



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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: July 22, 2004

Subject: Occupational and Residential Risk Assessment for Lactofen on Cotton and Peanuts

DP Barcode:	PC Code:	Trade Name:	EPA Reg#	MRID #	Class
D296972	128888	COBRA ® Herbicide	59639-34	N/A	herbicide

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INTRODUCTION

The Registration Division (RD) of the Office of Pesticide Programs (OPP) has requested that the Health Effects Division (HED) evaluate hazard and exposure data, and conduct occupational and residential exposure assessments, as needed, to estimate the risk to human health that will result from proposed new uses of the herbicide lactofen on peanuts. The HED previously addressed the human health risk resulting from dietary (food and water) exposure for purposes of tolerance reassessment (D292794, M. Metzger, 8/12/03 and D269621, C. Olinger, 10/12/00).

The EPA issued a Tolerance Reassessment Eligibility Decision (TRED) document on September 24, 2003. As part of the TRED, the EPA reassessed existing tolerances and considered petitions for establishment of new food uses and associated tolerances of lactofen on cotton and peanuts and determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate (food and water) exposure to lactofen. Uses of cotton were considered in the TRED (and are considered in this document as well) because, although these uses are currently on the label, there has been no official registration. As there are no residential uses associated with lactofen, a residential exposure risk assessment is not required. Therefore, this document addresses only occupational risk from exposure to lactofen when used on peanut and cotton crops.

1.0 EXECUTIVE SUMMARY

Lactofen is the active ingredient (ai) in COBRA® Herbicide (an emulsifiable concentrate) formulated for use in early postemergence control of broadleaf weeds and for a variety of postemergence weeds. COBRA® Herbicide contains 2 lbs lactofen/gal (23.2%). The name lactofen will be used for the ingredient being assessed, and will be referred to as the active ingredient or “ai.”

COBRA® Herbicide is first applied to peanuts and cotton crops when the plants are young, and is directed at the weeds, not the plants. Preharvest intervals (PHIs) for peanuts and cotton are 90 days and 70 days, respectively. Therefore, exposure to lactofen during early- to mid-season postapplication activities (*e.g.*, irrigation, scouting) is more likely than exposure to lactofen during late-season postapplication activities (*e.g.*, harvesting). For peanuts, the label prescribes 1-2 applications at a rate of 12.5 fl oz/A (0.2 lb ai/A), and proposes a maximum seasonal application rate of 28.5 fl oz/A (0.44 lb ai/A) which should be changed to 25 fl oz/A (0.4 lb ai/A) to be consistent with the use directions (maximum of 2 applications at a rate of 0.2 lb ai/A); additionally, the minimum interval between applications should be specified. For cotton, the label also prescribes an application rate of 12.5 fl oz/A (0.2 lb ai/A), but needs to specify the maximum number of applications, the minimum interval between applications and the maximum seasonal application (the residue data support two applications per season and a maximum seasonal application rate of 0.4 lb ai/A). The labels also indicate that applications should be made as a directed spray (for peanuts, the label states “do not apply to peanuts by air,” for cotton, the label states “do not apply COBRA Herbicide over-the-top of cotton,” and on the introduction to the COBRA® Herbicide label, it states “do not apply this product through any type of irrigation system”).

An occupational and/or residential exposure assessment is required for an ai if (1) certain toxicological criteria are triggered and (2) there is potential exposure to handlers (mixers, loaders, applicators, etc.) during use or to persons entering treated sites after application is complete. For lactofen both criteria have been met. Occupational exposure is expected for lactofen, and therefore occupational exposure and risk are assessed in this document. However, there are no residential uses registered or proposed for lactofen, and therefore residential exposure and risk are not assessed. The following occupational exposure scenarios are assessed

in this document:

- Handler:
 - mixer/loader: short- and intermediate-term inhalation and dermal (for groundboom application to peanuts and cotton)
 - applicator: short- and intermediate-term inhalation and dermal (for groundboom application to peanuts and cotton)
- Postapplication:
 - irrigation, scouting, weeding, harvesting: short- and intermediate-term dermal (for peanut and cotton crops)

Occupational handlers may be exposed to lactofen during mixing, loading, application and postapplication activities through the following routes:

- *Dermal*

A short- and intermediate-term dermal endpoint was identified based on the subchronic oral toxicity study in the rat (NOAEL = 14 mg/kg/day) based on body weight decrements in males, anemia in males, elevated serum enzymes (alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, alkaline phosphatase) in males, and increased bilirubin in males and females (45 days), decreased glucose in males, increased liver weights in males and females, and microscopic liver lesions in males at the LOAEL of 73.7 mg/kg/day. Absorption via dermal exposure was assumed to be 20% of oral absorption (20% dermal absorption factor) based on the dermal penetration study in the rat. The associated uncertainty factors (UFs) are 10X for intraspecies variation and 10X for interspecies extrapolation, which results in a target Margin of Exposure (MOE) of 100. A long-term dermal endpoint was also identified (based on a mechanistic study in mice, NOAEL = 0.3 mg/kg/day), however, long-term dermal occupational exposure is not expected. Therefore only short- and intermediate-term dermal exposures were assessed.

- *Inhalation*

The identified short- and intermediate-term inhalation endpoint was also based on the subchronic oral toxicity study in the rat (NOAEL = 14 mg/kg/day), based on the same effects as described above for the dermal short- and intermediate-term endpoint. Absorption via inhalation exposure was assumed to be 100% of oral absorption (100% inhalation absorption factor). The associated UFs are 10X for intraspecies variation and 10X for interspecies extrapolation, which results in a target MOE of 100. A long-term inhalation endpoint was also identified (based on a mechanistic study in mice, NOAEL = 0.3 mg/kg/day), however, long-term inhalation occupational exposure is not expected. Therefore only short- and intermediate-term inhalation exposures were assessed.

The inhalation and dermal exposure calculations resulted in Margins of Exposure (MOEs) which were compared to their target MOEs of 100. Because the endpoints are the same for both dermal and inhalation exposure, the individual dermal and inhalation exposures were combined and compared to the target MOE of 100.

No chemical-specific handler exposure data were submitted in support of this action. It is the policy of the HED to use data from the Pesticide Handlers Exposure Database (PHED) Version

1.1 as presented in the PHED Surrogate Exposure Guide (8/98) to assess handler exposures for regulatory actions when chemical-specific monitoring data are not available (HED Science Advisory Council for Exposure Draft SOP # 7, dated 1/28/99). Chemical-specific dislodgeable foliar residue (DFR) data (relevant to postapplication exposure assessment) were submitted in support of this action and screened; the screening indicated that the default values used in this assessment do not underestimate the exposure or risk. The interim transfer coefficient guidance developed by HED's Science Advisory Council for Exposure, which includes proprietary data from the Agricultural Re-entry Task Force (ARTF) database (SOP # 3.1), was used in estimating postapplication exposures, as well as the REI calculator.

MOEs for combined dermal and inhalation exposure from all occupational handler scenarios and MOEs for individual dermal exposures for all postapplication scenarios were above the target MOE of 100, and thus do not trigger HED concern. Inhalation exposure is considered negligible for postapplication activities, thus an occupational postapplication assessment for inhalation exposure was not required.

Lactofen is also classified as likely to be carcinogenic to humans at high enough doses to cause the biochemical and histopathological changes in the liver of rodents but unlikely to be carcinogenic to humans below those doses causing these changes. An MOE approach is the appropriate method to assess a cancer risk for exposure to lactofen; however, when using an MOE approach, a cancer assessment is required only when chronic or long-term exposures are expected. Chronic or long-term occupational exposure to lactofen is not expected. Therefore, a cancer assessment for occupational exposure was not conducted.

Acute eye irritation and acute dermal toxicity tests result in toxicity category III for lactofen. Acute inhalation toxicity and acute dermal irritation tests result in toxicity category IV. Per the Worker Protection Standard (WPS), a 12 hour Restricted Entry Interval (REI) is required for chemicals classified under toxicity category III. Therefore, an interim WPS REI of 12 hours should be stated on all COBRA ® labels.

2.0 HAZARD PROFILE

References:

Lactofen studies/doses/endpoints selected by RRB1 for the non-dietary risk assessments for lactofen, email attachment, L. Taylor, 3/29/04. (Attachment 1)

LACTOFEN - Report of the Hazard Identification Assessment Review Committee, HED DOC. NO. 014025 L. Mendez, 3/6/00.

