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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

Date: 24-JUN-2005

Subject: Flumiclorac Pentyl. Summary of Residue Chemistry Data for the Tolerance Reassessment Eligibility Decision (TRED) Document and a Petition (PP#3F6767) for the Establishment of Tolerances on Cotton.

DP Number: D308674
PC Code: 128724
MRID Numbers: 46082803, 46082804, 46082805, 46082806, 46082808, and 46102801
40 CFR §180: 477
Chemical Class: Dicarboximide Herbicide

From: William H. Donovan, Ph.D., Chemist
Reregistration Branch 3 (RRB3)
Health Effects Division (HED) (7509C)

William H. Donovan

Through: Catherine Eiden, Branch Chief
RRB3, HED (7509C)

To: Twanda Spears, CRM
Reregistration Branch III
Special Review and Reregistration Division (SRRD) (7508C)

This document was originally prepared under contract by Dynamac Corporation (20440 Century Boulevard, Suite 100; Germantown, MD 20874; submitted 01/26/2005). The document has been reviewed by the Health Effects Division (HED) and revised to reflect current Office of Pesticide Programs (OPP) policies.

JUN 28 2005

Executive Summary

Flumiclorac pentyl [pentyl[2-chloro-4-fluoro-5-(1,3,4,5,6,7- hexahydro-1,3-dioxo-2H-isoindol-2-yl)phenoxy]acetate] is a contact herbicide with registered food/feed uses in the U.S. on field corn and soybean. A petition (PP#3F6767) has been submitted to support the proposed use of the herbicide as a harvest aid (desiccant) on cotton. This document summarizes the adequacy of the available residue chemistry data for food/feed crops eligible for reregistration which include field corn and soybean as well as the registration of a new use pattern on cotton.

Flumiclorac pentyl is used to control and/or suppress various weeds including ragweeds, pigweeds, velvetleaf, common lambsquarters, palmer amaranth, jimsonweed, prickly sida, cocklebur, redroot, spotted spurge, copperleaf, nightshade, waterhemp, hemp sesbania, and morning glories. Flumiclorac pentyl can be applied by broadcast, band, or aerial application methods, with up to two postemergence applications per growing season for a maximum seasonal rate of 0.054 lb ai/A for field corn and 0.11 lb ai/A for soybeans. On cotton, flumiclorac pentyl is proposed for harvest aid at a maximum single application rate of 0.054 lb ai/A and a maximum seasonal rate of 0.094 lb ai/A. The established preharvest interval (PHI) for soybeans is 60 days. A PHI is not listed on the product label for field corn, but the latest application time is at the 10-leaf growth stage. A 7-day PHI is proposed for cotton.

Current formulations include wettable powder (WP) and emulsifiable concentrate (EC). Flumiclorac pentyl products with food/feed uses are registered in the U.S. to Valent U.S.A. Corporation under the trade names Resource® (0.86 lb ai/gal EC), Stellar® (0.7 lb ai/gal EC), Resource® 80 (80% WP), and V-10097™ (0.056 lb ai/gal EC). All formulations are registered for use on soybean crops. Resource®, Resource® 80, and V-10097 are also registered for use on field corn. The petitioner wishes to amend the product label for Resource® in order to add a new use pattern on cotton.

Tolerances are currently established for residues of flumiclorac pentyl in 40 CFR §180.477 for soybean and field corn. The HED Metabolism Committee (7/27/94 memo, R. Loranger) determined that the residue of concern in plant commodities is flumiclorac pentyl *per se*.

Tolerances have been established in 40 CFR §180.477 for the grain, forage, and fodder of field corn at 0.01 ppm each as well as for soybean hulls at 0.02 ppm and soybean seed at 0.01 ppm. In conjunction with PP#3F6767, tolerances for residues of flumiclorac pentyl *per se* are proposed for undelinted cottonseed at 0.1 ppm and for cotton gin byproducts at 2.0 ppm. No tolerances have been established for meat, milk, and eggs.

The qualitative nature of the residue in plants is adequately understood. Acceptable plant metabolism studies were conducted on soybeans and field corn under outdoor conditions using test substances radiolabeled in the phenyl and tetrahydrophthalimide (THP) rings. The available metabolism data on soybeans and field corn may be used to support the proposed use on cotton. In the soybean study, the total radioactive residues (TRR) in mature soybeans declined from 0.12-0.35 ppm at a 61-day PHI to 0.011-0.025 ppm at a 91-day PHI after application at ~1x. In the field corn study, TRRs were <0.01 ppm (0.002-0.008 ppm) in mature corn grain harvested at

~90-day PHI following treatment at 0.5x and 4x rates. These studies indicate that flumiclorac pentyl is rapidly metabolized in soybeans and field corn with the parent herbicide comprising a maximum of about 3% of the total residue. Several metabolites were identified including those which are capable of conversion to tetrahydrophthalic acid (total 69% of the residue), those related to IMCA (25%), and those related to AFCA (20%); see Appendix I for chemical names and structures of metabolites identified from the plant and animal metabolism studies.

The qualitative nature of the residue in ruminants is adequately understood. The metabolism of flumiclorac pentyl in ruminants was investigated by orally dosing four lactating goats (2 goats/radiolabel) for five consecutive days with gelatin capsules containing flumiclorac pentyl radiolabeled in the phenyl or THP rings at ~20 ppm relative to feed intake (~27x the maximum theoretical dietary burden of 0.73 ppm for ruminants). TRR levels in the edible tissues were generally higher in the animals treated with [THP-^{14}C] flumiclorac pentyl than in the [phenyl-^{14}C] flumiclorac pentyl treated animals. TRR was highest in liver (0.0310-0.088 ppm for the phenyl-labeled study and 0.137-0.208 ppm for the THP-labeled study) and kidney (0.0291-0.0451 ppm for the phenyl-labeled study and 0.157-0.192 for the THP-labeled study). TRR levels in milk did not change much over the course of study and were generally highest on Day 3 (0.015 ppm for the phenyl-labeled study and 0.0234 ppm for the THP-labeled study). TRR levels in muscle (loin and leg) and fat (omental and perirenal) were <0.05 ppm. Tissues with TRR levels of >0.05 ppm and milk and THP-labeled perirenal fat (with TRR <0.05 ppm) were extracted with organic solvents, and the extracts were analyzed using several chromatographic techniques. The parent compound was only identified at 23.0% TRR (0.011 ppm) in the kidney of one goat treated with [phenyl-U-^{14}C]flumiclorac pentyl. The parent was also found at 10.3% TRR (0.018 ppm) in the kidney of one goat treated with [THP-^{14}C]flumiclorac pentyl. Other metabolites identified in the phenyl-labeled study include AFCA, IMCA, 4-OH-IMCA, SAT-IMCA, and SAT-4-OH-IMCA. Metabolites identified in the THP-labeled study include THPA, IMCA, HPA, 4-OH-THPA, 4-OH-IMCA, SAT-IMCA, and SAT-4-OH-IMCA. Although a few of these metabolites represent a high percentage of the TRR in some goat matrices, the identified metabolites were detected at low absolute levels (≤0.036 ppm for the THP-labeled study and ≤0.056 ppm for the phenyl-labeled study).

The qualitative nature of the residue in poultry remains inadequately understood. The registrant has submitted poultry metabolism studies which have been deemed unacceptable because information pertaining to sample storage conditions and intervals was not included in the study submissions. The studies may be upgraded if the petitioner submits the dates of hen sacrifice as well as the dates of initial and final analyses. Supporting storage stability data may be required if samples were stored for more than 4 to 6 months of collection. The poultry metabolism studies were conducted by orally dosing 20 leghorn laying hens (10 per radiolabel) for seven consecutive days with gelatin capsules containing flumiclorac pentyl radiolabeled in the phenyl or THP rings at ~10 ppm relative to feed intake (~1000x the maximum theoretical dietary burden of 0.010 ppm for poultry). TRR was low in egg yolk (0.008-0.009 ppm), egg white (0.001 ppm), and tissues (liver, breast muscle, thigh muscle, fat, and skin; ≤0.077 ppm). TRR levels were highest in gizzards (1.564-1.71 ppm) and kidneys (0.201-0.309 ppm) which are poultry matrices not typically regulated. Radioactive residues in egg yolk and tissues were adequately extracted with organic solvents, and the extracts were analyzed using several chromatographic techniques. The

parent compound was detected in the gizzard (29.1% TRR) and muscle and skin (1.1-9.1% TRR) of hens treated with [phenyl-U-^{14}C]flumiclorac pentyl. The parent was also found in the gizzard (26.2% TRR) of hens treated with [THP-^{14}C]flumiclorac pentyl. Other metabolites identified in the phenyl-labeled study include AFCA, IMCA, 4-OH-IMCA, SAT-IMCA, and SAT-4-OH-IMCA. Metabolites identified in the THP-labeled study include THPA, IMCA, 4-OH-IMCA, SAT-IMCA, and Δ^1-TPA. The identified metabolites were detected at low absolute levels (<0.001-<0.008 ppm) in egg yolk, fat, liver, thigh or breast muscle, and skin.

