological risk assessment, including an endangered species assessment, for all uses:
    - (GLN 850.4250) Vegetative Vigor (Tier 2) for lactofen
    - (GLN 850.4225) Seedling Emergence (Tier 2) for lactofen
    - (GLN 850.1350) Reproduction Estuarine/Marine Invertebrates for lactofen and degradate (acifluorfen)
    - (GLN 850.1400) Freshwater Fish Early-Life Stage for degradate (acifluorfen)

- (GLN 850.2300) Avian Reproduction Test with two species: bobwhite quail and mallard duck for lactofen

Human Health Risk:

- The Agency believes that previously completed dietary assessments are adequate and that there is no dietary risk that exceeds the Agency's level of concern (LOC). Thus, no additional data are needed.
- Occupational risk assessments may be needed for uses on soybeans, cotton, and in forestry; however, no additional data are needed to complete these assessments. Please refer to Section IV of this document, HED Scoping Document, for a detailed discussion of the anticipated risk assessment needs for human health.

Timeline:

EPA has created the following estimated timeline for the completion of the lactofen registration review. The Agency may conduct the occupational assessment for cotton, soybean and forestry uses much earlier in the process, allowing mitigation (if necessary) to occur well before the 5.5 years elapse.

Activities	**Estimated Month/Year**
Phase 1: Opening the docket	
Open Public Comment Period for Lactofen Docket	Jan. 2007
Close Public Comment Period	Apr. 2007
Phase 2: Case Development	
Develop Final Work Plan (FWP)	May 2007
Issue DCI	Mar. 2008
Data Submission	Mar. 2010
Open Public Comment Period for Preliminary Risk Assessments	July 2011
Close Public Comment Period	Sept. 2011
Phase 3: Registration Review Decision	
Open Public Comment Period for Proposed Reg. Review Decision	Dec. 2011
Close Public Comment Period	Feb. 2012
Final Decision and Begin Post-Decision Follow-up	June 2012
Total (years)	5.5

Guidance for Commenters:

The public is invited to comment on EPA's preliminary registration review work plan and rationale. The Agency will carefully consider all comments as well as any additional information or data provided prior to issuing a final work plan for the lactofen case.

Through the registration review process, the Agency intends to solicit information on trade irritants and, to the extent feasible, take steps toward facilitating irritant resolution. Growers and other stakeholders are asked to comment on any trade irritant issues

resulting from lack of Maximum Residue Limits (MRLs) or disparities between U.S. tolerances and MRLs in key export markets, providing as much specificity as possible regarding the nature of the concern.

Stakeholders are also specifically asked to provide information and data in the following areas.

1. What is the frequency of application, application intervals, and maximum number of applications per season for use sites for which you have experience or knowledge (especially forestry uses)?
2. What is the application timing, such as season and time of day for use sites?
3. Do you know of any emerging equipment or cultural practices that could reduce lactofen exposure to workers or the environment?
4. Neither lactofen nor sodium acifluorfen, a degradate of lactofen, are identified as causes of impairment for any waterbodies listed as impaired under section 303(d) of the Clean Water Act, based on information provided at http://oaspub.epa.gov/tmdl/waters_list.impairments?p_impid=3. The Agency invites submission of water quality data for these chemicals. To the extent possible, data should conform to the quality standards in Appendix A of the "OPP Standard Operating Procedure: Inclusion of Impaired Water Body and Other Water Quality Data in OPP's Registration Review Risk Assessment and Management Process" (reference document with this title in this docket), in order to ensure they can be used quantitatively or qualitatively in pesticide risk assessments.

Next Steps:

After the comment period closes in April 2007, the Agency will prepare a Final Work Plan for this pesticide.

II. FACT SHEET

Background Information:

- Lactofen registration review case number: 7210
- Lactofen PC Code: 128888 CAS#: 77501-63-4
- Technical registrant: Valent U.S.A Corporation
- First approved for use in a registered product in 1987
- Lactofen shares a common degradate, acifluorfen, with sodium acifluorfen (PC Code: 114402) (CAS#: 62476-59-9)
- Not subject to reregistration (no Reregistration Eligibility Decision [RED])
- Tolerance Reassessment Eligibility Decision (TRED) completed in 2003
- Special Review and Reregistration Division Chemical Review Manager (CRM): Amaris Johnson: johnson.amaris@epa.gov
- Registration Division Product Manager (PM): Joanne Miller: miller.joanne@epa.gov

Use & Usage Information: (For additional details, please refer to the BEAD Appendix A document in the lactofen docket.)

- Lactofen is an herbicide used on soybeans, snap beans, peanuts, and cotton; additionally there are uses on strawberries (non-bearing), kenaf (fibers), and in forestry.
- There are no residential uses.
- There are pending new use registrations for okra and fruiting vegetables.
- Approximately 85,000 pounds of lactofen are used annually.
- Lactofen accounts for 5% or less of the crop treated in each of its use sites.
- Pests controlled include amaranth, balloonvine, morning glory, common ragweed, and broadleaf weeds.
- There are six section 3 registrations, and eleven section 24(c) registrations (Special Local Need).

Recent Actions:

- In November 2006, the Agency conducted human health and ecological risk assessments based on pending new IR-4 uses for okra and fruiting vegetables. These assessments are included in the lactofen docket.
- A final rule for lactofen was issued on September 2004 (69 FR 57216) that established tolerances on peanuts and cotton seed and decreased tolerances in or on snap beans, and soybeans. This action included all tolerances, both the new tolerances and the tolerances reassessed by the 2003 TRED.

Ecological Risk Assessment Status:

The following ecological outcomes are anticipated based on the limited data and risk assessments currently available. Please refer to Section III, Ecological Risk Assessment Problem Formulation, for a detailed discussion of the anticipated ecological risk assessment needs. A summary follows:

- Acute and chronic risk to listed and non-listed birds may exceed the Agency's level of concern (LOC).
- Acute risk to listed and non-listed mammals is unlikely to exceed the Agency's LOC.
- Chronic risk to listed and non-listed mammals may excced the Agency's LOC.
- Acute and chronic risk to listed and non-listed fish is unlikely to exceed the Agency's LOC.
- Acute risk to listed and non-listed aquatic invertebrates is unlikely to exceed the Agency's LOC.
- Chronic risk to listed and non-listed marine/estuarine invertebrates may exceed the Agency's LOC.
- Risk to listed and non-listed terrestrial plants is likely to exceed the Agency's LOC due to the compounds mode of action.
- Risk to listed and non-listed aquatic plants is unlikely to exceed the Agency's LOC.

Human Health Risk Assessment Status:

Please refer to Section IV of this document, Human Health Effects Scoping Document, for a detailed discussion of the anticipated risk assessment needs for human health. A summary follows:

Dietary (Food and Water):

- The most recent acute and chronic dietary assessments were conducted in 2006 to support the registration of pending new uses on okra and fruiting vegetables.
- This 2006 assessment included an aggregate assessment that considered dietary exposure to lactofen from both food and water.
- Acifluorfen is a degradate of lactofen and sodium acifluorfen, and has been found in potential drinking water sources. The aggregate risks from exposure to acifluorfen from sodium acifluorfen, as well as from the environmental degradation of lactofen to acifluorfen, are included in the 2006 assessment.
- There are no dietary risks that exceed the Agency's LOC.

Residential:

- There are no residential uses of lactofen. However, there are two sodium acifluorfen registrations (EPA Reg. #s: 71995-3 and 4-433) that have residential uses.
- Aggregate risk assessments were conducted for the 2005 Sodium Acifluorfen RED, including all dietary exposures to acifluorfen (from sodium acifluorfen and lactofen) and the residential exposures.
- All aggregate acifluorfen exposures are below the Agency's LOC.

Occupational:

- An occupational assessment was conducted as a part of the 2006 risk assessments for the pending new uses on okra and fruiting vegetables.
- An occupational assessment on snap beans was conducted in 2005.

- An occupational assessment was conducted in 2004 for new use registration actions on peanuts and cotton.
- The most recent occupational assessments for cotton and forestry uses were conducted in 1987.

Tolerances:

- No MRLs for lactofen have been established or proposed by Codex for any agricultural commodities.
- There are no Canadian or Mexican MRLs for lactofen.
- U.S. tolerances are listed under 40 CFR 180.432 and are reassessed at 0.01 ppm except for cotton gin byproducts reassessed at 0.02 ppm.

Data Call-In Status:

- A data call-in was issued in January 2005 for the following studies from the 2003 Lactofen TRED:
    - Prenatal Developmental Toxicity Study in Rabbits (OPPTS Guideline Number 870.3700). In March 2003, the registrant submitted a 90-day response in which they requested a data waiver for this study; the Agency has granted this waiver.
    - Confined Rotational Crop Study (OPPTS Guideline Number 860.1850). This study has been reviewed; additional supporting information regarding the storage stability of some commodities is needed and has been requested.
    - UV/Visible Absorption (OPPTS Guideline Number 830.7050). This study has been received and is in review.

- A data call-in was issued in January 2006 for the class of light dependent peroxidizing herbicides (LDPHs), of which lactofen is one, that included a Special Ecotoxicity Study to assess the effect of light on LDPHs.

Labels:

- A list of registration numbers may be found in the lactofen docket and the labels can then be obtained from the Pesticide Product Label System (PPLS) website: http://oaspub.epa.gov/pestlabl/ppls.home.

III. ECOLOGICAL RISK ASSESSMENT PROBLEM FORMULATION

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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

PC Code: 128888
DP Barcode: 323196

MEMORANDUM

Subject: EFED Problem Formulation for Lactofen Registration Review

To: Amaris Johnson
Susan Lewis
Reregistration Division
U.S. EPA, Office of Pesticide Programs

From: Brian Anderson, Biologist
James Wolf, Soil Scientist
Environmental Risk Branch 3
Environmental Fate and Effects Division (7507P)

Thru: Daniel Rieder, Branch Chief
Environmental Risk Branch 3
Environmental Fate and Effects Division (7507P)

Date: December 13, 2006

Attached is EFED's problem formulation document in support of the lactofen registration review docket opening. This memorandum outlines (1) the methods that will likely be used in the ecological risk assessment of lactofen, (2) anticipated LOC exceedances, (3) data gaps, and (4) additional data needs.

1. Problem Formulation

1.1. Pesticide Type, Class, and Mode of Action

Lactofen is a light dependent photoreactive herbicide (LDPH). LDPHs are a class of weed control chemicals that act in plants by inhibiting the enzyme protoporphyrinogen oxidase (protox), which is the last common enzyme in the heme and chlorophyll biosynthetic pathways. Protox exists in both plants and animals, and the enzyme from both sources has been shown to be sensitive to many LDPHs.