Lactofen has low acute toxicity, categories III and IV, and the liver and kidneys are target organs. The results from acute studies with lactofen are shown below in Table 1.

Table 1. Acute Toxicity of Lactofen (technical formulation, unless otherwise indicated)

Guideline No.	Study Type	Accession No.	Results	Toxicity Category
870.1100	Acute oral toxicity	73859	LD ₅₀ > 5.96 g/kg	IV
870.1200	Acute dermal toxicity	73859	LD ₅₀ > 2.0 g/kg	III
870.1300	Acute inhalation toxicity	73859	LC ₅₀ > 6.3 m/L	IV
870.2400	Acute eye irritation (MUP)	73859	Moderate eye irritant	III
870.2500	Acute dermal irritation (MUP)	73859	Very slight dermal irritant	IV
870.2600	Skin sensitization	73859	Not a dermal sensitizer	

MUP - manufacturer's use product

On February 22, 2000 the HED Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology database for lactofen with regard to the acute and chronic Reference Doses (RfDs), as well as the potential for increased susceptibility of infants and children from exposure to lactofen as required by the FQPA; doses and toxicological endpoints for dietary exposure assessment were selected. On May 21, 2002, the HED Cancer Assessment Review Committee (CARC) issued a report (TXR# 0050184, S. Diwan, 5/21/02) that reclassified lactofen in light of new data and conclusions from the Mechanism of Toxicity Assessment Review Committee (MTARC). And, in March of 2004, the HED selected doses and toxicological endpoints for use in non-dietary exposure assessments. The decisions and toxicological endpoints from these committees and documents are summarized in Table 2 and in attachment 1.

Table 2. Summary of Toxicological Endpoints for Lactofen

Exposure Scenario	Dose (mg/kg/day)	Endpoint	Study
Dermal, Short-Term	NOAEL = 14 mg/kg/day	body weight decrements in males, anemia in males, elevated serum enzymes and bilirubin in males and females, decreased glucose in males, increased liver weights in males and females, and microscopic liver lesions in males.	subchronic oral toxicity study - rat
Dermal, Intermediate-Term	NOAEL= 14 mg/kg/day	body weight decrements in males, anemia in males, elevated serum enzymes and bilirubin in males and females, decreased glucose in males, increased liver weights in males and females, and microscopic liver lesions in males.	subchronic oral toxicity study - rat

Exposure Scenario	Dose (mg/kg/day)	Endpoint	Study
Dermal, Long-Term	NOAEL= 0.3 mg/kg/day	increases in relative liver weight (male mice), carnitine acetyl transferase and palmitoyl CoA oxidase (female mice)	mechanistic study [mouse]
Inhalation, Short-Term	NOAEL= 14 mg/kg/day	body weight decrements in males, anemia in males, elevated serum enzymes and bilirubin in males and females, decreased glucose in males, increased liver weights in males and females, and microscopic liver lesions in males.	subchronic oral toxicity study - rat
Inhalation, Intermediate-Term	NOAEL= 14 mg/kg/day	body weight decrements in males, anemia in males, elevated serum enzymes and bilirubin in males and females, decreased glucose in males, increased liver weights in males and females, and microscopic liver lesions in males.	subchronic oral toxicity study - rat
Inhalation, Long-Term	NOAEL= 0.3 mg/kg/day	increases in relative liver weight (male mice), carnitine acetyl transferase and palmitoyl CoA oxidase (female mice)	mechanistic study [mouse]
Cancer (oral, dermal, inhalation)	Classification: likely to be carcinogenic to humans at high enough doses to cause the biochemical and histopathological changes in the liver of rodents, but unlikely to be carcinogenic to humans below those doses causing these changes. NOAEL = 0.3 mg/kg/day based on increased activities of liver enzymes and increased incidence of liver histopathological findings at the LOAEL of 1.5 mg/kg/day [use an MOE approach for estimating human cancer risk]		

¹ UF = uncertainty factor, FQPA SF = FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose

For a more detailed hazard characterization, please refer to D269621 (C. Olinger, 10/12/00) and D292794 (M. Metzger, 8/12/03), as well as Attachment 1 of this document.

3.0 USE PROFILE

The uses addressed in this occupational risk assessment are for peanuts and cotton. The formulated end-use product for use on peanuts and cotton is COBRA® Herbicide. The use profile relevant for this action is summarized in Table 3.

Table 3: Proposed Use Profile for Lactofen

Applic. Type, Timing, and Equip.	Formulation [EPA Reg. No.]	Max. Single Rate (lb ai/A)	Max. No. per Season	Use Directions and Limitations
<i>peanuts</i>				
· Postemergence applications after peanuts have at least 6 true leaves. · Equipment: · groundboom	COBRA® Herbicide [59639-34] 2 lb/gal EC (23.2% ai)	0.2	2	Do not exceed 0.44 lb ai/A/season.* Apply in 10-50 gals spray solution per acre. Do not apply to peanuts later than 90 days before harvest.

Applic. Type, Timing, and Equip.	Formulation [EPA Reg. No.]	Max. Single Rate (lb ai/A)	Max. No. per Season	Use Directions and Limitations
<ul style="list-style-type: none"> row banding 				<p>Either an EPA approved non-ionic surfactant (at 0.25% v/v; 1 quart per 100 gallons of water) or an EPA approved petroleum or vegetable oil based crop oil concentrate (at 1-2 pts per acre) must be used. Do not apply to peanuts by air. Do not allow livestock to graze treated foliage. Do not use treated vines for feed or foliage. Cobra Herbicide may be tank mixed with Basagran, Select 2EC, Cadre, 2,4-DB**, and Pursuit.</p>
<i>cotton</i>				
<ul style="list-style-type: none"> Postemergence directed application to weeds below plant canopy. Apply when cotton is ≥6 inches in height and/or as a layby when cotton is ≥12 inches in height. Equipment: <ul style="list-style-type: none"> groundboom layby 	<p>COBRA® Herbicide [59639-34]</p> <p>2 lb/gal EC (23.2% ai)</p>	0.2	not stated	<p>A 70-day PHI is specified. Apply in 10-30 gals water per acre. Early season application should include either a crop oil concentrate (COC) at 0.5-1 pt/A or a non-ionic surfactant at 2 pts/100 gals. Layby application should include COC at 1-2 pts/A. Do not graze animals on green forage or stubble. Do not use hay or straw for animal feed or bedding. Cobra Herbicide may be tank mixed with Bladex, Karmex, or MSMA.</p>

*note: should be 0.4 lb ai/A/season

**not applicable, applied only once per growing season

4.0 OCCUPATIONAL EXPOSURES AND RISKS

4.1 Handler Exposure and Risk

There is potential for exposure to lactofen during mixing, loading, and application activities. Lactofen can be applied by groundboom, using row banding equipment or layby application; calculating exposure for groundboom application adequately

approximates these application methods.

An exposure/risk assessment using applicable endpoints selected by the HED (March 2004) was performed. Handler's exposure and risk were estimated for the following scenarios (for both peanuts and cotton): (1) mixer/loader: open mixing and loading all liquids for groundboom; (2) groundboom application of liquid: open cab.

No chemical-specific handler exposure data were submitted in support of this action. In accordance with HED's Exposure Science Advisory Council (ExpoSAC) policy (SOP # 7), exposure data from the PHED Version 1.1, as presented in PHED Surrogate Exposure Guide (8/98), were used with other HED standard values for areas treated per day (SOP # 9), body weight, and the level of personal protective equipment, to assess handler exposures. PHED was designed by a task force of representatives from the U.S. EPA, Health Canada, the California Department of Pesticide regulation, and member companies of the American Crop Protection Association. The basic assumption underlying PHED is that exposure to pesticide handlers can be calculated primarily as a function of the formulation type and the handling activities, rather than chemical-specific properties. Since lactofen is formulated as an emulsifiable concentrate (EC), and an EC is also known as a liquid formulation, liquid formulation data from the PHED was used in the exposure assessment. Also, the COBRA® Herbicide application rate was used in exposure calculations (0.2 lb ai/A). The unit exposure values calculated by PHED generally range from the geometric mean to the median of the selected data set, and therefore tend to be central tendency values. The application rates and other standard values used in this assessment tend to be upper-percentile values. Therefore, the potential dose is characterized as mid- to high-end.