Animal feeding studies (OPPTS 860.1480) and tolerances on eggs, milk, and edible tissues are not required to support the registered uses of flumiclorac pentyl on soybeans and field corn or the proposed use on cotton. Residues in ruminant and poultry commodities may be classified under 40 CFR §180.6(a)(3); i.e., no expectation of finite residues.

The available metabolism studies for flumiclorac pentyl all show extensive metabolism of the parent compound to yield a variety of compounds, all at low absolute levels (HED Metabolism Committee, R. Loranger, 27-JUL-1994). The submitted confined accumulation in rotational crops study shows low levels of residue uptake. Therefore, a plant back interval of 30 days is appropriate for all rotational crops except for cotton, field corn, and soybean [no restriction necessary for labeled crops]. However, if future uses of flumiclorac pentyl result in an increase in the maximum seasonal use rate of 0.11 lb ai/A, a new confined rotational crop study should be submitted and decisions regarding the PBI should be based on the results of the new study, which should characterize and identify the residues found.

Adequate enforcement methods are available for the determination of flumiclorac pentyl *per se* in/on plant commodities. At this time, HED has determined that animal enforcement methods are not required for the purposes of reregistration and PP#3F6767 since there is no expectation of finite secondary residues.

Gas chromatograph (GC) analytical methods for the determination of flumiclorac pentyl have been submitted for soybeans and its processed commodities (Method RM 29-2) and for field corn and its processed commodities (Method RM 29-1). These methods have been forwarded to the Food and Drug Administration (FDA) for inclusion in the Pesticide Analytical Manual (PAM), Volume II as Methods I and II, respectively. The methods have been accepted as enforcement methods by EPA provided that a procedure for calibrating the silica gel clean-up be incorporated in the soybean method and a procedure for calibrating chromatographic material be incorporated in the corn method. The two methods are similar, differing only in extraction and clean-up of certain corn matrices with a high content of coextractives.

Adequate storage stability data are available to validate the storage intervals and conditions of treated RAC samples used for tolerance assessment or reassessment. Flumiclorac pentyl was found to be relatively stable under frozen storage conditions in/on soybean seeds for up to 24 months, field corn matrices for 30-45 days, and corn processed commodities for 4 months with the exception of dry-milled grits. Additional data are available which indicate that fortified residues of flumiclorac pentyl are reasonably stable under frozen storage conditions in/on undelinted cottonseed and cotton gin byproducts for up to ~2 months. Finally, weathered

residues of flumiclorac pentyl have been determined to be reasonably stable under frozen storage conditions in/on cotton gin byproducts for up to ~4 months.

Adequate magnitude of the residue data are available for field corn grain, forage, and stover as well as for soybean seed. Crop field trials were conducted for field corn and soybeans using similar use patterns as indicated on the product labels. In soybean seed and in field corn grain, forage, and fodder samples, flumiclorac pentyl residues were consistently below the limit of quantitation (LOQ) of 0.01 ppm. HED concludes that the reassessed tolerances of 0.01 ppm each for the above RACs are appropriate.

Although the available residue data for soybean hay and forage indicate that residues of flumiclorac pentyl were detected above the LOQ, no tolerances are needed for these soybean RACs because the registered end-use products contain appropriate label restrictions which prohibit the feeding and grazing of livestock animals on treated soybean fields. The requirement for residue data on aspirated grain fractions may be waived since residues in/on samples of field corn grain and soybean seed, following treatment at 1x, were below the LOQ. In addition, one field corn trial conducted at an exaggerated rate of 5x also showed flumiclorac pentyl residue levels below LOQ in corn grain. Based on these findings, a tolerance for aspirated grain fractions need not be established.

Adequate residue data have been submitted to support the proposed uses on cotton pending submission of a revised Section F to reflect appropriate tolerance levels. Following a single postemergence foliar application of an EC formulation at ~1x the proposed seasonal rate, the maximum residues of flumiclorac pentyl were 0.11 and 0.06 ppm in/on treated samples of cottonseed harvested by stripper and picker equipment, respectively. The maximum residues of flumiclorac pentyl were 0.83 and 2.2 ppm in/on treated samples of cotton gin byproducts harvested by stripper and picker equipment, respectively. The petitioner needs to submit a revised Section F to increase the proposed tolerance levels on: (i) undelinted cottonseed from 0.1 ppm to 0.20 ppm; and (ii) cotton gin byproducts from 2.0 ppm to 3.0 ppm.

Processing studies were conducted with soybean and field corn treated at 5.0x the maximum application rate. Flumiclorac pentyl residues were not detected in the RACs. In the processed fractions, flumiclorac pentyl residues were detected in soybean hulls at 0.01 ppm (processing factor of 1x) and in crude oil from corn at 0.02 ppm (wet milled) to 0.08 ppm (dry milled). Crude oil, however, is not considered a regulated commodity of commerce.

A processing study with cottonseed has also been submitted. Residues of flumiclorac pentyl were 0.02-0.03 ppm in/on undelinted cottonseed treated with an EC formulation at ~1x. Residues of flumiclorac pentyl did not concentrate (0.3x processing factors) in the processed commodities of cottonseed; residues were at or below the LOD (0.01 ppm) in all samples of meal, hulls, and refined oil processed from treated cottonseed.

Regulatory Recommendations and Residue Chemistry Deficiencies

HED has examined the residue chemistry database for flumiclorac pentyl. Pending resolution of the deficiencies noted below, there are no residue chemistry issues that would preclude the reregistration of food/feed uses on field corn and soybean as well as the conditional registration of a new use pattern on cotton.

- The submitted poultry metabolism studies (MRIDs 46082805 and 46082806) have been deemed unacceptable because information pertaining to sample storage conditions and intervals was not provided. The studies may be upgraded if the petitioner submits the dates of hen sacrifice as well as the dates of initial and final analyses. Storage stability data in support of metabolism studies are not routinely required for samples analyzed within 4 to 6 months of collection. However, longer sample storage periods should be supported with storage stability data.

- The petitioner is required to submit a revised Section F to increase the proposed tolerance levels on: (i) undelinted cottonseed from 0.1 ppm to 0.20 ppm; and (ii) cotton gin byproducts from 2.0 ppm to 3.0 ppm.

A human health risk assessment will be prepared in a separate document.

Background

Flumiclorac pentyl is an N-phenylphthalimide derivative herbicide used for the control of broadleaf weeds. Its mode of action is through the accumulation of porphyrins in susceptible plants; the photosensitizing action of accumulated porphyrins may cause membrane lipid peroxidation which leads to irreversible damage of membrane function and structure in the plant. Flumiclorac pentyl is registered for postemergence application to field corn and soybeans; registration for use on cotton as a defoliant is pending. The PC code and nomenclature of flumiclorac pentyl are listed below in Table 1. The physicochemical properties of flumiclorac pentyl are listed in Table 2. The chemical names and structures of flumiclorac pentyl and its transformation products are presented in Appendix 1.

TABLE 1. Flumiclorac Pentyl Nomenclature

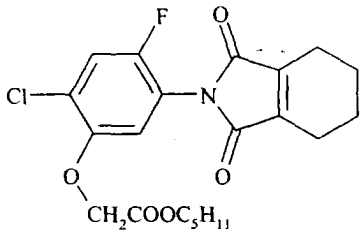
Chemical Structure	
Common name	Flumiclorac pentyl
Company experimental name	S-23031 or V-23031
Molecular Formula	$C_{21}H_{23}ClFNO_5$

TABLE 1. Flumiclorac Pentyl Nomenclature	
Molecular Weight	423.9
IUPAC name	Pentyl (2-chloro-5 (cyclohex-1-ene-1,2-dicarboximido)-4-fluorophenoxy) acetate
CAS names	Pentyl[2-chloro-4-fluoro-5-(1,3,4,5,6,7- hexahydro-1,3-dioxo-2H-isoindol-2-yl)phenoxy]acetate
CAS #	87546-18-7
PC Code	128724

TABLE 2. Physicochemical Properties of Flumiclorac Pentyl		
Parameter	Value	Reference
Melting point	88.9-90.1 °C	PP#2G4078; D174474, 7/28/92, J. Garbus
pH	6.03 at 25 °C	
Density, bulk density, or specific gravity	1.3316 g/mL at 20 °C	
Water solubility	0.189 mg/L at 25 °C	
Solvent solubility	g/100 mL at 25 °C: hexane 0.328 n-octanol 1.60 methanol 4.78 Solvesso 150 27.1 acetonitrile 58.9 acetone 59.0 tetrahydrofuran 69.7 N-methyl 2-pyrrolidinone 134.0 methylene chloride 288.0	
Vapor pressure	$<1 \times 10^{-7}$ mm Hg at 22.4 °C	
Dissociation constant, pK_a	No dissociation at pH ≤7; flumiclorac pentyl decomposes at pH ≥9.	
Octanol/water partition coefficient	Log P_{OW} = 4.99 at 19.7-21.0 °C	
UV/visible absorption spectrum	Not available	

60.1200 Directions for Use

Product List

Four registered flumiclorac pentyl end-use products (EPs) have been identified for use on food/feed sites. All four formulations are registered to Valent U.S.A. Corporation. Additionally, two SLN registrations for the state of Missouri containing 7.6% and 10.1% flumiclorac pentyl and an experimental use permit formulation containing 10.64% flumiclorac pentyl (EPA Registration No. 59639-EUP-3) were identified. These formulations are also registered to Valent U.S.A. Corporation. The EPs are listed in Table 3 below. A technical formulation containing 98.6% flumiclorac pentyl (EPA Registration No. 59639-81) was also identified. This formulation is also registered to Valent U.S.A. Corporation.

