

FILE NAME: NOF Fruiting Veg 3-19-04.wpd

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PP Number:

Summary of Petition

EPA has received a pesticide petition (insert petition number) from The Interregional Research Project No. 4, North Brunswick, N.J., proposing, pursuant to section 408(d) of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. 346a(d), to amend 40 CFR part 180.432 by establishing a tolerance for residues of the herbicide lactofen, 1-(carboethoxy) ethyl 5-[2-chloro-4-(trifluoromethyl)phenoxy]-2-nitrobenzoate, in or on the raw agricultural commodity crop group, vegetable, fruiting, Crop Group 8 and okra at 0.01 ppm. EPA has determined that the petition contains data or information regarding the elements set forth in section 408(d)(2) of the FFDCA; however, EPA has not fully evaluated the sufficiency of the submitted data at this time or whether the data supports granting of the petition. Additional data may be needed before EPA rules on the petition.

A. Residue Chemistry

1. *Plant metabolism.* The nature of the residue in plants is adequately understood based on plant metabolism studies conducted on cotton, peanut, soybean, and tomato. The regulated residue of concern is parent, lactofen.

2. *Analytical method.* Adequate analytical methodology is available for detecting and measuring levels of lactofen in or on raw agricultural commodities with a limit of detection that allows monitoring of food with residues at or above the level of the proposed tolerances. The method, RM-28D, has been successfully radiovalidated in conjunction with a tomato metabolism study, has undergone a successful independent laboratory validation trial, and was successfully validated by the EPA Analytical Chemistry Laboratory using peanut nutmeats and cottonseed. In general, the analytical method has a limit of detection of 0.005 ppm and a limit of quantitation of 0.01 ppm in crops.

3. *Magnitude of residues.* An adequate number of field trials has been conducted on tomatoes and peppers to determine lactofen residues resulting from the application of lactofen at the maximum proposed use rate.

i. Tomato: In five (5) residue trials conducted in Florida, residues of lactofen were each <0.01 ppm in/on tomatoes harvested 30 days following 2-3 applications of lactofen at 0.5 pounds active ingredient per acre (lbs. a.i./A). All applications were made either pre-transplant or via a shielded ground spray to tomato row middles at 14-67 day intervals. In a single residue trial conducted in Florida, residues of lactofen were <0.01 in/on tomatoes harvested 30 days following 2 applications of lactofen at 2.5 lbs. a.i./A (5x rate). Since no residues of lactofen were detected in samples treated at the 5x rate, a tomato processing study was not conducted.

ii. Peppers: In three (3) residue trials conducted in Florida (2 bell and 1 non-bell), residues of lactofen were each <0.01 ppm in/on peppers harvested 30 days following 2 applications of lactofen at 0.5 lbs. a.i./A. All applications were made either pre-transplant or via a shielded ground spray to pepper row middles at 46-67 day intervals.

All these data support the proposed tolerance for lactofen in/on vegetable, fruiting, Crop Group 8 and okra at 0.01 ppm. No separate tolerances are needed for tomato processed commodities. The number of field trials conducted (5 tomato, 3 pepper) and the location of the trials (northern Florida) support a product registration that is geographically limited to the states of Alabama, Arkansas, Florida, Georgia, Mississippi, North Carolina, South Carolina, Tennessee, and Virginia.

B. Toxicological Profile

1. *Acute toxicity.* Lactofen has very low acute toxicity. The acute oral LD₅₀ is 5.96 g/kg b.w. (Tox Category IV), the acute dermal LD₅₀ is >2.0 g/kg b.w. (Tox Category III) and the acute inhalation LD₅₀ is >6.3 mg/L (Tox Category IV). Lactofen is not a skin sensitizer but is a very slight dermal irritant.

2. *Genotoxicity.* Lactofen has very little mutagenic or genotoxic activity. While a positive mutagenic response was reported in one trial of a *Salmonella typhimurium*/mammalian microsome mutagenicity assay, this response was not observed in a repeat assay. In addition, lactofen did not induce chromosomal aberrations, unscheduled DNA synthesis or inhibit DNA repair.