Short- and intermediate-term dermal and inhalation endpoints were identified, and therefore short- and intermediate-term dermal and inhalation exposure and risk were assessed. The HED HIARC identified the same toxicity endpoint for short- and intermediate-term dermal and short- and intermediate-term inhalation exposure (NOAEL = 14 mg/kg/day, from the subchronic toxicity study in the rat). Because the endpoints for dermal and inhalation exposures are the same, the individual dermal and inhalation exposures were combined and compared to the NOAEL (14 mg/kg/day) to determine a total MOE. When the personal protective equipment (PPE) specified on the label is considered, the total MOEs range from 4,200 (mixer/loader: open mixing and loading liquid for groundboom, cotton) to 17,000 (groundboom application of liquid: open cab, peanuts). **These MOEs do not exceed HED's level of concern, i.e., they are above the target MOE of 100.** Exposure assumptions and estimates for occupational handlers are summarized in Table 4.

Table 4: Dermal and Inhalation Exposure and Risk for Occupational Handlers

PHED Exposure Scenario	PHED Unit Exposure ¹ (mg/lb ai)	Maximum Application Rate (lb ai/A)	PHED Data Confidence	Area Treated per Day (acres)	Body Weight (kg)	Daily Dose ² (mg/kg/day)	Short- and intermediate-term MOE ³	Total MOE ⁴
<i>peanuts</i>								
1a. mixer/loader: open mixing and loading liquid for groundboom (baseline) ⁵	dermal (baseline) ⁵ : 2.9	0.2	High	80	70	0.13	110	110
	inhalation: 0.0012		High			0.00027	51,000	
1b. mixer/loader: open mixing and loading liquid for groundboom (gloves) ⁶	dermal (gloves) ⁶ : 0.023	0.2	High	80	70	0.0011	13,000	11,000
	inhalation: 0.0012		High			0.00027	51,000	
2. groundboom application of liquid: open cab	dermal (baseline and gloves) ^{1,5,6} : 0.014	0.2	Medium	80	70	0.00064	22,000	17,000
	inhalation: 0.00074		High			0.00017	83,000	
<i>cotton</i>								
1a. mixer/loader: open mixing and loading liquid for groundboom (baseline) ⁵	dermal (baseline) ⁵ : 2.9	0.2	High	200	70	0.33	42	42
	inhalation: 0.0012		High			0.00027	51,000	
1b. mixer/loader: open mixing and loading liquid for groundboom (gloves) ⁶	dermal (gloves) ⁶ : 0.023	0.2	High	200	70	0.0026	5,300	4,200
	inhalation: 0.0012		High			0.00069	20,000	
2. groundboom application of liquid: open cab	dermal (baseline and gloves) ^{1,5,6} : 0.014	0.2	Medium	200	70	0.0016	8,800	6,900
	inhalation: 0.00074		High			0.00042	33,000	

¹ PHED unit exposure values are for "single layer, no gloves" and "single layer, gloves"; NOTE: these categories only affect unit exposure values for dermal exposure for the mixer/loader scenario; NOTE: COBRA® Herbicide label specifies "single layer, gloves" level PPE.

² Daily Dose = [Application Rate (lb ai/A) x Area Treated (A/day) x Unit Exposure (mg/lb ai) x Absorption Factor (20% for dermal; 100% for inhalation) / Body Weight: 70 kg BW

³ MOE = NOAEL/ Daily Dose. Short-and intermediate-term dermal and inhalation NOAELs =14 mg/kg/day

⁴ Total MOE = NOAEL/ (dermal daily dose + inhalation daily dose), NOAEL = 14 mg/kg/day, the target MOE is 100

⁵ Baseline = "single layer, no gloves" (i.e. the exposure a handler would receive when wearing either a long sleeve shirt and long pants or coveralls and no gloves and no respirator)

⁶ Gloves = "single layer, gloves" (*i.e.*, the exposure a handler would receive when wearing a long sleeve shirt and pants or coveralls and chemical resistant gloves and no respirator)

4.2 Postapplication Exposure and Risk

Occupational exposure can occur via the dermal and/or inhalation route(s). Inhalation exposure during postapplication activities is considered negligible for all lactofen use scenarios, and therefore a postapplication inhalation exposure assessment was not performed. On the other hand, short- and intermediate-term dermal exposures are expected, and because short- and intermediate-term dermal endpoints were identified (NOAEL = 14 mg/kg/day based on the subchronic toxicity study in the rat), a short- and intermediate-term dermal exposure and risk assessment was conducted.

Postapplication activities for peanut and cotton crops include irrigation, scouting, weeding and harvesting. The submitted chemical-specific postapplication data were screened and the screening indicated that the default DFRs used in this assessment do not underestimate postapplication exposure and risk (*i.e.*, the calculated dissipation rate was greater than the default assumption [22% versus 10%] and the amount of measured ai available for transfer was less than the default [8.5% vs. 20% of the amount applied]). These typical DFRs (the amount of ai available for transfer, assumed to be 20% of the amount of ai applied, and assumed to dissipate at a rate of 10% per day) were used to estimate postapplication exposure. These assumptions, as well as the typical postapplication activities considered, are from guidance developed by the ExpoSAC (SOP # 3.1). Additionally, standard dermal transfer coefficients (TCs, which relate the leaf residue values to activity patterns [*e.g.*, harvesting]) were used, these are from guidance developed using proprietary data from the Agricultural Re-entry Task Force (ARTF) database (SOP # 3.1). This SOP is periodically updated to incorporate additional information about agricultural practices in crops and new data on TCs. Much of this information originates from exposure studies currently being conducted by the ARTF, from further analysis of studies already submitted to the EPA, and from studies in the published scientific literature. The application rate, TCs, and DFR data used in this assessment are central tendency to upper-percentile values. Therefore, the daily dose is characterized as mid- to high-end.

This action for lactofen involves applications directed to weeds between crop rows of peanuts and cotton, earlier on in the growing season; therefore, for late-season postapplication activities that involve contact with the peanut or cotton plant (in particular harvesting, which is restricted by a 90 day and 70 day PHI, respectively), the potential for postapplication exposure is reduced. Furthermore, cotton harvesting is largely a mechanically assisted activity (where cotton is stripped from the plant by machine, thereby further reducing potential exposure); however, the cotton is subsequently tramped or raked into bales, a potentially high exposure activity. Yet, again, because lactofen is not directed at the cotton or peanut plants (and applied either 90 or 70 days before harvest), it is not expected to be present on the plant, and exposure from these activities is expected to be minimal. Due to the above considerations, an assessment of hand harvesting is not included in this document.

A summary of inputs, calculated exposures and risks from postapplication activities are summarized in Table 5 below. Risk calculations for postapplication workers on the day of application result in MOEs ranging from 910 (for irrigating and scouting peanuts) to 14,000 (for weeding peanuts by hand; and for irrigating, scouting and manually weeding cotton). **These**

MOEs do not exceed HED’s level of concern, i.e., they are above the target MOE of 100. And again, due to the application profile of lactofen (weed-directed, early-season application), actual MOEs are expected to be even higher.

Acute eye irritation and acute dermal toxicity tests result in toxicity category III for lactofen. Acute inhalation toxicity and acute dermal irritation tests result in toxicity category IV. Per the Worker Protection Standard (WPS), a 12 hour Restricted Entry Interval (REI) is required for chemicals classified under toxicity category III. Therefore, an interim WPS REI of 12 hours should be stated on all COBRA ® labels.

Table 5: Occupational Exposure and Risk Estimates for Postapplication Activities

Post-application Activity	Dermal Transfer Coefficient ¹ (cm ² /hr)	Post-application Day ² (t)	Dislodgeable Foliar Residue ³ (ug/cm ²)	Daily Dose ⁴ (mg/kg/day)	Short-/Int-term Dermal MOE ⁵
<i>peanuts</i>					
Irrigation and Scouting	1500	0	0.45	0.015	910
Weeding, hand ⁶	100	0	0.45	0.0010	14,000
<i>cotton</i>					
Irrigation, Scouting and Weeding, hand ⁶	100	0	0.45	0.0010	14,000

¹ Dermal Transfer Coefficient (TC) - transfer coefficients are from an interim transfer coefficient guidance developed by the HED's Science Advisory Council for Exposure using proprietary data from the Agricultural Re-entry Task Force (ARTF) database (SOP # 3.1)

² Postapplication Day (t) - the number of days after treatment, t = 0, is on the day of treatment, after sprays have dried; assumed approximately to be 12 hours

³ Dislodgeable Foliar Residue (DFR) - the amount of pesticide that is available for transfer from a pesticide treated surface; assumed to be 20% of amount applied with 10% dissipation per day, per Science Advisory Council for Exposure policy (SOP # 3.1).