TABLE 3. Flumiclorac pentyl End-Use Products (EPs) with Food/Feed Uses.

EPA Reg. No.	Formulation[1]	Registrant	Product Name	Commodity
59639-82	EC containing 10.1% (0.86 lb/gal) flumiclorac pentyl ester	Valent U.S.A. Corporation	Resource® Herbicide	Soybeans, field corn
59639-92	EC containing 7.6% (0.7 lb/gal) flumiclorac pentyl ester and 26.6% (2.4 lbs/gal) lactofen	Valent U.S.A. Corporation	Stellar® Herbicide	Soybeans
59639-100	WP containing 80% flumiclorac pentyl ester	Valent U.S.A. Corporation	Resource® 80 WP Herbicide	Soybeans, field corn
59639-122	EC containing 0.576% (0.056 lb/gal) flumiclorac pentyl ester and 40.7% (4.00 lbs/gal) glyphosate	Valent U.S.A. Corporation	V-10097 Herbicide	Soybeans, field corn
MO960009	7.6% flumiclorac pentyl and 26.6% lactofen	Valent U.S.A. Corporation	Stellar® Herbicide	Soybeans
MO980001	10.1% flumiclorac pentyl	Valent U.S.A. Corporation	Resource® Herbicide	Soybeans, field corn
59639-EUP-3	10.64% flumiclorac pentyl	Valent U.S.A. Corporation	NA	NA

[1] EC = emulsifiable concentrate, WP = wettable powder

Use Patterns

For the purposes of reregistration, the registered food/feed uses of flumiclorac pentyl have been re-evaluated for soybean and field corn. A summary of registered use patterns is presented in Table 4. In conjunction with PP#3F6767, the petitioner wishes to amend the product label for Resource® Herbicide (EPA Reg. No. 59639-82) to add a new use on cotton as a harvest aid. On cotton, the proposed maximum single application rate is 0.054 lb ai/A, and the proposed maximum seasonal rate is 0.094 lb ai/A, with a retreatment interval of 14 days. Application may be made with standard ground and aerial equipment. The proposed preharvest interval is 7 days.

A tabular summary of the chemistry science assessments is presented in Table 5. The conclusions listed in Table 5 regarding the reregistration eligibility of flumiclorac pentyl food/feed uses are based on the use patterns registered by the producer. When end-use product data call in's (DCIs) are developed (e.g., at issuance of the RED), the Registration Division (RD) should require that all end-use product labels (e.g., MAI labels, SLNs, and products subject to the generic data exemption) be amended such that they are consistent with the basic producer labels.

Table 4. Overall Use Patterns for Flumiclorac pentyl[1]

Crop	Max Single Rate (Lbs ai/A)	Applications/ Yr	Maximum Seasonal Rate (Lbs ai/A/Yr)	RTI[2] (days)	PHI[3] (days)
Corn, field	0.054	2	0.054	14	10-leaf stage[4]
Soybean	0.081	2	0.11	14	60
Cotton	0.054	2	0.094	14	7

[1] From Flumiclorac-pentyl Use Closure Memo, T. Spears, 29-SEP-2004; and Resource label
[2] Retreatment Interval
[3] Preharvest Interval
[4] No applications allowed after the 10-leaf growth stage of field corn

Table 5. Residue Chemistry Science Assessment for Reregistration of Flumiclorac Pentyl.			
GLN Data Requirements	**Current Tolerances (ppm) [40 CFR §180.477]**	**Additional Data Needed?**	**MRID Nos.**
860.1200: Directions for Use	N/A = Not Applicable	No [1]	See Table 4
860.1300: Nature of the Residue - Plants	N/A	No	42169849[2] 42169850[2] 42825843[3] 43283001[4]
860.1300: Nature of the Residue - Animals	N/A	Yes[5]	42169851[2] 42169852[2] 42169853[2] 42169854[2] 46082803[6] 46082804[6] 46082805[6] 46082806[6]
860.1340: Residue Analytical Method			
- Plant Commodities	N/A	No	42169855[2] 42169856[2] 42825844[3] 42883907[3] 42883908[3] 43439901[7] 43440101[4]
- Animal Commodities	N/A	No	None
860.1360: Multiresidue Method	N/A	No	42825851
860.1380: Storage Stability Data			
- Plant Commodities	N/A	No	42169858[2] 42169859[2] 42825848[3] 42825849[3] 42825850[3] 46082808[6] 46102801[6]
- Animal Commodities	N/A	No	None
860.1400: Magnitude of the Residue - Water, Fish, and Irrigated Crops	N/A	N/A	None
860.1460: Magnitude of the Residue - Food Handling	N/A	N/A	None
860.1480: Magnitude of the Residue - Meat, Milk, Poultry, Eggs			
- Milk and the Fat, Meat, and Meat Byproducts of Cattle, Goats, Hogs, Horses, and Sheep	None established	No[8]	None
- Eggs and the Fat, Meat, and Meat Byproducts of Poultry	None established	No[8]	None
860.1500: Crop Field Trials			
Vegetable, legume, group 6			
- Soybean, seed and aspirated grain fractions	soybean seed, 0.01	No[9]	42169855[2] 42169857[2] 42169858[2] 42169859[2] 42187407[2] 42825845[3]
Vegetable, foliage of legume, group 7			
- Soybean, forage and hay	None established	No[10]	42169857[2] 42825845[3]
Grain, cereal, group 15			

Table 5. Residue Chemistry Science Assessment for Reregistration of Flumiclorac Pentyl.			
GLN Data Requirements	**Current Tolerances (ppm) [40 CFR §180.477]**	**Additional Data Needed?**	**MRID Nos.**
- Corn, field, grain and aspirated grain fractions	grain, 0.01	No[9, 11]	42187408[2] 42825846[3] 42825847[3] 42825849[3] 42942901[12]
Grain, cereal, forage, fodder, and straw, group 16			
- Corn, field, forage and stover	forage and stover, 0.01 each	No[11]	42187408[2] 42825846[3] 42825847[3] 42825849[3] 42942901[12]
Miscellaneous Commodities			
- Cotton, undelinted seed and gin byproducts	None established	No[13]	46082808[6] 46102801[6]
860.1520: Processed Food/Feed			
- Corn, field	None established	No	42169856[2] 42187408[2] 42942901[12]
- Cotton	None established	No	46102801[6]
- Soybean	hulls, 0.01	No [14]	42169855[2] 42187407[2]
860.1650: Submittal of Analytical Reference Standards	N/A	No[15]	
860.1850: Confined Accumulation in Rotational Crops	N/A	No[16]	42825840[3] 42825841[3] 42825842[3] 43002301[3] 43283001[4]
860.1900: Field Accumulation in Rotational Crops	N/A	No	

1. The current label restriction limiting field corn applications to occur between the 2- and 10-leaf stage is supported by adequate crop field trial data. In addition, the field corn 28-day pregrazing interval is also supported by adequate crop field trial data.

2. DP Barcode D174474, 7/28/92, J. Garbus.

3. DP Barcodes D195816, D195822, D195861, D195864, and D197257, 5/25/94, J. Garbus.

4. No reviews of these submissions have been located in the flumiclorac pentyl database.

5. The submitted ruminant metabolism studies are acceptable to satisfy OPPTS GLN 860.1300 data requirements. However, the submitted poultry metabolism studies are inadequate because information pertaining to sample storage conditions and intervals was not provided. The studies may be upgraded if the petitioner submits the dates of hen sacrifice as well as the dates of initial and final analyses. Storage stability data are not normally required for samples analyzed within 4 to 6 months of collection, provided evidence is given that attempts were made to limit degradation of residues by appropriate storage of matrices and extracts during the analytical phase of the study.

6. DP Barcode D308674, 24-JUN-2005, W. Donovan.

7. DP Barcode D209204, 11/9/94, J. Garbus.

8. Residues in ruminant and poultry commodities may be classified under 40 CFR §180.6(a)(3); i.e., no expectation of finite residues. Feeding studies and tolerances for livestock commodities may be required if new feed uses are proposed in the future which would significantly increase the maximum theoretical dietary burdens.