3. *Reproductive and developmental toxicity.* Reproduction and teratology studies indicate that adverse effects, including embryotoxicity, occur only at doses that are also maternally toxic. Since lactofen causes effects only at levels which also produce systemic toxicity, the compound is not a reproductive hazard.

i. *Rat Reproduction:* In a 2-generation reproduction study in rats, decreased pup weight and decreased absolute and relative weights of the spleen were first reported at approximately 26.2 mg/kg/day (based on dose administered to the parental group). The same dose level elicited mortality and decreased male fertility in the parental groups. The NOEL for both systemic and reproductive toxicity in this study was 2.6 mg/kg/day.

ii. *Rat Developmental:* In the developmental toxicity study in rats, effects were observed at the 150 mg/kg/day dose level consisting of decreases in fetal weight as well as skeletal abnormalities. This dose level also elicited signs of toxicity in the parental group. The NOEL for this study was 50 mg/kg/day.

iii. *Rabbit Developmental:* Two developmental toxicity studies were conducted in rabbits. In the first study, pregnant rabbits were administered oral doses of 0, 5, 15 or 50 mg/kg bw/day lactofen technical on days 6-18 of gestation. Maternal toxicity (clinical signs and reduced weight gain) and developmental effects (increased embryonic death, decreased litter size and increased post-implantation loss) were reported at 15 and 50 mg/kg. The Agency concluded that the data were insufficient to establish a clear NOEL. A second rabbit developmental toxicity study was therefore conducted in which pregnant rabbits were exposed to 0, 1, 4 or 20 mg/kg bw/day oral doses on days 6-18 of gestation. Maternal toxicity (reduced food consumption) was observed at 20 mg/kg bw/day, but no developmental effects were observed at any dose. Therefore, the maternal NOEL was 4 mg/kg bw/day and the

developmental NOEL was greater than 20 mg/kg bw/day.

4. *Subchronic toxicity.* i. Rats 4-Week: Male and female rats were fed diets containing lactofen technical at concentrations of 0, 200, 1,000, 5,000, and 10,000 ppm for four weeks. A slight increase in spleen weight was the basis for a LOEL of 200 ppm (lowest dose tested). At doses of 1,000 ppm or higher, the following findings were reported: clinical signs of toxicity; decreased RBC, hemoglobin, hematocrit, and increased WBC; increased relative liver and spleen weights; and necrosis and pigmentation of hepatocytes. At 10,000 ppm, severe toxic signs were observed by day 7 and all animals were dead or killed *in extremis* by day 11. Hypocellularity of the spleen, thymus and bone marrow was also observed in animals exposed to 10,000 ppm.

ii. Rats 3-Month: lactofen technical was fed to male and female rats at dietary concentrations of 0, 40, 200, and 1,000 ppm for 13 weeks. Histopathological changes in the liver and significant changes in clinical chemistry associated with the liver were observed in rats exposed to 1,000 ppm dosage. Decreased RBC, hemoglobin and hematocrit values were also observed at 1,000 ppm. The NOEL in this study was 200 ppm (14.1 mg/kg/day).

iii. Dogs 4-week: In a range finding study, lactofen technical was fed in the diet of dogs at 0, 1,000, 3,000, and 10,000 ppm for four weeks. Toxic effects noted in dogs fed 10,000 ppm included decreased RBC count and hemocrit and increased BUN and SGPT. Food palatability problems led to greatly decreased feed consumption at higher dosages. The NOEL was 1,000 ppm (0.79 mg/kg/day).

iv. Mice 3-Month: Groups of male and female mice were fed diets containing lactofen technical at concentrations of 0, 40, 200, 1,000, 5,000, and 10,000 for 13 weeks. At week five, the dosage of the 40 ppm groups was increased to 2,000 ppm. Treatment related mortality occurred at dosages above 1,000 ppm. The LOEL was 200 ppm (28.6 mg/kg/day) based on: increased WBC; decreased hematocrit, hemoglobin and RBC; increased alkaline phosphatase, SGOT, SGPT, cholesterol and total serum protein levels; increased weights or enlargement of the spleen, liver, adrenals, heart and kidney; histopathological changes of the liver, kidney, thymus, spleen, ovaries and testes. In general, effects were slight in the 200 ppm groups, and moderate to severe in the 1,000 ppm groups.