⁴ Absorbed Daily Dermal Dose = [DFR (ug/cm²) x TC (cm²/hr) x conversion factor (1 mg/1,000 ug) x exposure time (8 hr/day) x dermal absorption (20% dermal absorption factor)]/body weight (70 kg)

⁵ Short-/Intermediate MOE = NOAEL (14 mg/kg/day)/absorbed daily dermal dose

⁶ Because this ai is an herbicide, hand-weeding is expected to occur only in rare instances.

5.0 NON-OCCUPATIONAL/RESIDENTIAL EXPOSURE

There are no existing or proposed residential uses for this product. However, spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure

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

6.0 DATA REQUIREMENTS/LABEL NEEDS

For peanuts, the label prescribes 1-2 applications at a rate of 12.5 fl oz/A (0.2 lb ai/A), and proposes a maximum seasonal application rate of 28.5 fl oz/A (0.44 lb ai/A) which should be changed to 25 fl oz/A (0.4 lb ai/A) to be consistent with the use directions (maximum of 2 applications at a rate of 0.2 lb ai/A); additionally, the minimum interval between applications should be specified.

For cotton, the label also prescribes an application rate of 12.5 fl oz/A (0.2 lb ai/A), but needs to specify the maximum number of applications, the minimum interval between applications and the maximum seasonal application (the residue data support two applications per season and a maximum seasonal application rate of 0.4 lb ai/A).

ATTACHMENTS:

1. *Lactofen studies/doses/endpoints selected by RRB1 for the non-dietary risk assessments for lactofen*, email attachment, L. Taylor, 3/29/04. (Attachment 1)

CC: RF

RDI: ORE Team Reviewers: J. Arthur, K. O'Rourke and Barry O'Keefe 06/30/04: S. Dapson
0X/XX/04

4. Incidental Oral Exposure: Short-Term (1-30 days)

Study: subchronic oral toxicity - rat

OPPTS 870.3100; §82-1

MRID No.: 00117564

EXECUTIVE SUMMARY: Executive Summary: In a subchronic toxicity study (MRID 00117564), PPG-844 72 (72.4%) was administered to 30 CD-Crl:CD(SD)BR rats/sex/group at dietary dose levels of 0, 40, 200, or 1 000 ppm for 13 weeks. There was an interim sacrifice of 10 rats/sex from each group at 45 days for clinical pathology testing. Doses were equivalent to 0, 2.9, 14.1, or 73.7 mg/kg/day in males and 0, 3.5, 17.0, or 84.5 mg/kg/day in females. An additional 10 rats/sex were used for determining baseline clinical pathology data.

No treatment-related clinical signs were observed. A number of rats in all treatment groups had nasal exudate beginning in the 2nd week of the study. This is not believed to interfere with study interpretation. One male (200 ppm) died during the 10th week of the study and one female (40 ppm) died during the 2nd week of the study. Neither death was attributed to treatment.

Mean body weights in high-dose males had statistically significant decrements in comparison to controls after week 5 (-6.2% compared to controls) till study termination at week 13 (-11.2% in comparison to controls). Body weight gains were decreased in high-dose males (-14.8% compared to controls at termination). Body weights and gains were comparable to controls in other male and female treatment groups. Mean weekly food consumption showed sporadic, but occasionally statistically significant decreases in food consumption in all 3 male treatment groups when compared to controls. Female groups had comparable food consumption to controls in all weekly intervals.

A slight anemia was present in high-dose males, hemoglobin was slightly reduced at 45 days (14.2 vs 16.1 g/dL in controls) as were the associated red blood cell count and hematocrit parameters. Hemoglobin was slightly reduced in high-dose females at 45 days (14.6 vs 16.0 g/dL in controls) but the red blood cell count and hematocrit were comparable to controls. By study termination, hematological parameters were comparable to controls in both high-dose groups. Hematological parameters in other treatment groups were similar to controls.

Several enzymes were elevated in high-dose males at 45 and 91 days. Elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity in high-dose males were indicative of liver toxicity. This was accompanied by increased lactate dehydrogenase (LDH) and serum alkaline phosphatase (SAP) activity, which may be indicative of liver toxicity. Enzyme activity in other male dose groups and in all female treatment groups were similar to controls. Bilirubin was slightly elevated in high-dose males and females at 45 days only and may reflect erythrocyte or hepatic toxicity. Glucose was decreased in high-dose males. Several other clinical chemistry parameters were slightly altered in high-dose males or females but are of uncertain toxicological significance. Urinalyses were similar between treatment groups and controls at the 45-day interim sacrifice and the terminal sacrifice.

Absolute (corrected) and relative liver weights were increased in high-dose males and relative liver weight

was increased in high-dose females. Relative kidney weights were increased in high-dose males and females. The only gross lesions were in liver and kidneys of high-dose animals. Dark livers in high-dose animals (males: 15/19; females: 4/21) and darkened renal cortex in high-dose animals (males: 15/19 and females: 3/21) were noted. No similar findings were reported in other dose groups. The gross discoloration of liver and kidneys was correlated with microscopic pigmentation.

Microscopic liver lesions in high-dose animals included brown pigment in hepatocytes and/or Kupffer cells (males: 17/19; females: 7/21; none in controls); acidophilic hepatocellular degeneration (males: 10/19; females: 1/21; none in controls); and hyperplasia of bile ductules in males (high-dose males: 6/19; controls: 1/20). Brown pigment in tubular epithelium of the kidneys occurred in high-dose animals (males: 12/19; females: 3/21; none in controls),

The NOAEL is 200 ppm (males: 14.1 mg/kg/day; females: 17.0 mg/kg/day) and the LOAEL is 1 000 ppm (males: 73.7 mg/kg/day; females: 84.5 mg/kg/day) based upon body weight decrements in males, anemia in males, elevated serum enzymes and bilirubin in males and females, decreased glucose in males, increased liver weights in males and females, and microscopic liver lesions in males.

This subchronic toxicity study is classified **acceptable/guideline** and **satisfies** the guideline requirement for a subchronic oral toxicity study in rats.

Dose/Endpoint for Risk Assessment: NOAEL = 200 ppm [14 mg/kg/day], based on body weight decrements in males, anemia in males, **elevated serum enzymes** [alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, alkaline phosphatase] in males, and increased bilirubin in males and females [45 days], decreased glucose in males, increased liver weights in males and females, and microscopic liver lesions in males at the LOAEL of 1000 ppm [73.7 mg/kg/day].

Uncertainty Factor(s): 100X [10X for intraspecies variation and 10X for interspecies variation].

Comments about Study/Margins of Exposure: The liver is a target organ for lactofen. In the rat subchronic toxicity study, increases in the serum enzymes indicative of liver toxicity were observed at the high-dose level in males [73.7 mg/kg/day (1000 ppm)] at 45 days and 90 days [NOAEL 14.1 mg/kg/day (200 ppm)]. In the chronic study in rats, increases in aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase were observed at 19 mg/kg/day (500 ppm) at 18 months and at 38 mg/kg/day (1000 ppm) and above at 6 months, 12 months, and 18 months. Thus, the chronic rat study supports the 14 mg/kg/day dose as a NOAEL at early time points.

Although the chronic study gives a higher NOAEL than the subchronic study for an early time point [6 months], this is considered an artifact of dose selection. Additionally, the overall NOAEL for the chronic study is 50 ppm [2 mg/kg/day], based on, among other effects, increased hepatic enzymes at 500 ppm [19 mg/kg/day] and above. However, there is a temporal aspect to the liver toxicity produced by lactofen; i.e., the higher the dose, the sooner the effect is observed, as evidenced by the results that show that the increases in hepatic enzymes at 500 ppm [19 mg/kg/day] were not observed until 18 months [see original DER], while the increases at 1000 ppm [38 mg/kg/day] were observed at 6 months, 12 months, and 18 months and those at 2000 ppm [76 mg/kg/day] occurred throughout the study. NOTE: The earliest time point monitored in the chronic rat study was **6 months**.

Although the maternal NOAEL in the 2-generation reproduction study is lower than the NOAEL selected from the rat subchronic oral toxicity study [3.3 mg/kg/day, based on F1 female rat deaths during the pre-mating period], the deaths in the F1 rats at the mid-dose level [LOAEL F1 females 32.9 mg/kg/day] did not occur until days 197 and 213. At the high-dose level [F1 males 115.4/F1 females 138.9 mg/kg/day], the deaths [both sexes] occurred early [F1 females (days 9, 9, 25, 27, 47); F1 males (days 13, 15, 20, 27 30)], and this dose and endpoint might be considered appropriate for short-term dermal/inhalation exposure risk. However, the NOAEL for early deaths would then be the mid-dose; i.e., 32.9 mg/kg/day, which is greater than the dose proposed [14 mg/kg/day].