9. The requirements for residue data on the aspirated grain fractions may be waived since residues in/on samples of field corn grain and soybean seed, following treatment at 1x, were below the LOQ. Based on this determination, a tolerance for aspirated grain fractions need not be established.

10. Although the available residue data for soybean hay and forage indicate that residues of flumiclorac pentyl residues were detected above the LOQ, no tolerances are needed for these soybean RACs because the registered end-use products contain appropriate label restrictions which prohibit the feeding and grazing of livestock animals on treated soybean fields.

11. No additional field trial data are required for field corn. However, label revisions are required to specify preharvest and pregrazing intervals. The available data suggest that a pregrazing interval of 21 days for forage and a 92-day preharvest interval for grain and fodder would be appropriate for field corn.

12. DP Barcode D198103, 8/2/94, J. Garbus.

13. The submitted residue data for cotton commodities indicate that the proposed tolerances may be exceeded when the proposed formulation is used according to the maximum label use pattern. The petitioner is required to submit a revised Section F to increase the proposed tolerance levels on: (i) undelinted cottonseed from 0.1 ppm to 0.20 ppm; and (ii) cotton gin byproducts from 2.0 ppm to 3.0 ppm.

14. An acceptable soybean processing study has been submitted. HED is recommending the revocation of the established tolerance on soybean hulls since this item is no longer considered a major livestock feed commodity and has been deleted from Table 1 of OPPTS 860.1000.

15. As of 8/28/04, an analytical reference standard for flumiclorac pentyl is available in the National Pesticide Standards Repository. Analytical reference standards of flumiclorac pentyl must be supplied and supplies replenished as requested by the Repository. The reference standards should be sent to the Analytical

Chemistry Lab, which is located at Fort Meade, to the attention of either Theresa Cole or Frederic Siegelman at the following address:

USEPA
National Pesticide Standards Repository/Analytical Chemistry Branch/OPP
701 Mapes Road
Fort George G. Meade, MD 20755-5350
(Note that the mail will be returned if the extended zip code is not used.)

16. The available metabolism studies for flumiclorac pentyl all show extensive metabolism of the parent compound to yield a variety of compounds, all at low levels in the various matrices studied. The submitted confined accumulation in rotational crops study shows low levels of residue uptake. Therefore, a plant back interval (PBI) of 30 days is appropriate for all rotational crops except for cotton, field corn, and soybean [no restriction necessary for labeled crops]. However, if future uses of flumiclorac pentyl result in an increase in the maximum seasonal use rate of 0.11 lb ai/A, a new confined rotational crop study should be submitted and decisions regarding the PBI should be based on the results of the new study, which should characterize and identify the residues found.

SUMMARY OF SCIENCE FINDINGS

860.1300 Nature of the Residue - Plants

Adequate metabolism studies were submitted for soybeans and field corn. Detailed summaries of these studies are presented below. The results of the studies indicate that flumiclorac pentyl is rapidly degraded to several polar metabolites with no substantial residues of the parent. The pathways of degradation include hydrolysis of the ester and imide linkages and hydroxylation and reduction of the tetrahydrophthalimide moiety. Further metabolism and conjugation leads to the incorporation of 25-50% of the applied label into bound residues.

Initially, the Agency noted that further identification of the residue in corn and soybeans was needed because of the large percentage of unidentified metabolites. For soybeans, 41-52% of the recovered radioactivity was identified, 24-32% was characterized as "polar metabolites", and 14-18% was nonextractable. For corn, corresponding values were 1-3% identifiable, 46-68% "polar metabolites", 4-16% "other", and 26-34% nonextractable. The petitioner responded stating that the polar fraction consisted of several polar metabolites, none of which represented more than 10% of the recovered radioactivity, and all of which represented about 0.01 ppm under conditions maximizing residue levels. Therefore, in the petitioner's view, additional identification of individual metabolites was not necessary (DP Barcode D195816, 5/25/94, J. Garbus). The HED Metabolism Committee (Memo dated 7/27/94, R. Loranger) determined that the metabolites of flumiclorac pentyl in plants are not of toxicological concern considering the following: (i) the parent compound exhibits relatively low toxicity; (ii) based on the results of a rat metabolism study, the toxicology studies do reflect exposure to the metabolites; and (iii) even though they represent a high percentage of the total residue, the metabolites are expected to be present at low absolute levels (<0.1 ppm in most cases) from the proposed use.

Soybeans

Flumiclorac pentyl, uniformly labeled with ^{14}C in its phenyl ring or at positions 1 and 2 of the tetrahydrophthalimide (THP) ring, was applied to seedling (2 to 3 leaf stage) soybean plants or to plants 61 days prior to harvest. Application rates were equivalent to 52 g ai/acre (0.11 lb ai/A; 1x the maximum label rate) and 104 g ai/acre (0.23 lb ai/A; 2x). For the early application, plants were sampled at 0, 3, 14, and 91 days after treatment. For the late application, plants were sampled at 0, 15, 40, and 61 days after treatment. Immature whole plants were extracted with ethyl acetate. Aliquots of the extracts and post-extraction residues were combusted for the determination of total radioactivity and subjected to chromatographic procedures for the determination of metabolites. Mature plant and harvest seed samples were repeatedly extracted with acidified acetonitrile and acetonitrile/water. Aliquots of the combined filtrates and the post-extraction residual filter cake were combusted for liquid scintillation counting. Aliquots of the filtrates were subjected to TLC and HPLC for the determination of metabolites.

Quantitation of ^{14}C-residues in the extracts of mature seed harvested 61 days after the application of [phenyl-U-^{14}C]flumiclorac pentyl at 52 g ai/A (0.11 lb ai/A) resulted in 19.2% AFCA, 20.0% SAT-4-OH-IMCA, 5.8% 4-OH-IMCA, 2.5% flumiclorac pentyl, 31.7% polar unknowns, 3.3%

other unknowns, and 18.0% nonextractable. Quantitation of ^{14}C-residues in the extracts of mature seed harvested 61 days after the application of [THP-1,2-^{14}C]flumiclorac pentyl at 52 g ai/A (0.11 lb ai/A) resulted in 36.9% OH-THPA, 26.0% unknowns related to THPA, 5.7% THPA, 6.3% SAT-4-OH-IMCA, 2.3% 4-OH-IMCA, 0.6% flumiclorac pentyl, 4.6% polar unknowns, 4.0% other unknowns, and 14.3% nonextractable (DP Barcode D195816, 5/25/94, J. Garbus).

Quantitation of ^{14}C-residues in the extracts of mature seed harvested 61 days after the application of [phenyl-U-^{14}C]flumiclorac pentyl at 104 g ai/A (0.23 lb ai/A) resulted in 16.6% AFCA, 17.9% SAT-4-OH-IMCA, 5.0% 4-OH-IMCA, 1.8% flumiclorac pentyl, 26.4% polar unknowns, 4.9% other unknowns, and 23.8% nonextractable. Quantitation of ^{14}C-residues in the extracts of mature seed harvested 61 days after the application of [THP-1,2-^{14}C]flumiclorac pentyl at 104 g ai/A (0.23 lb ai/A) resulted in 38.2% OH-THPA, 19.1% unknowns related to THPA, 6.1% THPA, 5.2% SAT-4-OH-IMCA, 2.0% 4-OH-IMCA, 0.5% flumiclorac pentyl, 5.5% polar unknowns, 4.3% other unknowns, and 18.2% nonextractable (DP Barcode D195816, 5/25/94, J. Garbus).

Field corn

Flumiclorac pentyl, uniformly labeled with ^{14}C in its phenyl ring or at positions 1 and 2 of the THP ring, was applied to corn plants at the 6-8 leaf stage. Application rates were equivalent to 12 g ai/acre (0.026 lb ai/A; 0.5x the maximum label rate) and 96 g ai/acre (0.21 lb ai/A; ~4x). For the low application rate, plants were sampled at 0, 7, 14, 28, 42 and 90 days after treatment; for the higher application rate, plants were samples at 0, 5, and 97 days after treatment. Immature plants were analyzed for residues as such; mature plants were separated into grain, husks, stem, and leaves. Plant samples were extracted with hexane followed by acidified acetonitrile:water (1:1, v:v). Aliquots of the combined filtrates and the post-extraction residual filter cake were combusted for liquid scintillation counting. Aliquots of the filtrates were subjected to TLC and HPLC for the determination of metabolites.

Quantitation of ^{14}C-residues in the extracts of immature corn plants harvested 28 days after the application of [phenyl-U-^{14}C]flumiclorac pentyl at 12 g ai/A (0.026 lb ai/A) resulted in 2.3% flumiclorac pentyl, 1.8% IMCA, 46.2% polar unknowns,16.0% other unknowns, and 33.7% nonextractable. Quantitation of ^{14}C-residues in the extracts of immature corn plants harvested 28 days after the application of [THP-1,2-^{14}C]flumiclorac pentyl at 12 g ai/A (0.026 lb ai/A) resulted in 1.2% flumiclorac pentyl, 68.2% polar unknowns, 4.4% other unknowns, and 26.3% nonextractable (DP Barcode D195816, 5/25/94, J. Garbus).