1.2. Stressor Source and Distribution

Environmental stressors include the active ingredient, lactofen (PC Code 128888), and a primary degradate, acifluorfen. The sodium salt of acifluorfen is also a registered herbicide (PC Code 114402).

The source of environmental exposures to lactofen is from its labeled uses as an herbicide (see Section 1.3.). Lactofen is applied preemergence and/or postemergence by ground or air spray. The release rates for a single application are as high as 0.5 lbs a.i./acre (D319594) and 1 lb a.i./Acre is the highest seasonal limit, although these release rates have not yet been approved. The extent of acreage treated is unknown, but the crops on which it is registered are, collectively, grown throughout the United States.

The primary degradate, acifluorfen, is released to the environment by lactofen degradation via both biotic and abiotic processes. Acifluorfen has been shown to form up to 64% of the applied mass of lactofen in aerobic soil metabolism studies (average was 58%).

1.3. Overview of Pesticide Usage

Lactofen is currently registered nationally on cotton and soybeans. It is also registered for use on conifers, kenaf, peanuts, and strawberries. Lactofen is applied as a preemergence and/or postemergence by ground or air spray.

The currently approved lactofen application rates range from 0.1953 to 0.375 lb a.i./acre for a single application (BEAD, 2005) with a seasonal maximum label rate of 0.40 lb ai/acre. However, single application rates up to 0.5 lbs a.i./Acre (1.0 lb a.i./Acre per season) have been proposed for fruiting vegetables and okra (D319594).

Figures 1.1 and 1.2 below illustrate the extent of soybean and cotton acreage in the United States. These two commodities have the most extensive acreage of the crops labeled for lactofen use.

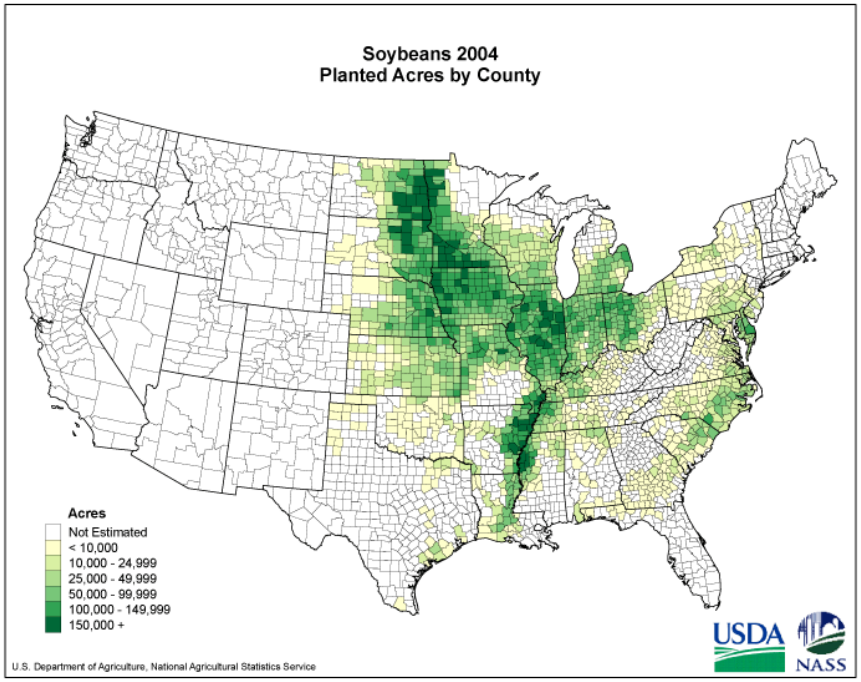


Figure 1.1. Acreage of Soybeans Planted in the United States

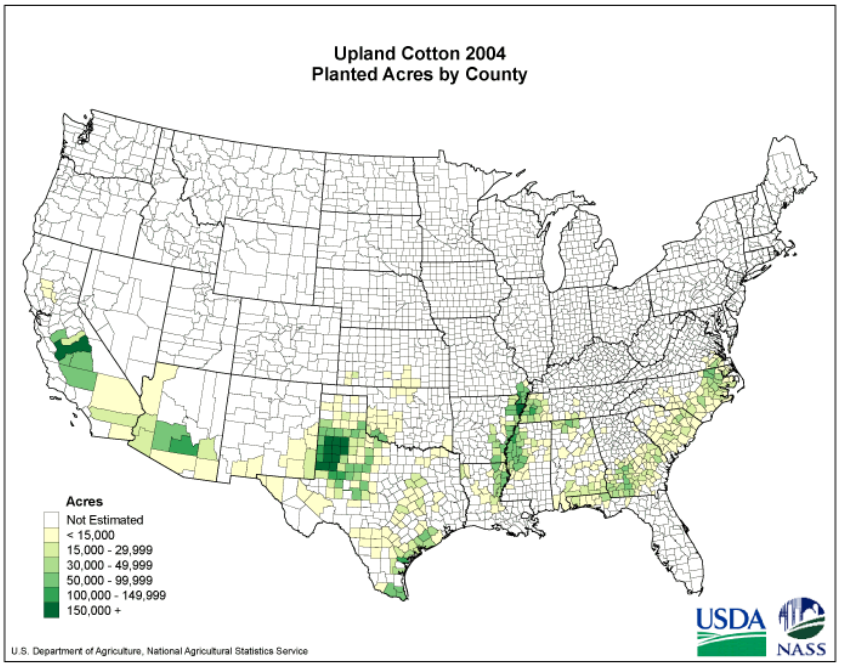


Figure 1.2. Acreage of cotton planted in the United States

1.4. Environmental Fate Summary

1.4.1. Lactofen

When lactofen is released into the environment, it degrades quickly primarily via aerobic soil metabolism and hydrolysis. Lactofen is not persistent (half-life less than 3 days) in the environment, has a high affinity for binding to soil (high K_{oc} values, > 6600 ml/g), and low solubility. Lactofen is not expected to leach to ground water because of its high binding potential and short half-life, which has been confirmed by a prospective ground water (PGW) monitoring study (D283774).

Lactofen degrades to desethyl lactofen and acifluorfen; desethyl lactofen will also degrade to acifluorfen. Other degradates include amino acifluorfen. Desethyl lactofen appears relatively stable to photolysis and hydrolysis at least for the duration of the available studies.

The fate of lactofen in an aquatic system (surface water) is less clear because microbial degradation studies in aquatic systems have not been submitted. However, lactofen is not expected to persist in water because it is subject to hydrolysis and degrades fast in terrestrial environments. Also, it is expected to bind to sediment rather than remain in solution when introduced to aqueous systems. Whether soil- or sediment-bound lactofen will degrade to acifluorfen is not known.

1.4.2. Acifluorfen

Acifluorfen has been shown to form up to 64% (average of 58%) of the applied lactofen in aerobic soil metabolism studies. Acifluorfen can be quite persistent, is highly soluble, and is highly mobile with K_{ads} values ranging from 0.148 to 3.1 mL/g (Table 8, D232775) suggesting a potential to leach to ground water. This has been confirmed by monitoring data. Fate properties and monitoring data from a prospective ground-water study suggest that acifluorfen is persistent in ground water. There is also evidence in that sorption of acifluorfen to different soils can be highly variable depending upon specific soil properties. This variability may explain the difference in leaching seen at different locations.

Acifluorfen will tend to remain in solution rather than bind to sediment, therefore; acifluorfen in runoff will remain in solution. Acifluorfen appear relatively stable to photolysis and hydrolysis at least for the duration of the available studies. Acifluorfen reduces to amino acifluorfen under anaerobic conditions. Amino acifluorfen appears to be persistent but less mobile than acifluorfen in non-sandy soils. Photolysis in water may be one of the possible ways for acifluorfen to degrade in surface water as the aqueous photolysis half-life ranges from 0.9 to 15 days. However, when light penetration is restricted the rate of photolysis would be reduced.

1.5. Ecological Effects Summary

A summary of the available ecotoxicity data on lactofen and acifluorfen is below. Additional information is presented in Section 1.9.

1.5.1. Lactofen

The toxicity of lactofen varies across taxa. It is highly toxic to fish (lowest LC50 is 0.46 mg/L, MRID 153260), moderately toxic to freshwater invertebrates (EC50 = 4.8 mg/L, MRID 153261), and very highly toxic to marine/estuarine invertebrates (LC50 = 0.02 mg/L).

Reproduction studies indicate that lactofen is considerably more toxic on a chronic basis compared with its acute toxicity (at least in fish, chronic studies in other taxa have not been submitted). The only available NOAEC in fish was from an early life stage study and was 0.0014 mg/L (MRID 153264).

The lowest NOAEC in aquatic plants was 0.00064 mg/L. The lowest EC50 in aquatic plants was approximately 0.001 mg/L (MRID 45445805).

Lactofen is classified as practically non-toxic to birds and mammals on an acute oral basis. Reproduction studies in birds are not available. In mammals, a reproduction NOAEC of 50 ppm was reported based on reduced pup weight, which occurred at the LOAEC of 500 ppm.

1.5.2. Acifluorfen

Acifluorfen has been shown to be less toxic to aquatic animals and plants than lactofen. Acifluorfen is slightly toxic to fish (LC50 = 17 mg/L, MRID 122752) and freshwater invertebrates (EC50 = 28 mg/L, MRID 071901) and moderately toxic to marine/estuarine invertebrates (LC50 = 3.8 mg/L, MRID 122755). No definitive chronic or reproduction studies are available on acifluorfen in aquatic animals. The most sensitive aquatic plant NOAEC and EC50 are 0.18 mg/L and 0.378 mg/L, respectively.

Acifluorfen is moderately toxic to birds (LD50 = 325 mg/kg-bw, MRID 122747) and slightly toxic to mammals (LD50 = 1540 mg/kg-bw, MRID 071887) on an acute oral basis. No reproductive effects occurred in a rat 2-generation toxicity study at dietary concentrations up to 2500 ppm (MRID 155548). However, the available reproduction study in birds produced a NOAEC of 20 ppm based on a reduction in viable embryos at 100 ppm.

1.6. Ecosystems at Risk

The terrestrial ecosystems potentially at risk include the treated area and areas immediately adjacent to the treated area that might receive drift or runoff, and might include other cultivated fields, fencerows and hedgerows, meadows, fallow fields or

grasslands, woodlands, riparian habitats and other uncultivated areas. The ecosystems and communities at risk will tend to be those in close proximity to and downwind/downstream/down gradient from these and other registered use sites.
For Tier 1 assessment purposes, risk will be assessed to terrestrial animals that are assumed to feed on and otherwise occupy the treated area. Exposure to animals off the treated site is also possible, but exposure and risk estimates are not likely to be higher than on the treated site. Risk is not assessed to plants occurring on the treated sites, but will be assessed to terrestrial plants assumed to occur in areas immediately adjacent to, and in wetlands receiving runoff from treated areas.

