

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.

HED Registration Review Scoping Document for Lactofen (PC Code 128888)

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 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 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 <u>Lactofen</u> for Use in Dietary and Non-Occupational Human Health Risk Assessments¹				
Exposure/ Scenario	Point of Departure	Uncertainty/FQP A 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 litter 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)	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.
Dermal Intermediate-Term (1-6 months)				
Inhalation Short-Term (1-30 days)	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 Intermediate-term (1-6 months)				
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. 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 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.

Population Subgroup	Acute Dietary (95 th 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

Population Subgroup	Acute Dietary (95 th 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

Population Subgroup	Acute Dietary (95 th Percentile)		Chronic Dietary	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD
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

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 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.

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 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 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.

<i>Crop</i>	<i>Reassessed Tolerance</i>
Beans, Snap	0.01
Cotton, Gin Byproducts	0.02
Cotton, undelinted seed	0.01
Peanut	0.01
Soybean, seed	0.01

Section 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 9. Reference Memoranda

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

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