Total radioactive residues in/on mature corn grain and fodder treated with [phenyl-U-^{14}C] or [THP-1,2-^{14}C] flumiclorac pentyl at 12 g ai/A were <0.02 ppm and residues were not quantitated. The Agency concluded that additional metabolic studies were not needed for corn, because the metabolism of flumiclorac pentyl in corn was similar to that in soybeans.

860.1300 Nature of the Residue - Livestock

Metabolism studies were conducted on lactating goats and laying hens using test substances uniformly labeled with ^{14}C in its phenyl ring or at positions 1 and 2 of the tetrahydrophthalimide (THP) ring. Detailed summaries of these studies are presented below. The ruminant studies were deemed acceptable whereas the poultry studies were deemed inadequate because information pertaining to sample storage conditions and intervals was not included in the study submissions. The poultry studies may be upgraded if the petitioner submits the dates of hen sacrifice as well as the dates of initial and final analyses. Supporting storage stability data may be required if samples were stored for more than 4 to 6 months of collection.

Goat (Phenyl Label)

46082803.der.wpd

Valent U.S.A. Corporation has submitted a study investigating the metabolism of [phenyl-U-^{14}C]flumiclorac pentyl in lactating goats. Information concerning the in-life phase of this study was previously submitted in MRID 42169852 and reviewed (DP Barcode D174474, 7/28/92, J. Garbus) in conjunction with PP#2G4078. The current submission reports the identification/characterization of radioactive residues in goat milk and tissues.

The test substance, [phenyl-U-^{14}C]flumiclorac pentyl, was administered orally to two goats at 20 ppm in the diet (~27x the maximum theoretical dietary burden of 0.73 ppm for ruminants; see Table 6). The goats were dosed once per day for five consecutive days. Milk was collected twice daily and composited each day, and tissues (kidney, liver, muscle, and fat) were collected at sacrifice. The in-life phase of the study was conducted by ABC Laboratories (Columbia, MO), and the analytical phase was conducted by Ricerca, Inc. (Painsville, OH).

Radioactivity was low in all goat matrices, with the highest levels observed in kidney and liver. Total radioactive residues were 0.006-0.016 ppm in milk, 0.0291-0.0451 ppm in kidney, 0.0310-0.088 ppm in liver, <0.0007-0.0009 ppm in fat (perirenal and omental), and 0.0013 ppm in muscle (loin and leg) from goats dosed with [phenyl-U-^{14}C]flumiclorac pentyl. Residues appear to remain fairly consistent in milk throughout the study period; approximately 3% of the milk radioactivity was determined to represent butterfat. The study reported that a large portion of the administered dose was excreted, with urine accounting for 27-30% and feces accounting for 29-36% of the administered dose.

Because of low radioactivity, residue characterization of fat and muscle samples was not conducted. The majority of the radioactivity (~74-99% TRR) in milk, kidney, and liver was extractable with organic solvents; nonextractable residues accounted only for 1-13% of TRR. Adequate storage stability data were submitted for milk, kidney, and liver, demonstrating the stability of the metabolite profile in these matrices for ~8-9 months. The parent compound significantly declined in the stored kidney sample.

Radioactive residues in milk, kidney, and liver were initially characterized by various chromatographic techniques (HPLC, TLC, and LC/MS); the identification of residues was confirmed by GC/MS analysis. Approximately 48-89% of the TRR in milk, kidney and liver were identified. The parent was only detected in the kidney of one goat at 23.0% TRR (0.011 ppm). A later re-analysis showed that most of the parent compound was degraded during freezer storage. Several metabolites were identified including: AFCA, IMCA, 4-OH-IMCA, SAT-IMCA, and SAT-4-OH-IMCA; the chemical names and structures of these metabolites are listed in Appendix 1. Although certain of these metabolites represent a high percentage of the TRR in some analyzed goat matrices, the identified metabolites were detected at low absolute levels (≤0.056 ppm). In milk, the metabolite AFCA was the principal residue component accounting for 56.0-64.6% TRR. The metabolite IMCA was detected in all samples except liver, even though it was not a major metabolite.

Based on the results of this study, the petitioner concluded that flumiclorac pentyl is rapidly metabolized and excreted in goats. Initial hydrolysis of the pentyl ester of flumiclorac pentyl yields IMCA. No significant metabolites with the intact pentyl ester group were detected in goat matrices. IMCA is further metabolized by cleavage of the imide ring to AFCA, which is readily excreted. The major residue in goat liver and kidney, SAT-IMCA is formed by a reduction process, where IMCA is further metabolized by gut microflora.

Goat (THP Label)

46082804.der.wpd

Valent U.S.A. Corporation has submitted a study investigating the metabolism of [tetrahydrophthaloyl-1,2-^{14}C]flumiclorac pentyl in lactating goats. Information concerning the in-life phase of this study was previously submitted in MRID 42169851 and reviewed (DP Barcode D174474, 7/28/92, J. Garbus) in conjunction with PP#2G4078. The current submission reports the identification/characterization of radioactive residues in goat milk and tissues.

The test substance, [THP-1,2-^{14}C]flumiclorac pentyl, was administered orally to two goats at 20 ppm in the diet (~27x the maximum theoretical dietary burden of 0.73 ppm for ruminants). The goats were dosed once per day for five consecutive days. Milk was collected twice daily and composited each day, and tissues (kidney, liver, muscle, and fat) were collected at sacrifice. The in-life phase of the study was conducted by ABC Laboratories (Columbia, MO), and the analytical phase was conducted by Ricerca, Inc. (Painsville, OH).

Total radioactive residues were 0.0049-0.0234 ppm in milk, 0.157-0.192 ppm in kidney, 0.137-0.208 ppm in liver, 0.017-0.021 ppm in perirenal fat, 0.007-0.011 ppm in omental fat, and 0.005-0.006 ppm in muscle (loin and leg) from goats dosed with [THP-1,2-^{14}C]flumiclorac pentyl. Radioactivity was lowest in muscle and highest in kidney and liver. Residues appear to remain fairly consistent in milk throughout the study period; approximately 3% of the milk radioactivity was determined to represent butterfat. The study reported that a large portion of the administered dose was excreted, with urine accounting for 22-29% and feces accounting for 37-39% of the administered dose.

Because of low radioactivity, residue characterization in omental fat and muscle samples was not conducted. The majority of the radioactivity (~64-93% TRR) in milk, perirenal fat, kidney, and liver was extractable with organic solvents. Protease hydrolysis released additional radioactivity (9.8-29.0% TRR) from the nonextractable solids of kidney and liver. Nonextractable residues remaining after solvent extraction and/or enzyme hydrolysis accounted for 5.1-13.5% TRR in milk, perirenal fat, kidney, and liver. Adequate storage stability data were submitted for milk, fat, kidney, and liver, demonstrating the stability of the metabolite profile in these matrices for ~8-9 months. The parent compound significantly declined in the stored kidney sample.

Approximately 64-89% of the TRR in milk, perirenal fat, kidney, and liver were identified. Residues were characterized primarily by HPLC analysis; confirmatory analyses utilized various TLC, LC/MS, and GC/MS techniques. The parent was only found in the kidney of one goat at 10.3% TRR (0.018 ppm). A later re-analysis showed that most of the parent compound was degraded during freezer storage. Several metabolites were identified including: THPA, IMCA, HPA, 4-OH-THPA, 4-OH-IMCA, SAT-IMCA, and SAT-4-OH-IMCA; the chemical names and structures of these metabolites are listed in Appendix 1. Although certain of these metabolites represent a high percentage of the TRR in some analyzed goat matrices, the identified metabolites were detected at low absolute levels ($\leq$0.036 ppm). In milk, the metabolite THPA was the principal residue component accounting for 23.3-40.1% TRR. The metabolite IMCA was detected in all samples except in perirenal fat, even though it was not a major metabolite.

Based on the results of this study, the petitioner concluded that flumiclorac pentyl is rapidly metabolized and excreted in goats. Initial hydrolysis of the pentyl ester of flumiclorac pentyl yields IMCA. No significant metabolites with the intact pentyl ester group were detected in goat matrices. IMCA is further metabolized by cleavage of the imide ring to THPA which is readily excreted. A major residue in goat liver and kidney, SAT-IMCA, is formed by a reduction process, where IMCA is further metabolized by gut microflora. Hydrolysis of SAT-IMCA likely forms HPA in kidney, urine, and feces of goat.

Poultry (Phenyl Label)

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Valent U.S.A. Corporation has submitted a study investigating the metabolism of [phenyl-U-^{14}C]flumiclorac pentyl in laying hens. Information concerning the in-life phase of this study was previously submitted in MRID 42169853 and reviewed (DP Barcode D174474, 7/28/92, J. Garbus) in conjunction with PP#2G4078. The current submission reports the characterization and identification of radioactive residues in hen eggs and tissues.