Aquatic ecosystems potentially at risk include water bodies adjacent to, or down stream from the treated field and might include impounded bodies such as ponds, lakes and reservoirs, or flowing waterways such as streams or rivers. For uses in coastal areas, aquatic habitat also includes marine ecosystems including estuaries. For tier 1 assessment purposes, risk will be assessed to aquatic animals and plants assumed to occur in small ponds receiving runoff and drift from treated areas.

1.6.1 Receptors

The aquatic receptors likely to be exposed include fish, invertebrates, aquatic stages of amphibians and plants living in waterways adjacent to or downstream from treated areas.

Terrestrial receptors likely to be exposed to lactofen include birds, mammals, reptiles and terrestrial stages of amphibians that may occur in treated fields and terrestrial plants adjacent to, or down slope from treated areas.

1.6.2. Assessment Endpoints

Assessment endpoints include reduced survival of individuals or reproduction within populations and/or adverse effects to communities. Organisms potentially exposed include terrestrial and aquatic plants and animals. Potential effects are determined through testing of surrogate representatives within those taxonomic groups, or from other related taxonomic groups. Assessment endpoints and toxicity data used to evaluate the assessment endpoints are identified in Table 1.

Table 1. Summary of assessment endpoints and proposed measures of effects for screening level risk assessment of lactofen and its primary degradate, acifluorfen

Assessment Endpoint	Measurement Endpoint
1. Survival, reproduction, and growth of **birds** (Birds also serve as surrogates for reptiles and terrestrial phase amphibians in that birds are generally more sensitive than species from these other taxonomic groups.)	Acute oral LD_{50} values, subacute 5-d dietary LC_{50} values (lactofen, degradate) Avian reproduction study NOAEC (lactofen, degradate)* *Currently, no reproduction study using lactofen has been submitted, requesting a study for mallard duck and bobwhite quail (71-4) has been proposed.
2. Survival, reproduction, and growth of **mammals**	Acute oral mammalian LD_{50} values (lactofen, degradate) Mammal 2-generation reproduction study NOAEC or NOAEL (lactofen, degradate)
3. Survival and reproduction of **freshwater fish** and **invertebrates** (Fish also serve as surrogates for aquatic phase amphibians because fish are generally more sensitive than amphibians)	Freshwater fish 96-h LC_{50} and early life-stage NOAEC (lactofen, degradate)* Freshwater invertebrate 48-h EC50 and life cycle NOAEC (lactofen, degradate)* *Currently, no acceptable reproduction study in fish using acifluorfen has been submitted, requesting a study (72-4) has been proposed. Also, reproduction studies in freshwater invertebrates are not available for either lactofen or acifluorfen. See Table 4 for an evaluation of the need for these studies.
4. Survival and reproduction of **estuarine/marine fish** and **invertebrates**	Estuarine/marine fish 96-h LC_{50} and early life-stage NOAEC (lactofen, degradate)* Estuarine/marine invertebrate 96-h LC_{50} (lactofen and acifluorfen) and life cycle NOAEC (lactofen, degradate)* *Currently, no reproduction study using lactofen or acifluorfen has been submitted, requesting a study (72-4) has been proposed for mysid shrimp. Existing (or other requested) data are thought to be sufficient to allow for risk conclusions regarding marine/estuarine fish.
5. Perpetuation of non-target **terrestrial plants** (crops and non-crop species)	Monocot and dicot seedling emergence EC_{25}, EC_{05}, or NOAEC (lactofen* and degradate) Monocot and dicot vegetative vigor EC_{25}, EC_{05}, or NOAEC (Lactofen*) * Currently, no acceptable study using lactofen has been submitted, requesting a study (123-1) has been proposed.
6. Survival of beneficial insect populations (Terrestrial invertebrates are represented by the honey bee)	Honey bee acute contact LD_{50} (lactofen, degradate)
7. Maintenance and growth of **aquatic plants** from standing crop or biomass	Aquatic plant growth and biomass 96-h EC_{50} (lactofen, degradate) Aquatic plant growth and biomass 96-h EC_{05} or NOAEC (lactofen, degradate)

LD_{50} : Lethal dose to 50% of test population
LC_{50} : Lethal concentration to 50% of the test population
EC_{50} : median effect concentration is the concentration that results in a specific effect (e.g., immobility, emergence) to 50% of the exposed test population
EC_{05} and EC_{25} : the concentration that results in a specific effect to 5% and 25%, respectively, of the exposed test population.
NOAEC = No observed adverse effect concentration

1.7. Conceptual Model

The conceptual model is generally that once released from agricultural sprayers, most lactofen will settle on the target site and some will drift off site. That which settles on the target site will either remain there, percolate into the soil, or runoff with surface water. Some may also volatilize. Because lactofen is expected to degrade to acifluorfen rapidly in the environment, and the sodium salt of acifluorfen is an herbicide, this assessment will consider exposure to both lactofen and acifluorfen.

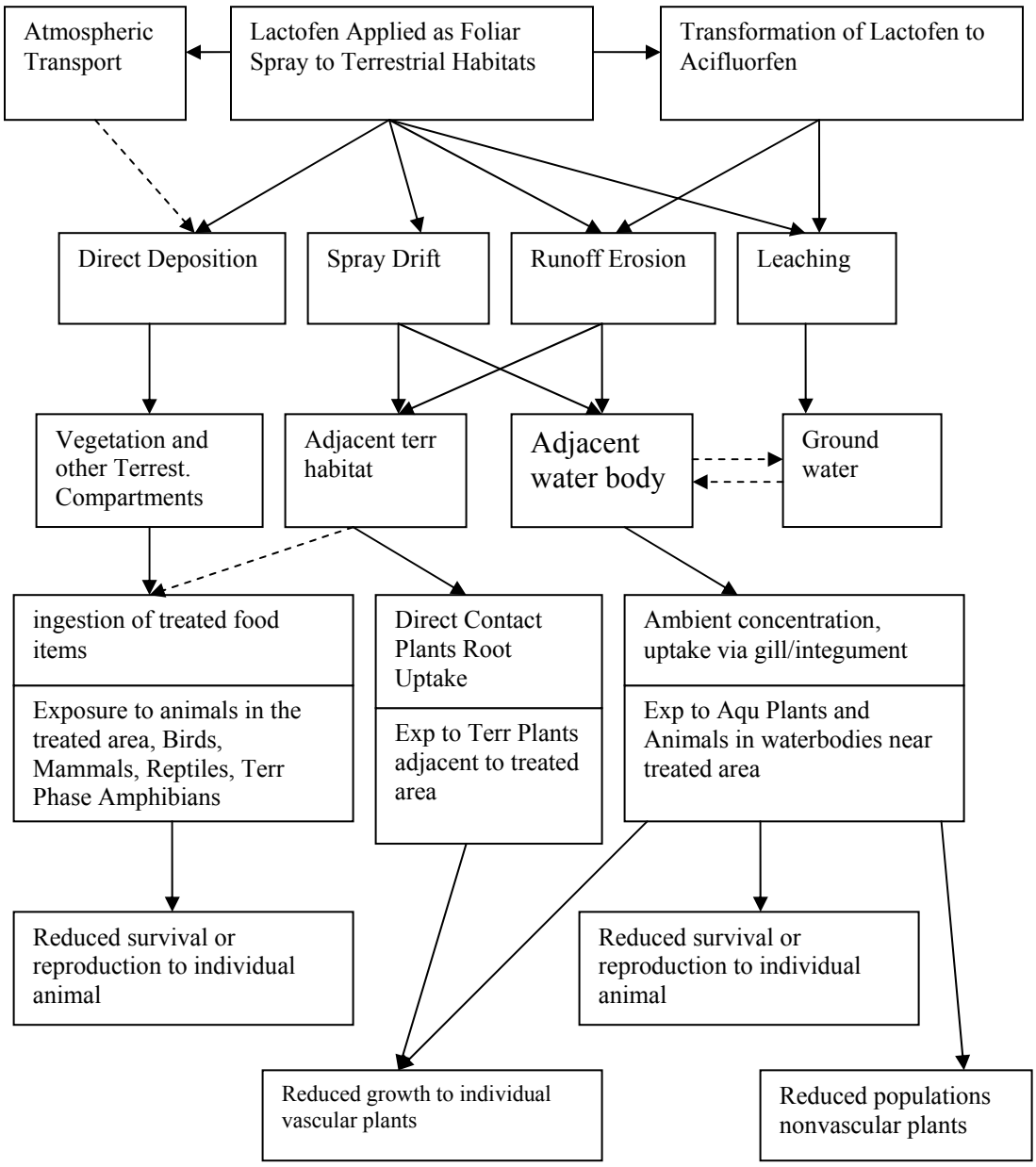


Figure 3. Conceptual Model Diagram: Foliar Spray to Terrestrial Habitats

1.8. Risk Hypotheses

Hypothesis: *Nontarget terrestrial and aquatic plants and animals are at risk of direct and indirect effects resulting from labeled uses of lactofen.*

1.9. Analysis Plan

The analysis plan is the final step in Problem Formulation. During this step, measurements of effect and exposure used to evaluate the risk hypotheses are delineated, and initial data gaps and assumptions required to address them are identified. The Analysis Plan provides a synopsis of measures that will be used to evaluate risk hypotheses. There are three categories of measures: exposure, effects, and risk.

1.9.1. Measures of Exposure

The measures of exposure will be estimated using models. Aquatic exposure will consist of aquatic EECs derived using a waterbody that is vulnerable and representative of static ponds and first order waterways. Terrestrial exposure will be estimated using a model that assumes direct application to a variety of avian, mammalian and reptilian food items. Exposure to terrestrial plants will be estimated using a model that assumes lactofen drifts or moves with runoff to adjacent habitats.

Exposures will be estimated for both lactofen and acifluorfen. For both aquatic and terrestrial exposures, acifluorfen concentrations will be simulated separately from lactofen using the assumption that acifluorfen forms 58% of the lactofen rate. This will be performed by applying a 58% adjustment factor to the maximum labeled lactofen application rate (maximum labeled application rate x 0.58 = acifluorfen "application rate") by ground application seven days after lactofen is applied. The spray drift contribution will be assumed to be zero for acifluorfen.