NOTE: There is a datagap for a rabbit developmental toxicity study. In the available rabbit study, no significant effects were observed at 20 mg/kg/day [the highest dose tested], which is considered inadequate. The current acute RfD for females 13+ is 0.5 mg/kg, based on a NOAEL of 50 mg/kg from the rat developmental toxicity study [decreased fetal weight and skeletal abnormalities observed at 150 mg/kg]. The required rabbit developmental toxicity study is not likely to provide a lower NOAEL than the 14 mg/kg/day proposed for this risk assessment, but it is plausible that it might identify a dose and endpoint for an acute RfD for the general population, including infants and children. Therefore, no additional uncertainty factor is recommended for the short-term incidental oral exposure risk assessment.

Supporting Study: Chronic toxicity/carcinogenicity

870.4300/§83-5

MRID No.: 00150329

Executive Summary: In a combined chronic/carcinogenicity study [MRID 150329], lactofen technical (75.88% a. I., average) was administered to Charles River CD rats (84/sex/dose) in the diet at concentrations of 0, 50, 500, 1000, or 2000 ppm (approximately 0, 37.9, 379.4, 758.8, or 1517.6 ppm based on active ingredient) or 0, 2, 19, 38, 76 mg/kg/day (conversion factor 20 ppm = 1 mg/kg) for 104 weeks.

A statistically significant decrease in mean body weights was noted for both males and females at the 2000 ppm dose level. In males, this decrease in body weight occurred between weeks 1 - 86 of the study while female weight loss began at week 4 and persisted until week 102 of the study period. This observation is consistent with the concomitant decrease in food consumption (statistically significant) reported for males and females in the 2000 ppm dose group. A statistically significant decrease in food consumption was also reported for 1000 ppm males during the first 13 weeks of the study. Overall body weight decreases at the high dose level were \approx 16% and 12% for males and females, respectively, during the first 12 months of the study.

A statistically significant increase in the incidence of mottled or diffusely dark livers and kidneys was first noted in the 500 ppm dose group during the 12-month scheduled sacrifice. Furthermore, at the time of terminal sacrifice (24 months) a dark discoloration of the testes was also observed in males treated at the 1000 and 2000 dose levels.

Males in the 2000 ppm dose group had an increase in early deaths at the 12 months evaluation period (8 at 2000 ppm vs. 1 in control group). This reflected 25% of all deaths in the study for the 2000 ppm dose group in contrast to 2% of all deaths for the control group. Interestingly, the mortality rate appeared to stabilize after the 1-year evaluation and the final mortality tallies for males were 42, 45, 37, 29, and 32 for the 0, 50, 500, 1000, and 2000 ppm dose groups, respectively. In the case of females, there was a slight (not

statistically significant) increase in mortality at the 1000 and 2000 ppm dose levels reported during the 1 - year evaluation. However, overall survival at the 18 and 24 month intervals were comparable between the control groups and all test groups.

A statistically significant reduction in hematocrit and hemoglobin was reported for females in the 2000 ppm dose group during the 6 and 12 month evaluation periods. For their part, males showed evidence of a statistically significant reduction in these parameters at the 1-year evaluation for the 1 000 ppm and 2000 ppm. These changes in hemoglobin and hematocrit, however, were no longer evident by the 18 month examination period.

Blood chemistry analysis revealed dose- and compound-related increases in aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase at the 500, 1000, and 2000 ppm dose levels. Additionally, compound-related decreases in cholesterol, total protein, globulin, and BUN were also reported. These changes in blood chemistry were deemed to be indicative of liver toxicity.

Non-neoplastic lesions discovered during microscopic examination included pigmentation of hepatocytes, Kupffer cells, and renal cortical tubule cells. At the 1 000 and 2000 ppm dose levels, the incidences of these lesions attained statistical significance for females while males showed evidence of a statistically significant increase in the incidence of pigmented Kupffer cells and renal cortical tubule cells only.

Pre-neoplastic and neoplastic lesions were evident at the 500 ppm dose level and higher. Males and females in the high-dose group (2000 ppm) had an increased incidence of basophilic foci of cellular alteration and neoplastic nodules in the liver. Males in this dose group also showed evidence of an increase in eosinophilic foci of cellular alteration. An increase in uterine endometrial stromal polyps was seen in females exposed to the test substance at all dose levels. Statistical significance, however, was attained at the 500 ppm dose level and higher. It is noteworthy that - while statistically significant - these lesions (even at 50 ppm dose level) are within the historical control data provided by the testing facility and did not appear to be dose-related. Consequently, the toxicological relevance of these observations is uncertain. No other neoplastic lesions that could be considered compound-related were seen during the study period.

Based on the statistically significant decreases in body weight and food consumption, significant changes in blood chemistry parameters as well as histopathology findings in the liver and kidneys, seen in this study, the highest dose of lactofen tested was considered adequate for the assessment of the carcinogenicity potential of this compound.

Under the conditions of this study, the LOAEL is established at 500 ppm (19 mg/kg/day) based on the findings of statistically significant increases in mottled or discolored livers and kidneys and changes in blood chemistry parameters. The NOAEL is established at 50 ppm (2 mg/kg/day).

This study is classified as **Acceptable/guideline** and **satisfies** the requirement for a combined chronic toxicity/carcinogenicity study in rats (OPPTS 870.4300; §83-5).

Comments about Study/Margins of Exposure/Uncertainty Factor(s): Although the overall NOAEL for the study is 50 ppm [2 mg/kg/day], based on, among other effects, increased hepatic enzyme activities, increases at 500 ppm were not observed until 18 months [see original DER]. Increases at 1000 ppm were observed at 6, 12, and 18 months and those at 2000 ppm occurred throughout the study. In the rat subchronic toxicity

study, increases in these enzymes were observed at the high-dose level [1000 ppm; 73.7/84.5 mg/kg/day] at 45 and 90 days [NOAEL 14.1/17.0 mg/kg/day]. Although the chronic study gives a higher NOAEL than the subchronic study for the early time point, this is considered an artifact of dose selection. See Comments above.

5. Incidental Oral Exposure: Intermediate-Term (1 - 6 Months)

Study: subchronic oral toxicity - rat

OPPTS 870.3100/§82-1

MRID No.: 00117564

Executive Summary: See above under Short-Term Incidental Oral

Dose/Endpoint for Risk Assessment: **NOAEL** = 200 ppm [14 mg/kg/day], based on body weight decrements in males, anemia in males, **elevated serum enzymes** [alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, alkaline phosphatase] in males, and increased bilirubin in males and females [45 days], decreased glucose in males, increased liver weights in males and females, and microscopic liver lesions in males at the LOAEL of 1000 ppm [73.7 mg/kg/day].

Comments about Study/Margins of Exposure/Uncertainty Factor(s): See above under Short-Term Incidental Oral

6. Dermal Absorption

OPPTS 870.7600

There is a dermal penetration study in rats available [classified acceptable/nonguideline]. The original reviewer noted that the study was performed prior to the implementation of the current OPPTS Harmonized Test Guidelines [OPPTS 870.7600] but that it is a well-conducted study that provides sufficient and adequate information for risk assessment. It is to be noted that the application site was 5 cm² instead of 10 cm² required by the guideline. At 72 hours, approximately 8%-10% of the applied dose was absorbed through the skin. At the 1 hour and 10 hour time points, 1%-4% of the applied dose was absorbed through the skin. Although the size of the application site is inadequate, considering the fact that: (1) acifluorfen, a metabolite of lactofen, has a dermal absorption factor of 20%; (2) another phenoxy compound, oxyfluorfen, has a dermal absorption factor of 18%; the use of a dermal absorption factor of 20% appears reasonable for lactofen.