The test substance, [phenyl-U-^{14}C]flumiclorac pentyl, was administered orally to ten hens at 9.9 ppm in the diet (~990x the maximum theoretical dietary burden of 0.010 ppm for poultry). The hens were dosed once per day for seven consecutive days. During the study period, eggs were collected twice daily, separated into whites and yolks, and composited each day. Tissues (gizzard, kidney, liver, muscle, skin, and fat) were collected at hen sacrifice. The in-life phase of the study was conducted by ABC Laboratories (Columbia, MO), and the analytical phase was conducted by Ricerca, Inc. (Painesville, OH).

Total radioactive residues, determined by the analytical laboratory, were <0.001 ppm in egg whites (Day 4), 0.006 ppm in fat, 0.009 ppm in breast muscle, 0.015 ppm in egg yolk (Day 5), 0.026 ppm in skin, 0.056 ppm in liver, 0.223 ppm in kidney, and 1.634 ppm in gizzards from hens dosed with [phenyl-U-^{14}C]flumiclorac pentyl. Radioactivity was low in most hen matrices, with the highest levels in gizzards and kidney which are poultry matrices not typically regulated. The study reported that 78% of the administered dose was excreted.

Because of low radioactivity, no residue characterization was conducted on egg white samples; the remainder of poultry matrices were subjected to residue extraction and characterization. The majority of the radioactivity (~73-92% TRR) in egg yolk, gizzards, fat, kidney, liver, breast muscle, and skin was extractable with organic solvents. Protease hydrolysis released additional radioactivity (2.7-14.1% TRR) from the nonextractable solids of the above-listed matrices. Nonextractable residues remaining after solvent extraction and/or enzyme hydrolysis accounted for <10% TRR in all matrices. Information pertaining to the collection, extraction and analysis dates was not provided, and sample storage stability conditions and durations were not addressed.

The parent was identified as a major component in gizzard (29.1% TRR) but was a minor component in muscle and skin (1.1-9.1% TRR). Several other metabolites were identified including: AFCA, IMCA, 4-OH-IMCA, SAT-IMCA, and SAT-4-OH-IMCA; the chemical names and structures of these metabolites are listed in Appendix 1. The identified metabolites were detected at low absolute levels (<0.001-0.008 ppm) in egg yolk, fat, liver, breast muscle, and skin. Some metabolites were present at up to 0.477 ppm in gizzards and 0.026 ppm in kidney. The metabolite IMCA was detected in all poultry matrices analyzed.

The petitioner concluded that flumiclorac pentyl is rapidly metabolized and excreted in hens. Based on the phenyl- and THP-labeled hen metabolism studies, the proposed metabolic reactions in hens involve: (i) initial hydrolysis of the pentyl ester of flumiclorac pentyl to form IMCA; (ii) hydrolysis of the imide and subsequent formed amide; (iii) hydroxylation of the cyclohexane ring; and (iv) olefin reduction.

Poultry (THP Label)

46082806.der.wpd

Valent U.S.A. Corporation has submitted a study investigating the metabolism of [tetrahydrophthaloyl-1,2-^{14}C]flumiclorac pentyl in laying hens. Information concerning the in-life phase of this study was previously submitted in MRID 42169854 and reviewed (DP Barcode D174474, 7/28/92, J. Garbus) in conjunction with PP#2G4078. The current submission reports the characterization and identification of radioactive residues in poultry eggs and tissues.

The test substance, [THP-1,2-^{14}C]flumiclorac pentyl, was administered orally to ten hens at 10.5 ppm (~1050x the maximum theoretical dietary burden of 0.010 ppm for poultry) in the diet. The hens were dosed once per day for seven consecutive days. Eggs were collected twice daily, separated into whites and yolks, and composited for each study day. Hen tissues (gizzard, kidney, liver, muscle, skin, and fat) were collected at sacrifice. The in-life phase of the study was

conducted by ABC Laboratories (Columbia, MO), and the analytical phase was conducted by Ricerca, Inc. (Painesville, OH).

Total radioactive residues, determined by the analytical laboratory, were 0.002 ppm in egg whites (Day 5), 0.027 ppm in egg yolk (Day 5), 0.008 ppm in fat, 0.009 ppm in thigh muscle, 0.036 ppm in skin, 0.079 ppm in liver, 0.312 ppm in kidney, and 1.586 ppm in gizzards from hens dosed with [THP-1,2-^{14}C]flumiclorac pentyl. Radioactivity was low in most hen matrices, with the highest levels observed in gizzards and kidney which are poultry matrices not typically regulated. The study reported that about 85% of the administered dose was excreted.

Because of low radioactivity, no residue characterization was conducted on egg white and breast muscle; the remainder of poultry matrices were subjected to residue extraction and characterization. The majority of the radioactivity (~44-95% TRR) in egg yolk, gizzards, fat, kidney, liver, thigh muscle, and skin was extractable with organic solvents. Protease hydrolysis released additional radioactivity (0.6-33.6% TRR) from the nonextractable solids of the above-listed matrices. Nonextractable residues remaining after solvent extraction and/or enzyme hydrolysis accounted for <10% TRR in all matrices. The collection, extraction, and analysis dates were not provided, and sample storage stability conditions and durations were not addressed in the study submission.

The parent was only identified in gizzards at 26.2% TRR. Several other metabolites were identified including: THPA, IMCA, 4-OH-IMCA, SAT-IMCA, Δ^1-TPA; the chemical names and structures of these metabolites are listed in Appendix 1. The identified metabolites were detected at low absolute levels (<0.001-<0.008 ppm) in egg yolk, fat, liver, thigh muscle, and skin. Some metabolites were present at up to 0.416 ppm in gizzards and 0.02 ppm in kidney. The metabolite IMCA was detected in all poultry matrices analyzed.

The petitioner concluded that flumiclorac pentyl is rapidly metabolized and excreted in hens. Based on the phenyl- and THP-labeled hen metabolism studies, the proposed metabolic reactions in hens involve: (i) initial hydrolysis of the pentyl ester of flumiclorac pentyl to form IMCA; (ii) hydrolysis of the imide and subsequent formed amide; (iii) hydroxylation of the cyclohexane ring; and (iv) olefin reduction.

860.1340 Residue Analytical Methods

Adequate enforcement methods are available for the determination of flumiclorac pentyl *per se* in/on plant commodities. The HED Metabolism Committee has previously determined that additional analytical methodology for the plant metabolites of flumiclorac pentyl are not needed based on the overall toxicology profile. At this time, HED has determined that animal enforcement methods are not required for the purposes of reregistration and PP#3F6767 since there are no expectation of finite secondary residues.

Gas chromatograph (GC) analytical methods for the determination of flumiclorac pentyl have been submitted for soybeans and its processed commodities (Method RM 29-2) and for field corn and its processed commodities (Method RM 29-1). The methods have undergone an EPA method

validation trial. The results indicate recoveries ranging from 80-97% in soybean seeds fortified at 0.01 and 0.02 ppm, 92-104% in soybean hulls fortified at 0.02 and 0.04 ppm, 93.3-132% in corn grain fortified at 0.01 and 0.02 ppm, and 101-121% in corn fodder fortified at 0.01 and 0.02 ppm. The LOQ was determined to be 0.01 ppm for soybeans, corn grain, and corn forage and 0.02 ppm for other corn fractions (Memo dated 10/27/94, G. Kramer and Memos dated 10/19/94, J. Garbus). The methods have been accepted as enforcement methods by EPA provided that a procedure for calibrating the silica gel clean-up be incorporated in the soybean method and a procedure for calibrating chromatographic material be incorporated in the corn method. The methods for soybeans and corn have been forwarded to FDA for inclusion in PAM, Vol. II as Methods I and II, respectively (12/6/94; M. Bradley). The two methods are similar, differing only in extraction and clean-up of certain corn matrices with a high content of coextractives. These methods are also adequate for determining residues of flumiclorac pentyl *per se* in cotton matrices. A description of the methods is provided below.

Soybeans

For soybeans and soybean hulls, powdered samples were sequentially extracted with acidified (2% acetic acid) acetonitrile and acetonitrile:water (1:1, v:v) and filtered. The extracts were partitioned with aqueous NaCl and dichloromethane, then re-extracted with dichloromethane. The dichloromethane extracts were evaporated to dryness then dissolved in hexane:ethyl acetate (3:1, v:v) and transferred to a silica gel (phosphoric acid-treated) column. The residues were eluted with hexane:ethyl acetate, concentrated to dryness and dissolved in acetone prior to GC analysis. For GC analysis, three sets of conditions with various column packings and temperature programs were used. If the preferred set of conditions resulted in matrix interference, the alternative condition was used (DP Barcode D195816, 5/25/94, J. Garbus).