Based on preliminary modeling for this problem formulation, an application rate of 0.5 lb ai/acre twice a season (slightly higher than any current labeled rates) may produce aquatic lactofen EECs of 0.48 ug ai/L (peak), 0.095 ug a.i./L (21-day) and 0.051 ug a.i./L (60-day). The peak acifluorfen aquatic EEC was approximately 18 ug/L. Based on acifluorfen's expected persistence in water, longer term EECs used in ecological risk assessment are expected to be slightly lower than 18 ug/L. Preliminary terrestrial EECs are presented in Section 1.12 for both lactofen and acifluorfen.

1.9.2. Measures of Effect

Aquatic Plants and Animals

The technical grade (TG) of lactofen is only slightly soluble (0.1 mg a.i./L), and studies with the TGAI on aquatic animals yielded questionable results because of solubility problems. The typical end-use product (TEP) is formulated to increase its solubility.

EFED has reviewed studies with a TEP that found that lactofen is highly toxic to fish (Bluegill sunfish LC_{50} = 0.46 mg a.i./L [460 ug a.i./L]) and moderately toxic to daphnids (LC_{50} = 4.85 mg a.i./L). Technical grade lactofen was shown to be very highly toxic to mysid shrimp (LC50 = 0.020 mg/L).

The available data suggests that acifluorfen is less toxic than lactofen to aquatic animals on an acute basis. Acute LC50s in freshwater fish and invertebrates are 17 mg/L and 28 mg/L, respectively, which classify acifluorfen as slightly toxic. Acifluorfen is moderately toxic to mysid shrimp with an LC50 of 3.8 mg/L.

Early life stage studies in fathead minnows have been submitted on both lactofen and acifluorfen. The NOAEC for lactofen was 0.0014 mg/L (MRID 153264). A NOAEC for acifluorfen was not achieved in the available study (MRID 124222, effects occurred at all concentrations, 1.5 mg/L and higher).

The most sensitive aquatic plant tested for lactofen was *Skeletonema costatum.* The NOAEC and EC50 for *S. costatum* were 0.64 ug/L and 0.99 ug/L, respectively (MRID 42445808). NOAECs in other aquatic plants ranged from 3 ug/L to 31 ug/L for lactofen. Sodium acifluorfen is considerably less toxic to aquatic plants. The lowest NOAEC and EC50 for sodium acifluorfen were 180 ug/L and 378 ug/L, respectively (MRID 41680702).

Terrestrial Organisms

Lactofen is practically nontoxic to birds on an acute oral and subacute dietary basis (LD_{50} >2510 mg/kg-bw (MRID 119529), LC_{50} >5620 ppm (MRID 118530)). Acifluorfen is moderately toxic to birds (LD50 = 325 mg/kg-bw, MRID 122747) on an acute oral basis, but is practically non-toxic to birds on a dietary subacute basis with LC50s >5620 ppm to >10,000 ppm (MRID 083060 and MRID 122749). Avian reproduction tests on lactofen were not submitted and are not available from open literature. An avian NOAEC of 20 ppm was observed in bobwhite quail (MRID 107491) and 100 ppm (MRID 107492) in mallard ducks for sodium acifluorfen.

Lactofen is practically non-toxic to mammals (LD50 = 5960 mg/kg-bw) and acifluorfen is slightly toxic (LD50 = 1540 mg/kg-bw) on an acute oral basis. The rat 2-generation NOAEC was 50 ppm for lactofen based on reduced pup weight at the LOAEC of 500 ppm. The reproductive rat 2-generation NOAEC was 2500 ppm for acifluorfen (the highest concentration tested, MRID 155548).

Lactofen is practically non-toxic to honey bees with an LD50 of >160 µg a.i./bee. Honey bee data on acifluorfen are not available.

The terrestrial plant studies on lactofen did not fulfill the data requirements for plants. Repeat of these studies using the formulated end-use product Cobra 2E (22%) with Crop oil (0.125% to 1 % v/v) would provide useful information. If these studies are repeated, the crop oil must be in the ratio of volume of the oil to **total** volume of the mix.

The measures of effects will either be the results of actual tests or will be derived or assumed based on other data. Where data are lacking and extrapolated effects endpoints cannot be reliably estimated, risk will be presumed unless data are submitted. In cases where risk is presumed, but cannot be quantified based on lack of data, conservative assumptions will be made, and some analyses will not be able to be conducted. For example, effectiveness of risk mitigation measures cannot be evaluated without quantification of RQs.

The following table lists the specific toxicity values that will be used to assess risk to receptors.

Table 2. Summary of assessment endpoints and proposed measures of effects for screening level risk assessment of lactofen

Assessment Endpoint	Measurement Endpoint	
1. Survival, reproduction, and growth of **birds**	Acute oral LD_{50}	Lactofen LD50>2510 mg/kg bw Degradate LD50: 325 mg/kg-bw
	5-day dietary LC_{50}:	Lactofen and degradate LC50>5620 ppm
	Avian reproduction	Lactofen NOAEC: Data not available Degradate NOAEC: 20 mg/kg-diet
2. Survival, reproduction, and growth of **mammals**	Acute oral LD_{50}	Lactofen LD50: 5960 mg/kg bw Degradate LD50: 1540 mg/kg-bw
	Reproduction	Lactofen NOAEC: 50 ppm Degradate NOAEC: 2500 mg/kg-diet
3. Survival and reproduction of **freshwater fish** and **invertebrates**	Fish, Acute	Lactofen 96-h LC_{50}: 0.460 mg/L Degradate 96-hr LC50: 17 mg/L
	Fish, Chronic	Lactofen Early life stage NOAEC: 0.0014 mg/L Degradate Early life stage NOAEC: Not available
	Invertebrate, Acute	Lactofen 48-hr EC50: 4.85 mg/L Degradate 48-hr EC50: 28 mg/L
	Invertebrate, chronic	Lactofen and degradate: NOAEC: None available
4. Survival and reproduction of **estuarine/marine fish** and **invertebrates**	Fish, Acute	Lactofen 96-h LC_{50} >0.032 mg/L
	Fish, Chronic	Degradate 96-hr LC50: 39 mg/L
	Invertebrate, acute	Lactofen 96-hr LC50: 0.02 mg/L Degradate 96-hr LC50: 3.8 mg/L
	Invertebrate, chronic	Lactofen and degradate NOAEC: None available
5. Perpetuation of non-target **terrestrial plants** (crops and non-crop species)	Seedling Emergence:	Lactofen: No valid data available Degradate: EC25, 0.088 lbs a.i./Acre
	Vegetative Vigor	Lactofen: No valid data available
6. Survival of beneficial insect populations		Lactofen: Honey bee acute contact LD_{50}>160 ug/bee Acifluorfen: Honey bee acute contact LD_{50}
7. Maintenance and growth of **aquatic plants** from standing crop or biomass		Lactofen: EC50 1 ug/L; NOAEC 0.6 ug/L Degradate: EC50 378 ug/L; NOAEC 180 ug/L

1.9.3. Preliminary Identification of Data Gaps

The following table identifies the studies that are missing or unacceptable, but that are normally available to derive toxicity results used to assess risk to the environment. Because lactofen breaks down rapidly to acifluorfen, data for both substances are needed for risk assessment. An evaluation of the uncertainty that each of these data gaps introduces to ecological risk assessment is discussed below.

Table 3. Preliminary Identification of Data Gaps

Taxa	Acute study	Chronic/Reproduction study
Freshwater Fish		Acifluorfen
Saltwater Fish		Lactofen, Acifluorfen
Freshwater Invertebrates		Lactofen, Acifluorfen
Saltwater Invertebrates		Lactofen, Acifluorfen
Birds		Lactofen
Terrestrial Plants, Vegetative Vigor	Lactofen	
Terrestrial Plants, Seedling Emergence	Lactofen, Acifluorfen	
Phototoxicity		Lactofen, Acifluorfen

1.9.4. Status of Data Requirements

Fate

Limited environmental fate data have been submitted by the registrant of lactofen (and sodium acifluorfen). Although most of the data requirements have been met, the sample size and/or number of studies are quite small. Thus, there are a number of uncertainties concerning the range and variability of many fate properties. Also many of the studies are quite old (pre-1990), and, therefore, may not meet all the conditions of the current study guidelines. However, additional fate studies are not required at this time to complete a screening-level ecological risk assessment.

Effects

A number of toxicity data gaps have been identified for both lactofen and acifluorfen. The following table presents an evaluation of the uncertainty resulting from the data gap. In some cases, strategies were used to make use of existing data. There is inherent uncertainty associated with not receiving data to fulfill data gaps. However, submission of some studies is unlikely to affect conclusions in the risk assessment, whereas some data gaps are more critical. This determination is made on a case-by-case basis.

Table 4. Evaluation of the need for additional effects data on lactofen

Assessment endpoint with data gap	Chemical	Projected status of data gap	Basis for decision
Perpetuation of non-target terrestrial plants, crops and non-crop species (123-1, vegetative vigor and seedling emergence)	Lactofen	**Proposed to request study**	Scientifically justifiable alternative assumptions to be made concerning potential risk to terrestrial plants in the absence of terrestrial plant toxicity data for an herbicide were not derived. These data are considered critical for herbicides. An action area for endangered species is dependent on toxicity to terrestrial plants. Also, potential mitigation measures cannot be evaluated without valid terrestrial plant studies.
Reproduction and growth of birds (71-4)	Lactofen	**Proposed to request study**	Avian reproduction data are available for acifluorfen, but not lactofen. Lactofen was considerably more toxic than acifluorfen to mammals in reproduction studies. Mammalian reproduction NOAEC is 50 ppm for lactofen compared with the reproduction NOAEC of 2500 ppm for acifluorfen in 2-generation reproduction toxicity studies. Therefore, lactofen may be considerably more toxic than acifluorfen to reproductive endpoints in birds, which suggests that use of an acifluorfen avian NOAEC may result in an under-estimation of risk to birds from use of lactofen. The value of an additional study would be in refining risks to birds including defining an action area for endangered species. Also, risk mitigation strategies could not be evaluated without lactofen data (e.g., would not be able to determine the highest application rate not resulting in LOC exceedance).
Early life-stage FW fish toxicity study (72-4),	**Acifluorfen**	**Proposed to request study**	The available study did not achieve a NOAEC (effects occurred at all concentrations). Assuming equivalent toxicity between lactofen and acifluorfen, RQs would be about 10 – 13 (NOAEC of 1.4 ppb [lactofen]; maximum 60-day acifluorfen EEC expected to be slightly lower than 18 ppb). Dose-response analysis was performed to estimate a NOAEC; however, results were highly uncertain.
Reproduction, estuarine/marine Invertebrates (72-4, 850.1350)	**Lactofen and acifluorfen**	**Proposed to request study**	Mysid shrimp were considerably more sensitive than any other aquatic animal tested in acute studies. Based on acute to chronic ratio for lactofen in fish, RQs would be above the LOC for saltwater invertebrates. Without submission of a study, risk would be presumed to be above the LOC. However, the magnitude of potential risks could not be determined without a study, and an indirect effects assessment would be highly uncertain for listed species that depend on saltwater aquatic invertebrates for sustanence, e.g. shorebirds.
Reproduction, freshwater invertebrates (72-4)	Lactofen, Acifluorefen	Study **not** requested at this time	**Lactofen.** Comparison of the lowest EC50 (4800 ppb) to the 21-day EEC (0.09 ppb) suggests that lactofen would need to be more than 50,000 times more toxic on a chronic basis compared with its acute toxicity to result in chronic LOC exceedances, which is unlikely. **Acifluorfen.** Requested data on saltwater invertebrates are expected to allow for an estimation of toxicity to freshwater invertebrates.