Dermal Absorption Factor: 20%

Study: dermal penetration study - rat

870.7600/§85-3

MRID No.: 00150332

Executive Summary: In a dermal absorption study [MRID 00150332], groups of male Sprague-Dawley (CrI:CD(SD)BR) rats [20 rats/dose] received a topical application of lactofen (0.5% a.i.) At dose levels of 3.6, 18.1, and 72.3 µg/cm². Two rats were used as controls. The extent of absorption was determined at 0.5, 1, 2, 4, 10, and 72 hours after exposure to the test article (terminal sacrifice). Determination of lactofen absorption and horizontal movement (at 3.6 and 72.3 µg/cm²) in the skin after 24 and 72 hours was

examined by exposing 4 rats/dose/time period. The vertical distribution of lactofen ($72.3 \mu\text{g}/\text{cm}^2$) was also studied during this study. Furthermore, the recovery of the test article from the application site patches, swabs, and from the skin after 2 different washing regimens was tested also.

Under the conditions of this study, no systemic toxicity was reported. The test article, ^{14}C -PPG-844, was detected in the blood 2 hours after application, the levels of the test compound continuing to rise over the next 24 hours, and appeared to plateau remaining constant up to 72 hours after treatment. At this time, approximately 8%-10% of the applied dose was absorbed through the skin. The maximum levels of the compound in the skin were obtained 1 hour post-application (5%-6% of the applied dose). Approximately 0.5%-1% of the applied dose remained in the skin 62 hours post treatment after a water and acetone wash; 72 hours without the water and acetone wash. Of the administered dose 2% was excreted in the urine and 4%-6% in the feces 72 hours after exposure to the test article. At the 4- and 10-hours time points, 1%-4% of the applied dose was absorbed through the skin.

The study is classified Acceptable/non-guideline, and it satisfies the guideline requirement for a dermal penetration study [OPPTS 870.7600; §85-3] in rats. **This study was conducted prior to the implementation of the current OPPTS Harmonized Test Guidelines; it is, however, a well-conducted study that provides sufficient and adequate data for use in risk characterization.** NOTE: Due to the fact that the size of the application site is inadequate [5 cm^2 instead of 10 cm^2 required by the guideline], this study should be considered as not satisfying the guideline requirement.

7. Short-Term Dermal (1 - 30 days) Exposure

Study: Subchronic toxicity - rat

870.3100/§82-1

MRID No.: 00117564

Executive Summary: In a subchronic toxicity study (MRID 00117564), PPG-844 72 (72.4%) was administered to 30 CD-Crl:CD(SD)BR rats/sex/group at dietary dose levels of 0, 40, 200, or 1 000 ppm for 13 weeks. There was an interim sacrifice of 10 rats/sex from each group at 45 days for clinical pathology testing. Doses were equivalent to 0, 2.9, 14.1, or 73.7 mg/kg/day in males and 0, 3.5, 17.0, or 84.5 mg/kg/day in females. An additional 10 rats/sex were used for determining baseline clinical pathology data.

No treatment-related clinical signs were observed. A number of rats in all treatment groups had nasal exudate beginning in the 2nd week of the study. This is not believed to interfere with study interpretation. One male (200 ppm) died during the 10th week of the study and one female (40 ppm) died during the 2nd week of the study. Neither death was attributed to treatment.

Mean body weights in high-dose males had statistically significant decrements in comparison to controls after week 5 (-6.2% compared to controls) till study termination at week 13 (-11.2% in comparison to controls). Body weight gains were decreased in high-dose males (-14.8% compared to controls at termination). Body weights and gains were comparable to controls in other male and female treatment groups. Mean weekly food consumption showed sporadic, but occasionally statistically significant decreases in food consumption in all 3 male treatment groups when compared to controls. Female groups had comparable food consumption to controls in all weekly intervals.

A slight anemia was present in high-dose males, hemoglobin was slightly reduced at 45 days (14.2 vs 16.1 g/dL in controls) as were the associated red blood cell count and hematocrit parameters. Hemoglobin was slightly reduced in high-dose females at 45 days (14.6 vs 16.0 g/dL in controls) but the red blood cell count and hematocrit were comparable to controls. By study termination, hematological parameters were comparable to controls in both high-dose groups. Hematological parameters in other treatment groups were similar to controls.

Several enzymes were elevated in high-dose males at 45 and 91 days. Elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity in high-dose males were indicative of liver toxicity. This was accompanied by increased lactate dehydrogenase (LDH) and serum alkaline phosphatase (SAP) activity, which may be indicative of liver toxicity. Enzyme activity in other male dose groups and in all female treatment groups were similar to controls. Bilirubin was slightly elevated in high-dose males and females at 45 days only and may reflect erythrocyte or hepatic toxicity. Glucose was decreased in high-dose males. Several other clinical chemistry parameters were slightly altered in high-dose males or females but are of uncertain toxicological significance. Urinalyses were similar between treatment groups and controls at the 45-day interim sacrifice and the terminal sacrifice.

Absolute (corrected) and relative liver weights were increased in high-dose males and relative liver weight was increased in high-dose females. Relative kidney weights were increased in high-dose males and females. The only gross lesions were in liver and kidneys of high-dose animals. Dark livers in high-dose animals (males: 15/19; females: 4/21) and darkened renal cortex in high-dose animals (males: 15/19 and females: 3/21) were noted. No similar findings were reported in other dose groups. The gross discoloration of liver and kidneys was correlated with microscopic pigmentation.

Microscopic liver lesions in high-dose animals included brown pigment in hepatocytes and/or Kupffer cells (males: 17/19; females: 7/21; none in controls); acidophilic hepatocellular degeneration (males: 10/19; females: 1/21; none in controls); and hyperplasia of bile ductules in males (high-dose males: 6/19; controls: 1/20). Brown pigment in tubular epithelium of the kidneys occurred in high-dose animals (males: 12/19; females: 3/21; none in controls),

The NOAEL is 200 ppm (males: 14.1 mg/kg/day; females: 17.0 mg/kg/day) and the LOAEL is 1 000 ppm (males: 73.7 mg/kg/day; females: 84.5 mg/kg/day) based upon body weight decrements in males, anemia in males, elevated serum enzymes and bilirubin in males and females, decreased glucose in males, increased liver weights in males and females, and microscopic liver lesions in males.

This subchronic toxicity study is classified **acceptable/guideline** and **satisfies** the guideline requirement for a subchronic oral toxicity study in rats.

Dose/Endpoint for Risk Assessment: NOAEL = 200 ppm [14 mg/kg/day], based on body weight decrements in males, anemia in males, **elevated serum enzymes** [alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, alkaline phosphatase] in males, and increased bilirubin in males and females [45 days], decreased glucose in males, increased liver weights in males and females, and microscopic liver lesions in males at the LOAEL of 1000 ppm [73.7 mg/kg/day].

Uncertainty Factor(s): 100X [10X for intraspecies variation and 10X for interspecies variation].

Comments about Study/Margins of Exposure: The liver is a target organ for lactofen. In the rat subchronic toxicity study, increases in the serum enzymes indicative of liver toxicity were observed at the high-dose level in males [73.7 mg/kg/day (1000 ppm)] at 45 days and 90 days [NOAEL 14.1 mg/kg/day (200 ppm)]. In the chronic study in rats, increases in aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase were observed at 19 mg/kg/day (500 ppm) at 18 months and at 38 mg/kg/day (1000 ppm) and above at 6 months, 12 months, and 18 months. Thus, the chronic rat study supports the 14 mg/kg/day dose as a NOAEL at early time points.

Although the chronic study gives a higher NOAEL than the subchronic study for an early time point [6 months], this is considered an artifact of dose selection. Additionally, the overall NOAEL for the chronic study is 50 ppm [2 mg/kg/day], based on, among other effects, increased hepatic enzymes at 500 ppm [19 mg/kg/day] and above. However, there is a temporal aspect to the liver toxicity produced by lactofen; i.e., the higher the dose, the sooner the effect is observed, as evidenced by the results that show that the increases in hepatic enzymes at 500 ppm [19 mg/kg/day] were not observed until 18 months [see original DER], while the increases at 1000 ppm [38 mg/kg/day] were observed at 6 months, 12 months, and 18 months and those at 2000 ppm [76 mg/kg/day] occurred throughout the study. NOTE: The earliest time point monitored in the chronic rat study was **6 months**.

Although the maternal NOAEL in the 2-generation reproduction study is lower than the NOAEL selected from the rat subchronic oral toxicity study [3.3 mg/kg/day, based on F1 female rat deaths during the pre-mating period], the deaths in the F1 rats at the mid-dose level [LOAEL F1 females 32.9 mg/kg/day] did not occur until days 197 and 213. At the high-dose level [F1 males 115.4/F1 females 138.9 mg/kg/day], the deaths [both sexes] occurred early [F1 females (days 9, 9, 25, 27, 47); F1 males (days 13, 15, 20, 27 30)], and this dose and endpoint might be considered appropriate for short-term dermal/inhalation exposure risk. However, the NOAEL for early deaths would then be the mid-dose; i.e., 32.9 mg/kg/day, which is greater than the dose proposed [14 mg/kg/day].