An independent validation of the soybean analytical method was submitted. The method used for the determination of flumiclorac pentyl residues in the field trials and proposed as the analytical enforcement method, entitled "Method for the Determination of Residues of V-23031 in Soybean Crops and its Processing Fractions - Report Amendment Number One", Valent Doc. #2961-91-0191-MD-001-001, was validated by Analytical Development Corporation (Colorado Springs, CO). Adequate recoveries were obtained with the ILV study. The method, as written, was followed except for minor modifications; however, it was determined necessary to condition the chromatographic system with soybean extract prior to injecting an analytical set of extracts and standards (DP Barcode D195816, 5/25/94, J. Garbus).

Field Corn

For field corn RAC's, the powdered samples were sequentially extracted with acidified (2% acetic acid) acetonitrile and acetonitrile:water (1:1, v:v) and filtered. Except for fodder, the extracts were partitioned with aqueous NaCl and dichloromethane, then re-extracted with dichloromethane. The dichloromethane extracts were evaporated to dryness. For fodder, the extracts were partitioned with aqueous NaCl and hexane and evaporated to dryness. For field corn forage, silage, and grain, the residues were dissolved in acetonitrile followed by hexane. The hexane phase was re-extracted with acetonitrile and the ACN phase evaporated to dryness.

The residues were dissolved in hexane:ethyl acetate (4:1, v:v) and transferred to an activated Florisil column. Residues were eluted with hexane/ethyl acetate, concentrated to dryness and dissolved in acetone for GC analysis. For GC analysis, two sets of conditions with different column packings and temperature programs were used. If the selected set of conditions resulted in matrix interference, the alternative condition was used (DP Barcode D195816, 5/25/94, J. Garbus).

Field corn matrices were not analyzed as part of the independent laboratory validation. However, the corn method does not differ substantially from that of the soybean method except in the extraction and clean-up of matrices with a high content of coextractives.

Cotton

Samples of cotton undelinted seed and gin byproducts, from the field trials submitted in conjunction with PP#3F6767, were analyzed for residues of flumiclorac pentyl using a GC Method (RM-29-2a) entitled "Determination of Residues of Flumiclorac Pentyl Ester in Cotton Seed." This method is a modified version of Method RM-29-2 (current enforcement method for flumiclorac pentyl in/on soybeans), in which the cleanup step uses an alumina column instead of the silica column. The validated LOQ was 0.02 ppm for undelinted cottonseed and gin byproducts.

860.1360 Multiresidue Methods

The behavior of flumiclorac pentyl in FDA's multiresidue testing protocols has been investigated. The chemical structure of flumiclorac pentyl is such that testing in protocols A, B, and G is not required. The material gave no response when carried thru protocol C. As a result of the lack of response to protocol C, the material was not subjected to protocols D, E, and F (DP Barcode D195816, 5/25/94, J. Garbus).

860.1380 Storage Stability

Storage stability studies were submitted for soybeans, corn, and cotton. The soybean storage stability data adequately support the storage conditions and intervals of samples collected from the soybean crop field trials. The corn storage stability data do not adequately support the 1989 and 1990 crop field trial data for corn as residues of flumiclorac pentyl were not shown to be stable over the maximum storage duration. As a result of these findings, the petitioner submitted additional crop field trial data for corn that reported residues of flumiclorac pentyl from analyses conducted within the period of maximum residue stability (30 to 45 days). The cotton storage stability data, which adequately support the storage conditions and intervals of samples collected from the cotton crop field trials, indicate that fortified residues of flumiclorac pentyl are reasonably stable under frozen storage conditions in/on undelinted cottonseed and cotton gin byproducts for up to ~2 months. In addition, weathered residues of flumiclorac pentyl have been demonstrated to be reasonably stable under frozen storage conditions in/on cotton gin byproducts for up to ~4 months.

A summary of the storage stability studies conducted for soybeans, corn, and cotton is provided below.

Soybeans

The stability of flumiclorac pentyl was determined in fortified soybean seeds and in field treated samples of soybean forage and hay stored over a 24 month period. After 22 months of storage, 96% of the fortification level was found in the seed. For field treated forage samples, recoveries after 24 months averaged 88% and for field treated soybean hay, the corresponding value was 85%. These soybean storage stability data for the parent compound are adequate (DP Barcode D174474, 7/28/92, J. Garbus).

Corn

The stability of flumiclorac pentyl was determined in treated corn fodder, forage, silage and grain stored frozen for a year. At various intervals over this period, triplicate samples were taken and analyzed for the parent compound. The data indicate that over the maximum storage duration of approximately 1 year, residues of flumiclorac pentyl in/on forage, silage, and grain are not stable as the mean loss was about 40%. After over 210 days of storage, recoveries in these commodities ranged from 38% in silage to 71% in grain. Residues of the parent compound were found to be stable in fodder for up to 395 days (81% recovery). The maximum period of stability for flumiclorac pentyl residues in/on corn matrices was determined to be 30-45 days. The variability in recoveries over extended periods of storage prior to analysis reduced the reliability of residue values in samples stored for extended periods (DP Barcode D195816, 5/25/94, J. Garbus).

Residues appeared to be stable in corn processing commodities over a four month period with the exception of dry-milled grits. Recovery in corn flour ranged from 80-100% of the initial value when the spiked commodity was sampled at intervals over four months; corresponding values were 92-140% for crude oil, 88-110% for refined oil, and 65-95% for starch. However, with grits, there was a greater loss of recoverable residue (83% at 0 days, 79% at 14 days, and 23-57% between 30 and 130 days).

Cotton

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Valent U.S.A. Corporation has included the results of storage stability studies with flumiclorac pentyl as part of the cotton field trial submissions associated with PP#3F6767. In one study, untreated samples of undelinted cottonseed and gin byproducts were fortified with flumiclorac pentyl at 0.10 ppm and then stored frozen (- 20 °C) for 33 and 61 days. In another study, cotton gin byproduct samples with weathered residues from cotton field trials were stored frozen and re-extracted 99 and 124 days after the initial residue extraction. Fresh fortification samples were analyzed with the re-extracted samples. Samples were analyzed for residues of flumiclorac pentyl using a GC/NPD method (RM-29-2a) with a validated LOQ of 0.02 ppm. This method is adequate for data collection based on acceptable method recoveries.

The submitted storage stability data indicate that fortified residues of flumiclorac pentyl are reasonably stable under frozen storage conditions in/on undelinted cottonseed (storage stability recovery range of 80-102%) and cotton gin byproducts (storage stability recovery range of 87-120%) for up to 61 days (~2 months). The reviewed data also indicate that weathered residues of flumiclorac pentyl are reasonably stable under frozen storage conditions in/on cotton gin byproducts for up to 124 days (~4 months).

860.1400 Water, Fish, and Irrigated Crops

Flumiclorac pentyl is not registered or proposed for direct use on water and aquatic food and feed crops; therefore, no residue chemistry data are required under this guideline.

860.1460 Food Handling

Flumiclorac pentyl is not registered or proposed for use in food-handling establishments; therefore, no residue chemistry data are required under this guideline.

860.1480 Meat, Milk, Poultry, and Eggs

Based on the results of the animal metabolism studies, the registered uses of flumiclorac pentyl on soybeans and field corn as well as the proposed use on cotton are not expected to result in quantifiable residues in meat, milk, poultry, and eggs. Residues in ruminant and poultry commodities may be classified under 40 CFR §180.6(a)(3); i.e., no expectation of finite residues. Thus, animal feeding studies and tolerances for livestock commodities are not needed at this time. However, feeding studies and tolerances for livestock commodities may be required in the future if new feed uses are proposed which would significantly increase the maximum theoretical dietary burdens (see Table 6 below).

Table 6. Calculation of Maximum Dietary Burdens of Flumiclorac Pentyl to Livestock.

Feedstuff	% Dry Matter [1]	% Diet [1]	Estimated Tolerance (ppm)	Dietary Contribution (ppm) [2]
Beef Cattle				
Cotton, undelinted seed	88	25	0.2	0.057
Cotton gin byproducts	90	20	3.0	0.667
Corn, field, grain	88	55	0.01	0.006
TOTAL BURDEN	--	100	--	**0.73**
Dairy Cattle				
Cotton, undelinted seed	88	25	0.2	0.057
Cotton gin byproducts	90	20	3.0	0.667
Corn, field, grain	88	40	0.01	0.005
Corn, field, forage	40	15	0.01	0.004
TOTAL BURDEN	--	100	--	**0.73**
Swine				
Corn, field, grain	88	80	0.01	0.008

Table 6. Calculation of Maximum Dietary Burdens of Flumiclorac Pentyl to Livestock.				
Feedstuff	% Dry Matter [1]	% Diet [1]	Estimated Tolerance (ppm)	Dietary Contribution (ppm) [2]
Soybean, seed	89	20	0.01	0.002
TOTAL BURDEN	--	100	--	**0.010**
Poultry				
Corn, field, grain	88	80	0.01	0.008
Soybean, seed	89	20	0.01	0.002
TOTAL BURDEN	--	100	--	**0.010**

[1] Table 1 (OPPTS GLN 860.1000).

[2] Contribution = ([tolerance /% DM] x % diet) for beef and dairy cattle; contribution = (tolerance x % diet) for poultry and swine.