Reproduction of estuarine/marine fish (72-4)	Lactofen, Acifluorefen	Study **not** requested at this time	**Lactofen.** An acute to chronic ratio analysis may be used to evaluate the likelihood of LOC exceedance if data were submitted. The acute to chronic ratio is as follows: Freshwater fish LC50 = 460 ppb Freshwater fish chronic NOAEC = 1.4 ppb Acute to chronic ratio: 460 / 1.4 = 329 Estimated SW fish NOAEC = >32 ppb / 329 = >0.097 ppb Based on this analysis, the chronic RQ for estuarine/marine fish would be approximately 0.5 (60-day EEC of 0.05 ppb / estimated LC50 of 0.097 ppb = 0.5). This approach is thought to be conservative because a definitive LC50 was not observed in the submitted acute saltwater fish study (no effects were observed at any concentration). However, there is uncertainty in the acute to chronic ratio because acute and chronic data were not available in the same species. **Acifluorfen.** Requested data on freshwater fish are expected to allow for an estimation of toxicity to saltwater fish. Saltwater fish were less sensitive than freshwater fish in available acute studies.

As noted in the above table, some data gaps do not result in significant added uncertainty, whereas other data gaps are expected to contribute considerable uncertainty to the risk assessment. In summary, request of the following guideline studies is proposed:

Terrestrial Plant Seedling Emergence and Vegetative Vigor, 123-1 - Lactofen
Avian Reproduction, 71-4 - Lactofen
Mysid Shrimp Life-Cycle, 72-4 - Lactofen and Acifluorfen
Early Life Stage Freshwater Fish Study – Acifluorfen

Without these data, ecological risk assessment would be highly uncertain. Submission of other studies to fulfill data gaps identified in Table 4 would reduce uncertainty; however, supportable conclusions can be made without submission of studies outside of those proposed for testing identified in Table 4 (assuming the requested studies will be submitted).

1.9.5. Phototoxicity

The Aquatic Biology Tech Team (ABTT) recommends that phototoxicity studies be conducted on herbicides with this mode of action to determine if animals exposed to LDPHs and intense light (similar to sunlight) show increased toxicity relative to controls exposed to LDPHs and low intensity light. The results of these studies will help to determine if animals that are exposed to sunlight in LDPH use areas are at higher risk than guideline toxicity studies suggest.

Lactofen, its degradate acifluorfen, and flumiclorac (with which it is coformulated) are all LDPHs. Their end-use product should be assessed for the combination of three LDPH herbicides. A protocol has recently been submitted to the Agency that is expected to allow for a determination of whether (and to what extent) lactofen and its degradate are expected to exhibit increased toxicity in the presence of direct sunlight.

1.10. Open Literature

Before requesting that new ecological effects studies be conducted by the registrant to fulfill these potential data gaps, the Agency will conduct a search of the open literature to determine if the data are indeed already available. If so, an evaluation will be made as to whether or not the data are adequate for use in a risk assessment. The Agency uses the ECOTOX database as its mechanism for searching the open literature. ECOTOX integrates three previously independent databases - AQUIRE, PHYTOTOX, and TERRETOX - into a system which includes toxicity data derived predominately from the peer-reviewed literature, for aquatic life, terrestrial plants, and terrestrial wildlife, respectively. At this point in time, a full and complete ECOTOX search has not been performed, but will be done prior to issuance of any Data Call-In.

A scan of the on-line ECOTOX database shows that the only applicable data in that system are those that are in the EFED files. So far, no open literature studies have been found that might provide useful information in the areas of these data gaps.

1.11. BINNING DECISION

EFED needs additional data (or will apply alternative effects assumptions) and would need to conduct new assessments for all registered outdoor uses. Therefore Lactofen is recommended to be assigned to Bin 1. The new assessments are needed because:

a) Previous assessments did not include risk to terrestrial or aquatic plants, nor avian reproduction risk estimations.
b) Previous assessments were not done with current models and risk assessment calculations
c) Previous assessments did not include open literature as identified by ORD, MED ECOTOX literature search program
d) Some uses were not assessed for ecological risk including soybeans for national registration.

Drinking water is not expected to be a risk issue to humans based on modeling at rates slightly higher than currently registered uses.

1.12. SUMMARY OF RISKS

1.12.1. Summary of Risks identified from Preliminary Analysis for This Problem Formulation

Expected LOC exceedances for both lactofen and acifluorfen are summarized in Table 5 below. Additional discussion if the LOC exceedances are in Sections 1.13.2, 1.13.3, and 1.13.4. All conclusions are preliminary and may change during the risk assessment process.

Table 5. Preliminary identification of LOC exceedances for lactofen and acifluorfen*

Chemical Stressor	Endpoint	Birds	Mammals	Terr. Plants	Insects	Fish	FW Inverts	SW Inverts	Aquatic Plants
Acifluorfen	Acute	✓		✓					
	Reproduction	✓	P			P		✓	
Lactofen	Acute			✓					
	Reproduction	✓	✓					✓	

* All risk conclusions are preliminary and may change over the course of the risk assessment process
✓ Risk is anticipated to be > any of the Agency's LOC
P Risk may or may not be above the Agency's LOC
Blank cells indicate no LOC exceedance

1.12.2. Lactofen

Aquatic Organisms

A summary of anticipated LOC exceedances for lactofen is presented below. Additional detail is provided in Table 6 below. Based on preliminary modeling for this problem formulation, an application rate of 0.5 lb ai/acre twice a season (slightly higher than any current labeled rates) may produce aquatic lactofen EECs of 0.48 ug ai/L (peak), 0.095 ug a.i./L (21-day) and 0.051 ug a.i./L (60-day). Based on a fish LC50 of 460 ug a.i./L, the RQ is less than the acute endangered species LOC of 0.05. Based on a fish NOAEC of 1.4 ug a.i./L, the chronic RQ is less than the chronic LOC of 1. This modeling indicates minimal risk to aquatic animals for endpoints where data are available. However, preliminary risk to marine/estuarine invertebrates is presumed higher than the chronic LOC of 1. Although a chronic NOAEC is not available, chronic risk to marine/estuarine invertebrates is presumed because chronic NOAEC for this taxa would need to be 0.095 ug/L or less to result in LOC exceedance, which is approximately 200 times lower than the acute LC50 value for marine/estuarine invertebrates of 20 ug/L. Acute and chronic data in fish suggest that the acute to chronic ratio may be >200. Therefore, chronic risk to marine/estuarine invertebrates is anticipated to be above the LOC. Also, aquatic plant studies are anticipated to be upgraded from invalid to supplemental. These upgraded studies suggest that potential risks to aquatic plants is expected to be lower than LOCs.

Table 6. Aquatic EECs and RQs for lactofen based on two 0.5 lb ai/acre applications per season

Taxa	Toxicity	EEC	RQ
Fish	Acute LC50: 460 ug a.i./L	0.48 ug a.i./L (peak EEC)	RQ<LOC
	Chronic NOAEC: 1.4 ug a.i./L	0.051 ug a.i./L (60-day EEC)	RQ<LOC
Aquatic Invertebrate	Acute EC50: 4.85 mg a.i./L	0.48 ug a.i./L	RQ<LOC
	Chronic NOAEC: unavailable	0.095 ug/L	**
Aquatic plants	Lemna gibba, NOAEC 0.6 ug/L.	0.48 ug a.i./L	RQ<LOC
Estuarine/marine invertebrates	Mysid shrimp, LC50: 20 ug/L	0.48 ug a.i./L	RQ <LOC
	Mysid shrimp NOAEC: unknown	0.095 ug/L	**RQ > LOC**$^{++}$

** Valid chronic NOAEC is not available. However, chronic risks are not likely to be above the LOC of 1. Lactofen would need to be approximately 50,000 times more toxic on a chronic basis relative to its acute basis to result in risk at levels that exceed the LOC.

++ Chronic NOAEC is not available in marine/estuarine invertebrates. Risk is anticipated to be above the LOC of 1.0 based on the high sensitivity of mysid shrimp in acute studies relative to freshwater fish and the proximity of the freshwater fish chronic RQ to the LOC (e.g., the freshwater fish NOAEC is approximately 16 times higher than the 21-day EEC, and the mysid shrimp NOAEC is expected to be >16 times more sensitive than freshwater fish).

Terrestrial Organisms

Because submitted terrestrial plant studies did not provide useful information, definitive risk conclusions cannot be made for terrestrial plants. Since lactofen is an herbicide, there is a presumption of potential risk to plants including endangered species.

Lactofen is practically non-toxic to terrestrial animals from an acute standpoint. Analysis with the Agency's (Terrestrial Residue EXposure) T-REX model produced acute RQs for birds and mammals of <0.1 which is the acute endangered species LOC (Tables 7 - 9). This indicates that lactofen is expected to pose minimal acute risk to avian and mammalian non-target and endangered species. However, reproduction risk quotients for mammals were as high as 28 (Table 8) for lactofen, which is well above the LOC of 1.0. No lactofen reproduction data are available for birds; however, risk is presumably above the LOC for reproduction risk to birds of 1.0 for the following reasons:

- Lactofen was considerably more toxic than acifluorfen to mammals in 2-generation reproduction studies (mammalian reproduction NOAEC = 50 ppm for lactofen compared with the reproduction NOAEC of 2500 ppm for acifluorfen. Therefore, lactofen may be considerably more toxic than acifluorfen to reproductive endpoints in birds.
- LOCs for acifluorfen are expected to exceed the LOC of 1.0.
- Therefore, because lactofen may be more toxic to reproduction of birds than acifluorfen, and acifluorfen reproduction LOCs for birds are expected to be exceeded, reproduction risk to birds for lactofen is also expected. However, the magnitude of exceedances cannot be evaluated at this time.