NOTE: There is a datagap for a rabbit developmental toxicity study. In the available rabbit study, no significant effects were observed at 20 mg/kg/day [the highest dose tested], which is considered inadequate. The current acute RfD for females 13+ is 0.5 mg/kg, based on a NOAEL of 50 mg/kg from the rat developmental toxicity study [decreased fetal weight and skeletal abnormalities observed at 150 mg/kg]. The required rabbit developmental toxicity study is not likely to provide a lower NOAEL than the 14 mg/kg/day proposed for this risk assessment, but it is plausible that it might identify a dose and endpoint for an acute RfD for the general population, including infants and children. Therefore, no additional uncertainty factor was recommended for the short-term dermal exposure risk assessment.

Supporting Study: Chronic toxicity/carcinogenicity

870.4300/§83-5

MRID No.: 00150329

Executive Summary: In a combined chronic/carcinogenicity study [MRID 150329], lactofen technical (75.88% a. I., average) was administered to Charles River CD rats (84/sex/dose) in the diet at concentrations of 0, 50, 500, 1000, or 2000 ppm (approximately 0, 37.9, 379.4, 758.8, or 1517.6 ppm based on active ingredient) or 0, 2, 19, 38, 76 mg/kg/day (conversion factor 20 ppm = 1 mg/kg) for 104 weeks.

A statistically significant decrease in mean body weights was noted for both males and females at the 2000

ppm dose level. In males, this decrease in body weight occurred between weeks 1 - 86 of the study while female weight loss began at week 4 and persisted until week 102 of the study period. This observation is consistent with the concomitant decrease in food consumption (statistically significant) reported for males and females in the 2000 ppm dose group. A statistically significant decrease in food consumption was also reported for 1000 ppm males during the first 13 weeks of the study. Overall body weight decreases at the high dose level were \approx 16% and 12% for males and females, respectively, during the first 12 months of the study.

A statistically significant increase in the incidence of mottled or diffusely dark livers and kidneys was first noted in the 500 ppm dose group during the 12-month scheduled sacrifice. Furthermore, at the time of terminal sacrifice (24 months), a dark discoloration of the testes was also observed in males treated at the 1000 ppm and 2000 ppm dose levels.

Males in the 2000 ppm dose group had an increase in early deaths at the 12 months evaluation period (8 at 2000 ppm vs. 1 in control group). This reflected 25% of all deaths in the study for the 2000 ppm dose group in contrast to 2% of all deaths for the control group. Interestingly, the mortality rate appeared to stabilize after the 1-year evaluation and the final mortality tallies for males were 42, 45, 37, 29, and 32 for the 0, 50, 500, 1000, and 2000 ppm dose groups, respectively. In the case of females, there was a slight (not statistically significant) increase in mortality at the 1000 and 2000 ppm dose levels reported during the 1-year evaluation. However, overall survival at the 18 and 24 month intervals were comparable between the control groups and all test groups.

A statistically significant reduction in hematocrit and hemoglobin was reported for females in the 2000 ppm dose group during the 6 and 12 month evaluation periods. For their part, males showed evidence of a statistically significant reduction in these parameters at the 1-year evaluation for the 1000 ppm and 2000 ppm. These changes in hemoglobin and hematocrit, however, were no longer evident by the 18 month examination period.

Blood chemistry analysis revealed dose- and compound-related increases in aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase at the 500, 1000, and 2000 ppm dose levels. Additionally, compound-related decreases in cholesterol, total protein, globulin, and BUN were also reported. These changes in blood chemistry were deemed to be indicative of liver toxicity.

Non-neoplastic lesions discovered during microscopic examination included pigmentation of hepatocytes, Kupffer cells, and renal cortical tubule cells. At the 1000 and 2000 ppm dose levels, the incidences of these lesions attained statistical significance for females while males showed evidence of a statistically significant increase in the incidence of pigmented Kupffer cells and renal cortical tubule cells only.

Pre-neoplastic and neoplastic lesions were evident at the 500 ppm dose level and higher. Males and females in the high-dose group (2000 ppm) had an increased incidence of basophilic foci of cellular alteration and neoplastic nodules in the liver. Males in this dose group also showed evidence of an increase in eosinophilic foci of cellular alteration. An increase in uterine endometrial stromal polyps was seen in females exposed to the test substance at all dose levels. Statistical significance, however, was attained at the 500 ppm dose level and higher. It is noteworthy that - while statistically significant - these lesions (even at 50 ppm dose level) are within the historical control data provided by the testing facility and did not appear to be dose-related. Consequently, the toxicological relevance of these observations is uncertain. No other neoplastic lesions

that could be considered compound-related were seen during the study period.

Based on the statistically significant decreases in body weight and food consumption, significant changes in blood chemistry parameters, as well as histopathology findings in the liver and kidneys, seen in this study, the highest dose of lactofen tested was considered adequate for the assessment of the carcinogenicity potential of this compound.

Under the conditions of this study, the LOAEL is established at 500 ppm (19 mg/kg/day) based on the findings of statistically significant increases in mottled or discolored livers and kidneys and changes in blood chemistry parameters. The NOAEL is established at 50 ppm (2 mg/kg/day).

This study is classified as **Acceptable/guideline** and **satisfies** the requirement for a combined chronic toxicity/carcinogenicity study in rats (OPPTS 870.4300; §83-5).

Comments about Study/Margins of Exposure: Although the overall NOAEL for the study is 50 ppm [2 mg/kg/day], based on, among other effects, increased hepatic enzymes, increases at 500 ppm were not observed until 18 months [see original DER]. Increases at 1000 ppm were observed at 6, 12, and 18 months and those at 2000 ppm occurred throughout the study. In the rat subchronic toxicity study, increases in these enzymes were observed at the high-dose level [1000 ppm; 73.7/84.5 mg/kg/day] at 45 and 90 days [NOAEL 14.1/17.0 mg/kg/day]. Although the chronic study gives a higher NOAEL than the subchronic study for the early time point, this is considered an artifact of dose selection. See Comments above. Since an oral NOAEL is selected, a dermal absorption factor of 20% is proposed for route-to-route extrapolation.

8. Intermediate-Term Dermal (1 - 6 Months) Exposure

Study: subchronic oral toxicity - rat

OPPTS 870.3100/§ 82-1(a)

MRID No.: 00117564

Executive Summary: see under Short-Term Dermal

Dose/Endpoint for Risk Assessment: NOAEL = 200 ppm [14 mg/kg/day], based on body weight decrements in males, anemia in males, **elevated serum enzymes** [alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, alkaline phosphatase], and bilirubin in males and females, decreased glucose in males, increased liver weights in males and females, and microscopic liver lesions in males at the LOAEL of 1000 ppm [73.7 mg/kg/day].

Comments about Study/Margins of Exposure: The liver is a target organ for lactofen, and elevated levels of several enzymes indicative of liver toxicity are observed following exposure to lactofen. The higher the exposure the earlier the increase in enzyme levels. See above under Short-Term Dermal Exposure. Since an oral NOAEL is selected, a dermal absorption factor of 20% is proposed for route-to-route extrapolation.

9. Long-Term Dermal (> 6 Months) Exposure

Study: mechanistic study - mice

OPPTS none/§none

Accession No.: 45283904

Executive Summary: In a dietary study [MRID 45283904], male and female Crl:CD(SD)BR rats [8-week study] and Crl:CD1 mice [7-week study] were fed diets containing technical [78.2%] lactofen at 0, 2, 10, 50, and 250 ppm, pure [99.8%] lactofen at 250 ppm, or nafenopin at 250 ppm [positive control for peroxisome proliferation] at 500 ppm. Biochemical markers of peroxisomal proliferation included measurement of hepatic acyl CoA oxidase, catalase, and carnitine acetyl transferase activities. Light and electron microscopic examinations were used to evaluate livers for evidence of peroxisomal proliferation.

After 7 weeks of treatment, the mice were sacrificed and the livers examined biochemically and pathologically. Dose-dependent increases were observed in relative liver weights, catalase and acyl CoA oxidase (both sexes), and carnitine acetyl transferase (females only). Histological evaluations also revealed dose-dependent increases in nuclear enlargement, cytoplasmic eosinophilia, hypertrophy and peroxisomal staining in livers. Nafenopin-treated mice showed significant increases in all of the parameters measured.