5. *Chronic toxicity.* Lactofen causes adverse health effects when administered to animals for extended periods of time. These effects include proliferative changes in the liver, spleen, and kidney; hematological changes; and blood biochemistry changes.

i. Mouse 18-Month: In a dietary 18-month oncogenicity study in mice at dosages of 10, 50 and 250 ppm lactofen technical, an increase in liver adenomas and carcinomas, cataracts and liver pigmentation was observed at 250 ppm, a dose that clearly exceeded the MTD. The lowest dose, 10 ppm (1.4 mg/kg/day), was the LOEL based on increased liver weight and hepatocytomegaly.

ii. Rat 24-Month: In a 2-year chronic feeding/oncogenicity study of lactofen technical in rats at dosages of 0, 500, 1,000 and 2,000 ppm in the diet, an increase in liver neoplastic nodules and foci of cellular alteration was observed in both sexes at 2,000 ppm. The NOEL for systemic toxicity is 500 ppm (2 mg/kg/day) based on kidney and liver pigmentation.

iii. Dog 12-Month: In a 1-year study in dogs exposed to 40, 200, and 1,000 (week 1-17) or 3,000 ppm (week 18-52) lactofen technical in their diet, the NOEL was determined to be 200 ppm (0.79 mg/kg/day) based on renal dysfunction and decreased RBC, hemoglobin hematocrit and cholesterol observed at 1,000/3,000 ppm.

iv. Carcinogenicity: EPA's Cancer Assessment Review Committee (CARC) has recently revised the cancer classification of lactofen based on several mechanistic studies showing that lactofen oncogenicity occurs via a peroxisome proliferation mechanism [Tolerance Reassessment and Risk Management Decision (TRED) for Lactofen; Federal Register of January 28, 2004 (69 FR 4129) (OPP-2003-0294; FRL-7336-9)]. Lactofen is now classified under EPA's 1999 Cancer Risk Assessment Guidelines as "likely to be carcinogenic to humans at high enough doses to cause these biochemical and histopathological effects (peroxisome proliferation) in the livers of rodents but unlikely to be carcinogenic at doses below those causing these changes". Lactofen is a threshold carcinogen with the Margin of Exposure (MOE) calculated using the NOAEL of 2 ppm (0.3 mg/kg/day) from a special 7-week rodent study which evaluated peroxisome proliferation in the livers of rats and mice. In this study, mice were exposed to lactofen at 0, 2, 10, 50, or 250 ppm. 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, in two liver peroxisomal enzymes, catalase and acyl CoA oxidase, and in carnitine acetyltransferase. Histological evaluations also revealed dose-dependent increases in nuclear enlargement, cytoplasmic eosinophilia, hypertrophy and peroxisomal staining in livers. These results not only show dose-dependent increases in the parameters measured, but more importantly, a non-linear dose-response curve with a NOAEL. The NOAEL of 2 ppm (0.3 mg/kg/day) was based on increase in relative liver weight, carnitine acetyl transferase, and palmitoyl CoA oxidate at a LOAEL of 10 ppm (1.5 mg/kg/day). Similar effects were seen in rats, exposed to lactofen at 2000 ppm for 8 weeks. No endpoints were selected since the rats were exposed at only one high dose level.

6. *Animal metabolism.* In a rat metabolism study, lactofen was shown to metabolize to acifluorfen, 5-[2-chloro-4-(trifluoromethyl)phenoxy]-2-nitrobenzoate, which was eliminated via both urine and feces. While lactofen was the primary compound found in the feces, acifluorfen accounted for >90% of the radioactivity in the urine. Negligible amounts of the administered radioactivity were found in any tissue with less than 0.8% of the administered radioactivity being found in the liver (one of the main target organs).

7. *Metabolite toxicology.* Acifluorfen is also a hydrolytic metabolite of lactofen. The sodium salt of this benzoic acid is the registered herbicide, sodium acifluorfen. The chronic population adjusted dose (c-PAD) for acifluorfen is 0.004 mg/kg/day for infants, children and females 13-50 years old and 0.013 mg/kg/day for other population subgroups. EPA's Cancer Assessment Review Committee (CARC) has recently revised the cancer classification of acifluorfen based on mechanistic studies showing that acifluorfen oncogenicity occurs via a peroxisome proliferation mechanism [Reregistration Eligibility Decision (RED) for the pesticide active ingredient sodium acifluorfen; Federal Register of January 28, 2004 (69 FR 4136) (OPP-2003-0293; FRL-7337-1)]. Acifluorfen is now classified under EPA's 1999 Cancer Risk Assessment Guidelines as "likely to be carcinogenic to humans at high enough doses to cause these biochemical and histopathological effects (peroxisome proliferation) in the livers of rodents but unlikely to be carcinogenic at doses below those causing these changes". The CARC further recommended using a MOE approach for estimating human cancer risk from exposure to acifluorfen. A NOAEL of 25 ppm (1.25 mg/kg/day) was recommended for calculating the MOE. Because lactofen and its metabolites are not retained in the body, the potential for acute toxicity from *in situ* formed metabolites is low. The potential for chronic

toxicity of lactofen metabolites has been adequately addressed by an extensive battery of lactofen chronic toxicity testing.