Table 7. Estimated acute dose-based risk quotients (RQs) for birds assuming two applications at 0.5 lb ai/acre

Food Material	Avian Acute RQs for birds of various weights		
	20 g	100 g	1000 g
Short Grass	0.1*	<0.1	<0.1
Tall Grass	<0.1	<0.1	<0.1
Broadleaf plants/sm insects	<0.1	<0.1	<0.1
Fruits/pods/seeds/lg insects	<0.1	<0.1	<0.1

*This RQ was calculated using a "greater than" toxicity value to represent the LD50. A definitive LD50 was not derived for birds, and there was no mortality at that level, so this RQ of 0.1 is not interpreted as representing a risk of acute effects to birds.

Table 8. Acute and Chronic risk to Mammals, 2 applications at 0.5 lb ai/acre						
Dose-based RQs (Dose-based EEC/LD50 or NOAEL)	**15 g mammal**		**35 g mammal**		**1000 g mammal**	
	Acute	**Chronic**	**Acute**	**Chronic**	**Acute**	**Chronic**
Short Grass	<0.1	27.83	<0.1	23.77	<0.1	12.74
Tall Grass	<0.1	12.75	<0.1	10.90	<0.1	5.84
Broadleaf plants/sm insects	<0.1	15.65	<0.1	13.37	<0.1	7.17
Fruits/pods/lg insects	<0.1	1.74	<0.1	1.49	<0.1	0.80
Seeds (granivore)	<0.1	0.39	<0.1	0.33	<0.1	0.18

Table 9. Acute and Chronic risk to Mammals, 1 application at 0.375 lb ai/acre

Dose-based RQs (Dose-based EEC/LD50 or NOAEL)	15 g mammal		35 g mammal		1000 g mammal	
	Acute	Chronic	Acute	Chronic	Acute	Chronic
Short Grass	<0.1	15.62	<0.1	13.34	<0.1	7.15
Tall Grass	<0.1	7.16	<0.1	6.11	<0.1	3.28
Broadleaf plants/sm insects	<0.1	8.78	<0.1	7.50	<0.1	4.02
Fruits/pods/lg insects	<0.1	0.98	<0.1	0.83	<0.1	0.45
Seeds (granivore)	<0.1	0.22	<0.1	0.19	<0.1	0.10

Insufficient terrestrial plant toxicity information has been received for lactofen. Exposure to nontarget terrestrial plants is possible from application of lactofen from spray drift or runoff. Terrestrial plants, including endangered species are presumed to be at risk because lactofen is an herbicide. However, distance from the treated field that risk may occur cannot be quantified at this time.

1.12.3. Acifluorfen

Aquatic Organisms

The maximum application rate (0.5 lb a.i./A twice a season) may produce a peak aquatic EEC of 18 µg a.i./L for acifluorfen as a degradate of lactofen. Based on the stability of acifluorfen in the environment, 21-day and 60-day EECs are also likely similar to 18 ug/L. This may or may not result in risk quotients above the LOC. These levels may result in potential chronic risks to marine/estuarine invertebrates and freshwater fish, although the available data are not sufficient to allow for chronic RQ calculation for either taxa (Table 10). Confirmatory studies are being requested to allow for risk estimation for these endpoints (see Table 4).

Table 10. Aquatic EECs and RQs for acifluorfen based on two lactofen applications of 0.5 lb ai/acre applications per season			
Taxa	Toxicity	EEC	RQ
Fish	Acute LC50: 17,000 ug a.i./L	18 ug a.i./L (peak EEC)	RQ<LOC
	Chronic NOAEC: None available.	<18 ug a.i./L	Not calculated due to insufficient information
Aquatic Invertebrate	Acute EC50: 28,000 mg a.i./L	18 ug a.i./L	RQ<LOC
	Chronic NOAEC: unavailable	<18 ug a.i./L	Not calculated due to insufficient information
Aquatic plants	Lemna gibba, NOAEC 180 ug/L.	18 ug a.i./L	RQ<LOC
Estuarine/marine invertebrates	Mysid shrimp, LC50: 3,800 ug/L	18 ug a.i./L	RQ <LOC
	Mysid shrimp NOAEC: unknown	<18 ug a.i./L	Not calculated due to insufficient information

Terrestrial Organisms

Analysis with the Agency's (Terrestrial Residue EXposure) T-REX model was performed using an acifluorfen application rate of 58% of the maximum allowed lactofen application rate of 0.5 lbs a.i./Acre, which results in an acifluorfen rate of 0.29 lbs a.i./Acre. The resulting risk quotients for birds and mammals are presented in Tables 11 – 14 below. Based on the assumptions of this analysis, RQs are expected to exceed the all acute LOCs and the chronic LOC for birds for some food items. No LOC exceedances are expected for mammals.

LOC exceedances are also anticipated for terrestrial plants given that acifluorfen is an herbicide.

Table 11. Preliminary Upper 90th Percentile Kenaga, Acute Avian Dose-Based Risk Quotients									
Size Class (grams)	**Adjusted LD50**	**EECs and RQs**							
		Short Grass		**Tall Grass**		**Broadleaf Plants/ Small Insects**		**Fruits/Pods/ Seeds/ Large Insects**	
		EEC	**RQ**	**EEC**	**RQ**	**EEC**	**RQ**	**EEC**	**RQ**
20	234	132	**0.56**	60	**0.258**	74	**0.32**	8.2	0.035
100	298	75	**0.25**	34	**0.115**	42	**0.14**	4.7	0.016
1000	421	34	0.08	15	0.037	19	0.04	2.1	0.005

Table 12. Preliminary Upper 90th Percentile Kenega, Chronic Avian Dietary Based Risk Quotients								
NOAEC (ppm)	**EECs and RQs**							
	Short Grass		**Tall Grass**		**Broadleaf Plants/ Small Insects**		**Fruits/Pods/ Seeds/ Large Insects**	
	EEC	**RQ**	**EEC**	**RQ**	**EEC**	**RQ**	**EEC**	**RQ**
20	116	**5.8**	53	**2.6**	65	**3.2**	7.2	0.36

Table 13. Preliminary Upper 90th Percentile Kenaga, Acute Mammalian Dose-Based Risk Quotients									
Size Class (grams)	**Adjusted LD50**	**EECs and RQs**							
		Short Grass		**Tall Grass**		**Broadleaf Plants/ Small Insects**		**Fruits/Pods/ Seeds/ Large Insects**	
		EEC	**RQ**	**EEC**	**RQ**	**EEC**	**RQ**	**EEC**	**RQ**
15	3385	110	0.033	50	0.015	62	0.018	6.9	0.002
35	2739	76	0.028	35	0.013	43	0.016	4.8	0.002
1000	1185	18	0.015	8.1	0.007	9.9	0.008	1.1	0.001

Table 14. Preliminary Upper 90th Percentile Kenega, Chronic Mammalian Dose-Based Risk Quotients									
Size Class (grams)	**Adjusted NOAEL**	**EECs and RQs**							
		Short Grass		**Tall Grass**		**Broadleaf Plants/ Small Insects**		**Fruits/Pods/ Seeds/ Large Insects**	
		EEC	**RQ**	**EEC**	**RQ**	**EEC**	**RQ**	**EEC**	**RQ**
15	274.73	110	0.40	50	0.18	62	0.23	6.9	0.025
35	222.28	76	0.34	35	0.16	43	0.19	4.8	0.021
1000	96.15	18	0.18	8.1	0.084	9.9	0.10	1.1	0.011

Preliminary terrestrial plant risk quotients were estimated for acifluorfen using the TERRPLANT model (v. 1.2.1.) assuming an application rate of 0.29 lbs a.i./Acre (58% of 0.5 lbs a.i./Acre), water solubility of >100 mg/L, and an EC25 value of 0.088 lbs a.i./Acre. Risk quotients for the most sensitive plant (onion) exceeded the LOC of 1 (RQ = 1.8) for semi-aquatic areas.

1.12.4. Summary of Expected Risks from Lactofen and Acifluorfen

Table 15. Summary discussion of LOC exceedances for lactofen and acifluorfen		
Taxa	**Anticipated Risk**	**Basis for Risk Conclusion**
Birds, Acute	**Lactofen**: RQ < LOC	**Lactofen**: Acute avian RQs could slightly exceed the endangered species LOC of 0.1 based on a foliar dissipation rate of 35 days and an LD50 of >2510 mg/kg-bw. However, given that a 35-day foliar dissipation half-life is expected to be conservative AND no mortality occurred at the dose used for RQ calculation, these slight exceedances are not expected to indicate risk at levels >LOC.

Table 15. Summary discussion of LOC exceedances for lactofen and acifluorfen		
Taxa	**Anticipated Risk**	**Basis for Risk Conclusion**
	Acifluorfen: **RQ > LOC**	**Acifluorfen:** The acute RQ is expected to be approximately 0.5 based on two lactofen application of 0.5 lbs a.i./Acre, 58% conversion to acifluorfen, and an LD50 of 325 mg/kg-bw, which exceeds the acute LOC.
Birds, reproduction	**Lactofen: RQ >LOC** **Acifluorfen: RQ >LOC**	**Lactofen**: No avian reproduction study is available. However, data in mammals suggests that lactofen is expected to be as toxic or more toxic to reproduction endpoints than acifluorfen, AND avian reproduction risk quotients are expected to be >LOC for acifluorfen. **Acifluorfen**: Preliminary RQ is approximately 5, which is above the LOC of 1.0.
Mammals, Acute	Lactofen and Acifluorfen: RQ < LOC	Based on application rate of 0.5 lbs a.i./Acre (2 applications) and LD50s of 5960 mg/kg-bw for lactofen and 1540 mg/kg-bw for acifluorfen, RQs are expected to be less than the endangered species LOC of 0.1.
Mammals, Reproduction	**Lactofen: RQ >LOC** Acifluorfen: RQ <LOC	**Lactofen**: Depending on the assumptions chosen for risk estimation, RQs for lactofen may be up to approximately 30, which is above the LOC of 1.0. **Acifluorfen**: All mammalian RQs are expected to be <LOC of 1.0.
Terrestrial Plants	**Lactofen: RQ>LOC** **Acifluorfen: RQ > LOC**	Data do not allow for risk estimation; however, as an herbicide, risk to plants is presumed. Risk to terrestrial plants is presumed because the sodium salt of acifluorfen is an herbicide.
Fish, Acute	Lactofen: RQ<LOC Acifluorfen: RQ < LOC	**Lactofen**: Based on a peak EEC of 0.48 ug/L and the lowest acute toxicity value (FW fish LC50 = 460 ug/L), RQs are expected to be considerably lower than the endangered species LOC of 0.05. **Acifluorfen**: Based on a peak EEC of 18 ug/L and an LC50 of 17,000 ug/L, RQs are expected to be considerably lower than the endangered species of 0.05.
Fish, reproduction	Lactofen: RQ < LOC	Based on a 60-day EEC of 0.05 ug/L and a NOAEC of 1.4 ug/L, the reproduction RQ is expected to be < the LOC of 1.0.
	Acifluorfen: uncertain	RQs cannot be calculated. Effects occurred at all concentrations tested in the available early life-stage study in freshwater fish (NOAEC is <1500 ug/L). Without submission of a study that achieves a NOAEC, it is not possible to determine if RQs are expected to exceed the LOC.
Freshwater Invertebrates, Acute	Lactofen: RQ<LOC Acifluorfen: RQ < LOC	**Lactofen**: Based on a peak EEC of 0.48 ug/L and a 48-hr EC 50 of 4800 ug/L, RQs are expected to be considerably lower than the endangered species LOC of 0.05. **Acifluorfen**: Based on a peak EEC of 18 ug/L and a 48-hr EC 50 of 28,000 ug/L, RQs are expected to be considerably lower than the endangered species LOC of 0.05.
Freshwater Invertebrates, Chronic	Lactofen: RQ<LOC Acifluorfen: Uncertain	**Lactofen**: No data are available; however, chronic/reproductive RQs for fish are <LOC. Similar conclusions for invertebrates are expected because freshwater invertebrates were less sensitive than fish in acute studies. Requested data in mysid shrimp will also provide additional support for risk conclusions for freshwater invertebrates. **Acifluorfen**: Risk quotients cannot be calculated. Requested chronic/reproduction data in fish and mysid shrimp are expected to allow for risk estimation for freshwater invertebrates. However, the surrogate freshwater invertebrate (daphnids) were the least sensitive of all aquatic species tested.