Similar findings were observed in the 8-week rat study. Lactofen-treated rats had significantly increased relative liver weights, carnitine acetyl transferase and acyl CoA oxidase. Histological examination revealed an increased incidence of nuclear enlargement, cytoplasmic eosinophilic eosinophilia, hypertrophy, and peroxisomal staining; catalase activity was not affected by treatment. Nafenopin-treated rats showed significant increases in all of the parameters indicative of peroxisome proliferation measured.

From the electron microscopic analysis of the male livers, the ratio of peroxisomes to mitochondria were determined [quantitative measurement of peroxisome proliferation] in both species. The ratios were 1/4.7 (21%) and 1/3.0 (33%) for control and treated male rats, respectively and 1/4.8 (21%) and 1.1.5 (66%) for control and treated male mice, respectively.

The mouse is more sensitive to the effects of lactofen on the liver than the rat.

The results not only showed dose-dependent increases in the parameters measured, but more importantly, a non-linear dose-response curve with a NOAEL. A NOAEL of 2 ppm (0.3 mg/kg/day; using a conversion factor of 1 ppm = 0.15 mg/kg/day) was based on increases in relative liver weight (male mice), carnitine acetyl transferase and palmitoyl CoA oxidase (female mice) at a LOAEL of 10 ppm (1.5 mg/kg/day).

This mechanistic study is classified Acceptable/non-guideline.

Dose/Endpoint for Risk Assessment: NOAEL 2 ppm (0.3 mg/kg/day), based on increases in relative liver weight (male mice), carnitine acetyl transferase and palmitoyl CoA oxidase (female mice) at a LOAEL of 10 ppm (1.5 mg/kg/day).

Uncertainty Factor(s): 100X [10X for intraspecies variation and 10X for interspecies variation]

Comments about Study/Margins of Exposure: Previously, the HIARC [HED Document No. 014025, dated 3/6/00] used the dog chronic oral toxicity study [MRID 00128446] for establishing chronic RfD [NOAEL of 0.79 mg/kg/day, based on the increased incidence of proteinaceous casts in the kidneys and statistically significant decreases in the absolute weight of the thyroid and adrenal glands in males at the LOAEL of 3.96 mg/kg/day]. Subsequently, the HED Mechanism of Toxicity Assessment Review Committee [MTARC]

concluded that, based on the weight-of-evidence from guideline, as well as non-guideline mechanistic studies, there are sufficient data to classify lactofen as a non-genotoxic hepatocarcinogen in rodents with peroxisome proliferation being a plausible mode of action [TXR No. 014590]. The HED Cancer Assessment Review Committee [CARC] concluded that lactofen should be classified as **likely to be carcinogenic to humans at high enough doses to cause the biochemical and histopathological effects observed in the livers of rodents but unlikely to be carcinogenic at doses below those causing these changes**. Further, the margin of exposure [MOE] approach should be used for estimating human cancer risk, using a NOAEL of 2 ppm (0.3 mg/kg/day) from this mechanistic study. The CARC also concluded that a NOAEL of 0.3 mg/kg/day can be used for chronic and reproductive NOAELs. The NOAEL of 0.3 mg/kg/day is also protective of carcinogenic effects, which has a NOAEL of 10 ppm [1.5 mg/kg/day].

10. Short-Term Inhalation (1 - 30 days) Exposure

Study: Subchronic toxicity - rat

OPPTS 870.3100; §82-1

MRID No.: 00117564

Executive Summary: see under Short-Term Dermal

Dose/Endpoint for Risk Assessment: NOAEL = 200 ppm [14 mg/kg/day], based on body weight decrements in males, anemia in males, **elevated serum enzymes** [alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, alkaline phosphatase], and bilirubin in males and females, decreased glucose in males, increased liver weights in males and females, and microscopic liver lesions in males at the LOAEL of 1000 ppm [73.7 mg/kg/day].

Comments about Study/Margins of Exposure: The liver is a target organ for lactofen, and elevated levels of several enzymes indicative of liver toxicity are observed following exposure to lactofen for various exposure durations. The higher the exposure, the earlier the increase in enzyme levels. See under Short-Term Dermal Exposure. Since an oral NOAEL is selected, an inhalation absorption factor of 100% should be used for route-to-route extrapolation.

11. Intermediate-Term Inhalation (1-6 Months) Exposure

Study: subchronic oral toxicity - rats

OPPTS870.3200/ §82-1

MRID No.: 00117564

Executive Summary: see under Short-Term Dermal Exposure

Dose/Endpoint for Risk Assessment: NOAEL = 200 ppm [14 mg/kg/day], based on body weight decrements in males, anemia in males, **elevated serum enzymes** [alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, alkaline phosphatase], and bilirubin in males and females, decreased glucose in males, increased liver weights in males and females, and microscopic liver lesions in males at the LOAEL of 1000 ppm [73.7 mg/kg/day].

Comments about Study/Margins of Exposure: see under Short-Term Dermal Exposure. Since the selected study is an oral study, the inhalation absorption factor of 100% should be used for route-to-route extrapolation.

12. Long-Term Inhalation (>6 Months) Exposure

Study: mechanistic study - mice

OPPTSnone/§none

MRID No.: 45283904

Executive Summary: see under Long-Term Dermal Exposure

Dose/Endpoint for Risk Assessment: NOAEL 2 ppm (0.3 mg/kg/day), based on increases in relative liver weight (male mice), carnitine acetyl transferase and palmitoyl CoA oxidase (female mice) at a LOAEL of 10 ppm (1.5 mg/kg/day).

Uncertainty Factor(s): 100X [10X for intraspecies variation and 10X for interspecies variation]

Comments about Study/Margins of Exposure: see under Long-Term Dermal Exposure. Since the selected study is an oral study, the inhalation absorption factor of 100% should be used for route-to-route extrapolation.

SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

Doses/toxicological endpoints for dermal and inhalation exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary Females 13+	NOAEL= 50 mg/kg b.w. UF = 100	decreased fetal weight and skeletal abnormalities.	developmental toxicity study - rat
	Acute RfD = 0.5 mg/kg b.w.		
Acute Dietary General Population including Infants and Children			
	no appropriate endpoint identified		
Chronic Dietary	NOAEL = 0.3 mg/kg/day UF = 100	increases in relative liver weight (male mice), carnitine acetyl transferase and palmitoyl CoA oxidase (female mice)	mechanistic study [mouse]
		Chronic RfD = 0.003 mg/kg/day	
Dermal, Short-Term	NOAEL = 14 mg/kg/day	body weight decrements in males, anemia in males, elevated serum enzymes and bilirubin in males and females, decreased glucose in males, increased liver weights in males and females, and microscopic liver lesions in males.	subchronic oral toxicity study - rat
Dermal, Intermediate-Term	NOAEL= 14 mg/kg/day	body weight decrements in males, anemia in males, elevated serum enzymes and bilirubin in males and females, decreased glucose in males, increased liver weights in males and females, and microscopic liver lesions in males.	subchronic oral toxicity study - rat
Dermal, Long-Term	NOAEL= 0.3 mg/kg/day	increases in relative liver weight (male mice), carnitine acetyl transferase and palmitoyl CoA oxidase (female mice)	mechanistic study [mouse]
Inhalation, Short-Term	NOAEL= 14 mg/kg/day	body weight decrements in males, anemia in males, elevated serum enzymes and bilirubin in males and females, decreased glucose in males, increased liver weights in males and females, and microscopic liver lesions in males.	subchronic oral toxicity study - rat
Inhalation, Intermediate-Term	NOAEL= 14 mg/kg/day	body weight decrements in males, anemia in males, elevated serum enzymes and bilirubin in males and females, decreased glucose in males, increased liver weights in males and females, and microscopic liver lesions in males.	subchronic oral toxicity study - rat
Inhalation, Long-Term	NOAEL= 0.3 mg/kg/day	increases in relative liver weight (male mice), carnitine acetyl transferase and palmitoyl CoA oxidase (female mice)	mechanistic study [mouse]
Cancer (oral, dermal, inhalation)	Classification: likely to be carcinogenic to humans at high enough doses to cause the biochemical and histopathological changes in the liver of rodents but unlikely to be carcinogenic to humans below those doses causing these changes [use an MOE approach for estimating human cancer risk]		

¹ UF = uncertainty factor, FQPA SF = FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, LOC = level of concern, MOE = margin of exposure