8. *Endocrine Disruption*: No special studies to investigate the potential for estrogenic or other endocrine effects of lactofen have been performed. However, a large and detailed toxicology database exists for the compound including studies acceptable to the Agency in all required categories. These studies include evaluations of reproduction and reproductive toxicity and detailed pathology and histology of endocrine organs following repeated or long-term exposure. These studies are considered capable of revealing endocrine effects and no such effects were observed.

C. Aggregate Exposure

1. *Dietary exposure*. Acute and chronic dietary analyses were conducted to estimate exposure to potential lactofen residues in/on the following crops: soybeans and snap beans (existing tolerances); cotton and peanuts (tolerances pending); and fruiting vegetables (tolerances proposed in the current petition). The Cumulative and Aggregate Risk Evaluation System (CARES) Version 2.0 was used to conduct this assessment. This analysis utilized tolerance level residues, consumption data from USDA's Continuing Survey of Food Intakes by Individuals (CSFII) from 1994-1996, 1998 (USDA, 2000), and the latest USEPA guidance (USEPA, 1999 and USEPA, 2000). The reported dietary exposure values are based on 100% crop treated.

i. *Food*. a. Acute-No endpoint has been established to assess the acute risk of exposure to lactofen for the general U.S. population. An acute Population Adjusted Dose (a-PAD) has, however, been established for females of child-bearing age (13-50 years old). This a-PAD was calculated to be 0.17 mg/kg/day using the NOEL from the rat developmental study, 50 mg/kg/day, an uncertainty factor of 100 to account for inter-species extrapolation (10x) and intra-species variation (10x) and an additional FQPA safety factor of 3. The potential acute exposure from food to females 13-50 years old was calculated to be 0.07% of the a-PAD.

b. Chronic-The NOEL from the chronic oral toxicity study in dogs, 0.79 mg/kg/day, was selected as the chronic oral toxicity endpoint. Based on this NOEL and an uncertainty factor of 100, the Chronic Population Adjusted Dose (c-PAD) for lactofen has been set at 0.008 mg/kg/day. The chronic dietary exposure estimate of lactofen residues in food at the 100th percentile was calculated to be, at most, 0.68% of the c-PAD with a MOE of 14,469. The population subgroup with the highest exposure was children 1-2 years old.

c. Cancer-Cancer margins of exposure, calculated using the 0.3 mg/kg/day endpoint from the 7-week rodent study which evaluated peroxisome proliferation in the liver of rats and mice, exceed 5,400 for all population subgroups. The 0.3 mg/kg/day endpoint is considered to be protective of cancer effects because the changes in liver enzymes and histopathology are believed to precede liver tumor formation for a peroxisome proliferation mode of action. The Agency, therefore, has no concern for cancer risks associated with exposure to lactofen in food.

ii. *Drinking water*. Lactofen has a low probability to contaminate drinking water because it has a short half-life (three days or less) and high binding potential ($K_{oc} > 1000$). The HED Metabolism Assessment Review Committee (MARC) has concluded that the residues of concern in drinking water are the degradates acifluorfen and amino acifluorfen. Insufficient

information is available to estimate the amino acifluorfen concentration in water, but it is likely to be less than that of acifluorfen. Laboratory studies have shown that acifluorfen reaches its maximum concentration of 53.3% of applied lactofen at 7 days following application and it is most likely to form under the soil surface. Thus, the formed acifluorfen is not subject to drift, erosion, or runoff forces that contribute to surface water contamination. Surface water, however, could be contaminated with acifluorfen from lactofen applications via spray drift. The registrant also has conducted two prospective groundwater studies which showed that neither lactofen nor acifluorfen (from lactofen applications) contaminate groundwater.

To assess the acute, chronic, and cancer risks associated with exposure to lactofen and acifluorfen (from applications of lactofen) in surface water, OPP has calculated drinking water levels of comparison (DWLOCs) and Estimated Drinking Water Concentrations (EDWCs) [Tolerance Reassessment of Risk Management Decision (TRED) for Lactofen; Federal Register of January 28, 2004 (69 FR 4129) (OPP-2003-0294; FRL-7336-9)]. EDWCs that are above the corresponding DWLOC exceed the Agency's level of concern.