Table 15. Summary discussion of LOC exceedances for lactofen and acifluorfen		
Taxa	**Anticipated Risk**	**Basis for Risk Conclusion**
Aquatic Plants	Lactofen: RQ<LOC	**Lactofen**: Based on a peak EEC of 0.48 ug/L and the lowest aquatic plant NOAEC of 0.6 ug/L, listed species and non-listed species RQs are expected to be less than the aquatic plant LOC of 1.0.
	Acifluorfen: RQ < LOC	**Acifluorfen**: Based on a peak EEC of 18 ug/L and the lowest aquatic plant NOAEC of 180 ug/L, listed species and non-listed species RQs are expected to be less than the aquatic plant LOC of 1.0.

1.13. Additional Uncertainties

In addition to known data gaps for taxonomic groups for which the Agency normally has data, there is a possibility that through public comment and literature searches, additional data may be found that identifies different adverse effects, effects to other taxonomic groups or effects at lower exposure levels. Current legislation and policy requires that the Agency search open literature to locate potentially useful data that may provide additional information on the potential effects of lactofen. Previous assessments did not include a search of open literature for such information.

Previous assessments have not addressed indirect effects. Direct effects to plants and other taxonomic groups have the potential to indirectly affect other species even if those other species may not be affected directly by lactofen. For example, if use of lactofen results in direct effects to terrestrial plants, there is a possibility of indirect effects to terrestrial organisms such as to birds, mammals and reptiles through loss of habitat or cover and reduced food supply. Aquatic animals might be at risk if riparian plant communities are impacted by reducing shading or resulting in increased erosion. Previous assessments have not taken into account indirect effects or effects to critical habitat of endangered species.

In addition to the need to assess risk to taxonomic groups for which data were not available, none of the currently registered uses have been assessed according to current tools and models which would be required to bring the Agency risk assessment on lactofen into compliance with the Endangered Species Act and Agency guidance on ecological risk assessment. Some recent changes to the methods of ecological risk assessment include a revised mammalian exposure model which tends to result in higher tier 1 risk quotients. Aquatic modeling is more refined with additional regionally specific scenarios that take into account local runoff and meteorological conditions. Drift has not been assessed using Agdrift, which is a drift model that takes into account several relevant factors such as wind speed, release height and droplet size.

A critical aspect of risk assessments that comply with current policy is risk refinements. If screening level risk assessments indicate potential risk of direct or indirect effects to endangered species these assessments must be refined at a local level to determine if potential affects are likely to adversely affect or not likely to adversely affect the listed species. None of the potential risks identified for lactofen have been refined. For example, the potential risk of reproductive effects to mammals has not been refined to determine if endangered mammals are likely to be exposed, and if that exposure might adversely affect the species. Likewise, the suspected risk to plants has not been refined to determine if endangered plants might be adversely affected or if direct effects to non-endangered plants might indirectly affect endangered animals.

1.14. Lactofen and Acifluorfen Residues in Water

Due to its lack of persistence and mobility, lactofen has limited potential to contaminated surface and ground water. The high sorption potential for lactofen suggests that lactofen is more likely to enter surface water bodies bound to sediment rather than in the runoff water. Lactofen appears to have very limited potential to contaminate ground water.

Acifluorfen is much more mobile and persistent, and therefore has a potential to contaminate both surface and ground water. The available information fate data and monitoring data confirm this. Typically, monitoring data in non-target studies report no or low concentrations of acifluorfen in both ground water and surface water. A Prospective Ground Water Study (sodium acifluorfen in Wisconsin) did find high concentrations (up to 46- µg/L) of acifluorfen in shallow ground water. This study occurred at an extremely vulnerable site with real agronomic practices, although (probably not realistic), not typical.

IV. HUMAN HEALTH EFFECTS SCOPING DOCUMENT

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

DATE: December 19, 2006

SUBJECT: **Lactofen:** Registration Review Scoping Document for Human Health Assessments; PC Code: 128888; DP Number: D323202

REVIEWER: Christine L. Olinger, Risk Assessor
Reregistration Branch 1
Health Effects Division (7509P)

THROUGH: Michael S. Metzger, Chief
Reregistration Branch 1
Health Effects Division (7509P)

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

Attached is the human health scoping document to support the registration review of the herbicide lactofen.

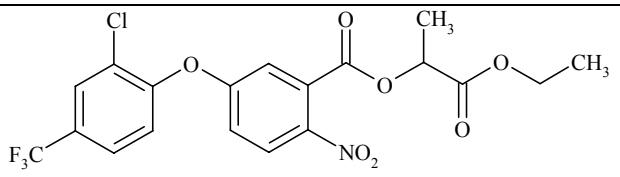
Introduction

The HED Lactofen Registration Review Team has evaluated the human health assessments for the herbicide lactofen to determine the scope of work necessary to support the registration review. The team considered the current use profile and the toxicity and exposure databases for lactofen. The primary sources for the status update were the risk assessments developed for the Tolerance Reassessment Eligibility Decision (Metzger, 2003 and Olinger, 2000) and the assessment currently in development for the new uses of lactofen on fruiting vegetables and okra. A comprehensive search of the open literature was not done primarily because a screening Google search (Google Scholar) and a Science Direct search indicated very little new information relevant to human health risk assessment has been published on this herbicide that had not already been considered in previous assessments. A comprehensive listing of the documents considered is presented in Section 9 of this document. The purpose of this screen is to determine whether sufficient data are available and whether a new human health risk assessment is needed to support registration review. The HED Risk Assessment team is Christine Olinger, Timothy Dole, and Whang Phang, with additional help from Elizabeth Mendez.

Lactofen and another registered herbicide, sodium acifluorfen, share a common environmental degradate, acifluorfen (also known as acifluorfen acid). Therefore, the assessments for lactofen include aggregate assessments for acifluorfen, resulting from the use of both sodium acifluorfen and lactofen. Accordingly, the acifluorfen database was considered in this document and is reflected in the list of references.

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. There are also non-food uses registered on strawberries, pine seedlings, and various trees. There are no residential uses of lactofen. IR-4 is proposing new uses on fruiting vegetables and okra and restricting the use to several southeastern states.

Section 3.1. Chemical Identity

Table 1.1 Chemical Identity	
Common Name	Lactofen
IUPAC name	ethyl O-[5-(2-chloro-α,α,α-trifluoro-p-tolyloxy)-2-nitrobenzoyl]-DL-lactate
CAS name	2-ethoxy-1-methyl-2-oxoethyl 5-[2-chloro-4-(trifluoromethyl)phenoxy]-2-nitrobenzoate
PC Code	128888
CAS registry number	77501-63-4
Registration Review Case No.	7210
Chemical Structure	

Section 3.2. Toxicology

No toxicity studies have been received since the last human health risk assessment (Metzger, 2003). A new rabbit developmental toxicity study had been required in the TRED, but the registrant has requested a waiver of this study and HED has recommended for granting the waiver (Phang, 2006). It is noted that no endocrine effects were identified in any of the submitted toxicity studies.

The risk assessment team has re-evaluated the toxicity endpoints and doses considering the waiver request and current policies on selecting endpoints and uncertainty factors. The team has recommended for an FQPA factor of 3x, for the use of a LOAEL as a point of departure. Tables 2.1 and 2.2 include the toxicity endpoints from the most recent risk assessment in support of the new uses. There are no outstanding toxicity studies for lactofen so it is not anticipated that further changes to this profile would be required in registration review.

Table 3.1 Toxicological Doses and Endpoints for Lactofen for Use in Dietary and Non-Occupational Human Health Risk Assessments [1]

Exposure/ Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary *General Population*	No endpoint has been identified for the general population based on a single exposure to lactofen.			
Acute Dietary *Females 13-49 years of age*	LOAEL = 5 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 3x (UF_L)	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 liver accompanied by increases in post implantation loss and in early embryonic death/litter.
Chronic Dietary *All Populations*	NOAEL= 0.79 mg/kg/day	UF_A = 10x UF_H = 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 at doses that do not cause the biochemical and histopathological changes in the liver of rodents. The chronic endpoint is protective of the carcinogenic effects so a separate cancer assessment is not needed.			
Endpoints and doses have not been selected for the following scenarios as there are no residential exposures to lactofen: Incidental Oral (Short- and Intermediate-Term), Dermal (Short- and Intermediate-Term), and Inhalation (Short- and Intermediate-Term).				

[1] **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_A = extrapolation from animal to human (intraspecies). UF_H = potential variation in sensitivity among members of the human population (interspecies). UF_L = 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.

Table 3.2 Summary of Toxicological Doses and Endpoints for Lactofen for Use in Occupational Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal Short-Term (1-30 days) Dermal Intermediate-Term (1-6 months)	NOAEL = 5 mg/kg/day	UF_A=10x UF_H=10x UF_L =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 Short-Term (1-30 days) Inhalation Intermediate-term (1-6 months)	NOAEL = 5 mg/kg/day	UF_A=10x UF_H=10x UF_L =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.
Cancer (oral, dermal, inhalation)	Classification: Not likely to be carcinogenic to humans at doses that do not cause the biochemical and histopathological changes in the liver of rodents. The chronic endpoint is protective of the carcinogenic effects so a separate cancer assessment is not needed.			