Dietary Exposure and Risk to Lactofen from Drinking Water

Exposure	EDWC (ppb)		DWLOC (ppb)
	Surface Water	Groundwater	
Acute	0.39	0.006	5100
Chronic (non-cancer)	0.008	0.006	80
Cancer	0.007	0.006	105

Dietary Exposure and Risk to Acifluorfen from Drinking Water

Exposure	EDWC (ppb)		DWLOC (ppb)
	Surface Water	Groundwater	
Acute	10	3.7	600
Chronic (non-cancer)	2.4	3.7	40
Cancer	1.3	3.7	455

The EDWC values for all exposures are less than the corresponding DWLOC values; therefore, the Agency has no concern for the aggregate risk of lactofen and acifluorfen from lactofen in drinking water.

2. *Non-dietary exposure.* Lactofen is proposed only for agricultural uses and no homeowner or turf uses. Thus, no non-dietary risk assessment is needed.

D. Cumulative Effects

Section 408(b)(2)(D)(v) requires that the Agency must consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." Available information in this context include not only toxicity, chemistry, and exposure data, but also scientific policies and methodologies for understanding common mechanisms of toxicity and conducting cumulative risk assessments. For most pesticides, although the Agency has some information in its files that may turn out to be helpful in eventually determining whether a pesticide shares a common mechanism of toxicity with any other substances, EPA does not at this time have the methodologies to resolve the complex scientific issues concerning common mechanism of toxicity in a meaningful way.

There are other pesticidal compounds that are structurally related to lactofen and have similar effects on animals. In consideration of potential cumulative effects of lactofen and other substances that may have a common mechanism of toxicity, there are currently no available data or other reliable information indicating that any toxic effects produced by lactofen would be cumulative with those of other chemical compounds. Thus, only the potential risks of lactofen have been considered in this assessment of aggregate exposure and effects.

Valent will submit information for EPA to consider concerning potential cumulative effects of lactofen consistent with the schedule established by EPA at 62 Federal Register 42020 (Aug. 4, 1997) and other subsequent EPA publications pursuant to the Food Quality Protection Act.

E. Safety Determination

Water is not expected to be a significant source of exposure for lactofen, as it degrades quickly in the environment to numerous degradates, including acifluorfen. Estimated drinking water concentrations (EDWCs) for lactofen and acifluorfen are well below the Drinking Water Levels of Comparison (DWLOCs) for chronic, acute, and cancer risk. Therefore, the only significant source of human exposure to lactofen is in food.

1. *U.S. population.* i. *Acute Risk.* No endpoint has been established to assess the acute risk of exposure to lactofen for the general U.S. population. An a-PAD has, however, been established for females of child-bearing age (13-50 years old) and it has been estimated that the potential acute exposure from food to this population subgroup will utilize 0.07% of the a-PAD. The Agency has no cause for concern if total acute residue contribution is less than 100% of the a-PAD. Therefore, it can be concluded that there is a reasonable certainty that no harm will result to this subpopulation from aggregate, acute exposure to lactofen residues.

ii. *Chronic Risk.* The potential chronic exposure from food to the U.S. Population and various non-child/infant population subgroups will utilize at most 0.66% of the c-PAD. The Agency has no cause for concern if total chronic residue contribution is less than 100% of the c-PAD. Therefore, it can be concluded that there is a reasonable certainty that no harm will result to the overall U.S. Population from aggregate, chronic exposure to lactofen residues.

iii. *Cancer Risk.* Cancer margins of exposure, calculated using the 0.3 mg/kg/day endpoint from the 7-week rodent study which evaluated peroxisome proliferation in the liver of rats and mice, exceed 5,600 for all non-child/infant population subgroups. The Agency, therefore, has no concern for cancer risks associated with exposure of the general population

to lactofen in food.

2. *Infants and children.* i. Safety Factor for Infants and Children. Reproduction and developmental effects have been found in toxicology studies for lactofen but only at levels that were also maternally toxic. This indicates that developing animals are not more sensitive than adults.

ii. Chronic Risk. The potential chronic exposure from food to children 1-2 years old (the most highly exposed child/infant subgroup) will utilize 0.68% of the c-PAD. Therefore, it can be concluded that there is a reasonable certainty that no harm will result to infants and children from aggregate, chronic exposure to flumioxazin residues.

iii. Cancer Risk. Cancer margins of exposure, calculated using the 0.3 mg/kg/day endpoint from the 7-week rodent study which evaluated peroxisome proliferation in the liver of rats and mice, exceed 5,400 for all child/infant population subgroups. The Agency, therefore, has no concern for cancer risks associated with exposure of infants and children to lactofen in food.

F. International Tolerances. There are no Codex Maximum Residue Limits (MRLs) established for lactofen on fruiting vegetable commodities, so there is no conflict between this proposed action and international residue limits.