[1] **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_A = extrapolation from animal to human (intraspecies). UF_H = potential variation in sensitivity among members of the human population (interspecies). UF_L = 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.

Section 3.3. Current Dietary Assessments

Comprehensive dietary assessments were recently conducted in association with the proposed new uses (Olinger, in review). For the acute and chronic dietary assessments for food alone and food plus water all exposures were at less than 1% of the population adjusted dose. These assessments are considered conservative as they were conducted assuming tolerance level residues and 100% crop treated. It is not expected that new dietary assessments would be required in registration review because they assumed the most recent toxicity information.

Section 3.4. Aggregate and Cumulative Exposure

There are no residential uses of lactofen so the aggregate assessments in the most recent assessment include only food and water. The acute and chronic assessments for food and water were at less than 1% of the population adjusted dose, so there are no risks of concern.

Lactofen and another herbicide, sodium acifluorfen, have a common environmental degradate, acifluorfen acid. There are residential uses of sodium acifluorfen, a spot herbicide treatment. Therefore, the most recent assessment for lactofen includes aggregate assessments for acifluorfen acid. Exposures considered in the aggregate acifluorfen acid assessments include food exposures from sodium acifluorfen applications, water exposures from lactofen applications, and residential exposures from sodium acifluorfen applications. It was not necessary to include water exposures from sodium acifluorfen applications as it is unlikely that lactofen and sodium acifluorfen will be used in the same area.

All of the aggregate exposures from all time intervals are below the level of concern. Aggregate tables from the most recent risk assessment (Olinger, in review) are provided in Tables 4.1, 4.2, and 4.3 below.

Table 4.1. Summary of Dietary Exposure and Risk for Lactofen – Food and Drinking Water

Population Subgroup	Acute Dietary (95th 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			**0.000052**	**<1**
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	**0.000066**	**<1**	0.000021	<1

Table 4.2. Summary of Dietary Exposure and Risk for Acifluorfen – Food and Drinking Water (Acifluorfen in Drinking Water From Lactofen Applications)

Population Subgroup	Acute Dietary (95th 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)			**0.000478**	**37**
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	**0.00119**	**6.0**	0.000143	11

Table 4.3. Short-Term Aggregate Risk Calculations for Acifluorfen

Population	Short-Term Scenario					
	NOAEL mg/kg/day	**LOC[1]**	**Target Maximum Exposure[2] mg/kg/day**	**Average Food & Water Exposure mg/kg/day**	**Residential Exposure[3] mg/kg/day**	**Aggregate MOE (food and residential)[4]**
Adult Female	20	1000	0.02	0.000143	0.0011	16000

[1] The LOC includes the standard inter- and intra- species uncertainty factors totaling 100.
[2] Target Maximum Exposure (mg/kg/day) = NOAEL/LOC
[3] Residential Exposure was obtained from the risk assessment for acifluorfen (Farwell, 2002).
[4] Aggregate MOE = NOAEL/(Average Food & Water Exposure + Residential Exposure)

It is not expected that any new aggregate assessments would be required in registration review as there are no new toxicity studies expected to be submitted. Lactofen is a member of the diphenyl ether group of herbicides, as are sodium acifluorfen and oxyfluorfen. EPA has not yet determined whether or not these compounds exhibit a common mechanism.

Section 3.5. Occupational Exposure

A summary of the available occupational exposure assessments is presented in Table 5.1. Occupational handler assessments have been conducted for peanuts, cotton, and the proposed new uses. All of these assessments were below HED's level of concern; some scenarios required a single layer of dermal protection (e.g. chemical-resistant gloves). Post-application assessments have been conducted for peanuts and cotton, and were not required for the proposed new uses. No risks of concern were identified.

The following occupational assessments will be required in registration review: handler assessments for soybeans, conifer seedlings, snap beans, and strawberries, and a post-application assessment for conifer seedlings. These assessments are needed because these scenarios involve different application techniques and/or greater amount of material handled than scenarios that have been previously assessed.

Table 5.1 ORE Assessments Required for Existing Lactofen Uses

Use	Application Rate (lb ai/acre)	Application Methods	Handler Assessment Required?	Post Exposure Assessment Required?
Soybeans	0.2	Aerial and Ground	Yes	No – Similar to peanuts.
Cotton	0.2	Ground Directed Spray	No – Previously assessed	No – Previously assessed
Peanuts	0.2	Aerial and Ground	No – Previously assessed	No – Previously assessed
Conifer Seedlings	0.25	Ground	Yes	Yes – can be applied over the top
Kenaf	0.20	Ground Directed Spray	No – Similar to peanuts	No – Cannot be applied over the top
Snap Beans (SLN)	0.25	Aerial and Ground	Yes	No – Applied within 2 days of planting and watered in
Strawberries (SLN)	0.38	Aerial and Ground	Yes	No – Applied only to dormant transplants. PHI is one year. Must be watered in.

Section 3.6. Anticipated Data Needs

A data call-in was issued in January 2005 for the following studies from the 2003 Lactofen TRED:

- Prenatal Developmental Toxicity Study in Rabbits (OPPTS Guideline Number 870.3700). The registrant has requested a waiver for this study and HED has recently recommended in favor of the waiver.
- Confined Rotational Crop Study (OPPTS Guideline Number 860.1850). This study has been reviewed; additional supporting information regarding the storage stability of some commodities is needed.
- UV/Visible Absorption (OPPTS Guideline Number 830.7050). This study has been received and has been sent to the contractor for review.

HED does not believe additional data are needed for registration review.

Section 3.7. Tolerances

No MRLs for lactofen have been established or proposed by Codex for any agricultural commodities and there are no Canadian or Mexican tolerances for lactofen. The US tolerances are listed under 40 CFR 180.432 and summarized below.

Crop	*Reassessed Tolerance*
Beans, Snap	0.01
Cotton, Gin Byproducts	0.02
Cotton, undelinted seed	0.01
Peanut	0.01
Soybean, seed	0.01

Section 3.8. Overall Conclusions

HED does not believe that new data are needed for registration review and that existing dietary risk assessments will support registration review, but new occupational assessments will be required. The recent risk assessment in support of the new uses includes a comprehensive assessment of aggregate exposure and no risks of concern were identified. Occupational assessments have never been conducted for several scenarios including: handler assessments for soybeans, conifer seedlings, snap beans, and strawberries, and a post-application assessment for conifer seedlings. These assessments should be conducted during registration review.

Section 3.9. Reference Memoranda

The memoranda listed in Table 9.1 were considered in the development of this document.

Table 9.1. HED Memoranda Relevant to Registration Review

Author	Barcode	Date	Title
C. Olinger	D319593	In review	Lactofen: Human Health Risk Assessment for Proposed Uses on Fruiting Vegetables and Okra.
C. Olinger	D333149	In review	Lactofen Acute, Chronic, and Cancer Aggregate Dietary and Drinking Water Exposure and Risk Assessments for the Section 3 Registration Action
C. Olinger	D333151	In review	Lactofen. Addition of New Uses: Fruiting Vegetables (Crop Group 8) and Okra. PRIA R17. Summary of Analytical Chemistry and Residue Data.
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

Table 9.1. HED Memoranda Relevant to Registration Review			
Author	Barcode	Date	Title
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

V. GLOSSARY of TERMS and ABBREVIATIONS

ai	Active Ingredient
AR	Anticipated Residue
CFR	Code of Federal Regulations
cPAD	Chronic Population Adjusted Dose
CSF	Confidential Statement of Formula
CSFII	USDA Continuing Surveys for Food Intake by Individuals
DCI	Data Call-In
DEEM	Dietary Exposure Evaluation Model
DFR	Dislodgeable Foliar Residue
DNT	Developmental Neurotoxicity
DWLOC	Drinking Water Level of Comparison
EC	Emulsifiable Concentrate Formulation
EDWC	Estimated Drinking Water Concentration
EEC	Estimated Environmental Concentration
EPA	Environmental Protection Agency
EUP	End-Use Product
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FFDCA	Federal Food, Drug, and Cosmetic Act
FQPA	Food Quality Protection Act
FOB	Functional Observation Battery
GENEEC	Tier I Surface Water Computer Model
IR	Index Reservoir
LC_{50}	Median Lethal Concentration. A statistically derived concentration of a substance that can be expected to cause death in 50% of test animals. It is usually expressed as the weight of substance per weight or volume of water, air or feed, e.g., mg/l, mg/kg or ppm.
LD_{50}	Median Lethal Dose. A statistically derived single dose that can be expected to cause death in 50% of the test animals when administered by the route indicated (oral, dermal, inhalation). It is expressed as a weight of substance per unit weight of animal, e.g., mg/kg.
LOC	Level of Concern
LOAEL	Lowest Observed Adverse Effect Level
µg/g	Micrograms Per Gram
µg/L	Micrograms Per Liter
mg/kg/day	Milligram Per Kilogram Per Day
mg/L	Milligrams Per Liter
MOE	Margin of Exposure
MRID	Master Record Identification (number). EPA's system of recording and tracking submitted studies.
MUP	Manufacturing-Use Product
NA	Not Applicable
NAWQA	USGS National Ambient Water Quality Assessment
NPDES	National Pollutant Discharge Elimination System
NR	Not Required
NOAEL	No Observed Adverse Effect Level
OPP	EPA Office of Pesticide Programs
OPPTS	EPA Office of Prevention, Pesticides and Toxic Substances
PAD	Population Adjusted Dose
PCA	Percent Crop Area
PDP	USDA Pesticide Data Program
PHED	Pesticide Handler's Exposure Data
PHI	Preharvest Interval

ppb	Parts Per Billion
PPE	Personal Protective Equipment
ppm	Parts Per Million
PRZM/EXAMS	Tier II Surface Water Computer Model
Q_1*	The Carcinogenic Potential of a Compound, Quantified by the EPA's Cancer Risk Model
RAC	Raw Agriculture Commodity
RED	Reregistration Eligibility Decision
REI	Restricted Entry Interval
RfD	Reference Dose
RQ	Risk Quotient
SCI-GROW	Tier I Ground Water Computer Model
SAP	Science Advisory Panel
SF	Safety Factor
SLN	Special Local Need (Registrations Under Section 24©) of FIFRA)
TGAI	Technical Grade Active Ingredient
USDA	United States Department of Agriculture
UF	Uncertainty Factor
WPS	Worker Protection Standard