860.1500 Crop Field Trials

Crop field trials were conducted for field corn and soybeans according to the maximum registered use patterns as indicated on the product labels. In all corn and soybean trials, the test substance was applied postemergence at the maximum label rate. The storage stability data adequately support the storage duration of the soybeans analyzed in the field trials. For corn, the storage stability data indicate that flumiclorac pentyl residues were not stable for the duration of storage used in the 1989 and 1990 field trials. Therefore, additional field trials were conducted in 1991, where the sample storage interval did not exceed 45 days. In soybean seed and field corn grain, forage, and stover samples, flumiclorac pentyl residues were consistently below the LOQ of 0.01 ppm.

HED notes that the field corn PHI is expressed in terms of a crop growth stage instead of a number of days. In this case, the label specifies that flumiclorac pentyl may not be applied to corn later than the 10-leaf stage. In addition, a pregrazing interval of 28 days is required before livestock are permitted to enter a treated field. These restrictions are supported by the crop field trial data collected and are appropriate.

HED concludes that the established tolerances of 0.01 ppm each for field corn grain, forage, and fodder are adequate; however the fodder term should be changed to stover to reflect current crop commodity definitions. HED also concludes that the established tolerance of 0.01 ppm for soybean seed is supported by adequate residue data. However, the established tolerance on soybean hulls should be revoked since this item is no longer considered a major livestock feed commodity and has been deleted from Table 1 of OPPTS 860.1000.

Although the available residue data for soybean hay and forage indicate that residues of flumiclorac pentyl residues were detected above the LOQ, no tolerances are needed for these soybean commodities because the registered end-use products contain adequate label restrictions which prohibit the feeding and grazing of livestock animals on treated soybean fields. HED allows this form of label restriction since soybean feedstuffs remain under the control of growers.

The requirement for residue data on aspirated grain fractions may be waived since residues in/on samples of field corn grain and soybean seed, following treatment at 1x, were below the LOQ. In addition, one field corn trial conducted at an exaggerated rate of 5x also showed flumiclorac pentyl residue levels below LOQ in corn grain. Based on these findings, a tolerance for aspirated grain fractions need not be established.

Crop field trials were also conducted for cotton according to the proposed use pattern. The cotton submission has been reviewed and deemed adequate pending submission of a revised Section F to reflect tolerance levels slightly higher than the levels proposed by the petitioner. Following a single postemergence foliar application of an EC formulation at a seasonal rate of ~0.094 lb ai/A (~1x), the maximum residues of flumiclorac pentyl were 0.11 and 0.06 ppm in/on treated samples of cottonseed harvested by stripper and picker equipment, respectively. The maximum residues of flumiclorac pentyl were 0.83 and 2.2 ppm in/on treated samples of cotton gin byproducts harvested by stripper and picker equipment, respectively. Based on these data, the petitioner is required to submit a revised Section F to increase the proposed tolerance levels on: (i) undelinted cottonseed, from 0.1 ppm to 0.2 ppm; and (ii) cotton gin byproducts, from 2.0 ppm to 3.0 ppm.

Detailed summaries of the crop field trials are presented below.

Soybeans

Residue trials were conducted in 1989 and 1990 in states representing 75% of the soybean producing areas. The formulated pesticide was applied at a rate of 52 g ai/A (0.11 lb ai/A; ~1x the maximum proposed seasonal rate for soybeans) as a postemergence application. In 1989, trials were conducted at sites in Illinois, Missouri, Minnesota, Indiana, Iowa, Ohio and Mississippi. Forage samples were harvested 13-14 days after application. Some forage samples were allowed to air dry as hay samples for an additional 3-16 days. Soybeans were harvested 60-93 days after application. No detectable flumiclorac pentyl residues were found in soybean seed samples. Forage samples had residues up to 0.10 ppm 14 days after application. Hay samples had residues up 0.17 ppm at 19 days (14 harvest + 5 drying) after application (DP Barcode D174474, 7/28/92, J. Garbus).

In 1990, the trials were conducted at sites in Arkansas, Illinois, Louisiana, Missouri, Minnesota, Indiana, Iowa, and Mississippi. Forage samples were harvested 14-21 days after application. Some forage samples were allowed to air dry as hay samples 2-12 days. Soybeans were harvested 60-64 days after application. No flumiclorac pentyl residues were found in soybean seed samples. Forage samples had residues up to 0.05 ppm 14 days after application. Hay samples had residues up to 0.11 ppm at 16 days after application and up to 0.08 ppm 27 days after application (DP Barcode D174474, 7/28/92, J. Garbus).

For permanent tolerance petition, fourteen trials were conducted in 1991 in 13 states representing 83% of the U.S. soybean production. Trials were conducted at sites in Arkansas, Nebraska, Georgia, Illinois, Minnesota, Tennessee, Missouri, Indiana, Iowa (2), Ohio, Kansas, North Carolina, and Mississippi. The formulated pesticide was applied at a rate of 52 g ai/A (0.11 lb

ai/A; ~1x) as a postemergence application. Forage samples were harvested 14-15 days after application. Some forage samples were allowed to air dry as hay samples for an additional 3-12 days. Soybeans were harvested 56-102 days after application. No quantifiable flumiclorac pentyl residues (<0.01 ppm) were found in any soybean seed samples. Forage samples had residues up to 0.07 ppm 14 days after application. Hay samples had residues up to 0.24 ppm at 27 days (14 harvest + 13 drying days) after application. In a residue decline study, residues were not quantifiable (<0.01 ppm) after 28 days in forage and straw (DP Barcode D195816, 5/25/94, J. Garbus).

Field Corn

Seven field corn trials were conducted in Illinois (1), Indiana (1), Iowa (2), Minnesota (1), Missouri (1) and Nebraska (1), representing 59% of commercial growing areas for this crop. Flumiclorac pentyl was applied to field corn at the V-8 stage, 8-leafed, at a rate of 24 g ai/A (0.053 lb ai/A; ~1x the maximum proposed seasonal rate for field corn). No residues of flumiclorac pentyl were detected in forage 21 days after application or in silage 56 to 81 days after application. No residues of flumiclorac pentyl were detected in grain or fodder at harvest 85 to 118 days after application (DP Barcode D174474, 7/28/92, J. Garbus).

For field corn permanent tolerance request, 14 field trials were conducted in 1991 in 13 corn growing states (Nebraska, Indiana, Wisconsin, Texas, Illinois, Minnesota, New York, Michigan, Missouri, Ohio, Pennsylvania, North Carolina, and Iowa (2)), representing 80% of the U.S. field corn production. Flumiclorac pentyl was applied to field corn at the V-10 stage, 10-leafed, at a rate of 24 g ai/A (0.053 lb ai/A; ~1x) as one postemergence application. No residues (≤0.01 ppm) of flumiclorac pentyl were reported in forage 21-28 days after application or in silage 47-82 days after application. Samples were stored 95-273 days prior to analysis. No residues of flumiclorac pentyl were reported in grain or fodder at harvest 82-100 days after application (DP Barcode D195816, 5/25/94, J. Garbus).

Six additional field trials (MRID 42942901; DP Barcode D198103, 8/2/94, J. Garbus) were conducted in 1992 in Nebraska, Indiana, Wisconsin, Illinois, Ohio, and Iowa representing 58% of the U.S. field corn production. These trials were conducted in which the analyses for residues would be done within the period of maximum stability (30-45 days after sampling) as requested based on the results of the storage stability data of field corn matrices. In these studies, flumiclorac pentyl was applied to field corn at the V-10 stage (10-leafed), at a rate of 25 g ai/A (0.053 lb ai/A; ~1x) as one postemergence application. Application was made using ground equipment with crop oil added to the spray solution. Forage samples were collected 3 or 4 weeks after application, silage samples were collected at the time of "physiological maturity" (53-87 days after application), and grain and stover at the time of harvest (92-116 days after application). In addition, in one trial, 125 g ai/A (0.28 lb ai/A) was applied to provide residue-bearing grain for processing studies. All corn RAC samples were analyzed within 41 days of receipt after freezer storage. No residues of flumiclorac pentyl were reported in forage 21-28 days after application, in silage 53-87 days after application, or in corn grain or stover at the time of harvest 92-116 days after application (treated at the 5x rate).

Cotton

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Valent U.S.A. Corporation has submitted residue field trial data for flumiclorac pentyl on cotton. Thirteen trials were conducted in Regions 2 (NC; 1 trial), 4 (AR, LA, and MS; 3 trials), 8 (OK and TX; 6 trials), and 10 (AZ and CA; 3 trials) between the 1997 and 2002 growing seasons. Cotton was harvested from six trials using stripper equipment and from seven trials using picker equipment. The number and locations of conducted field trials are in accordance with OPPTS Guideline 860.1500.

At each field trial site, cotton plants were treated with a single postemergence foliar application of Resource Herbicide®, an emulsifiable concentrate (EC) formulation containing 0.86 lb ai/gal of flumiclorac pentyl, at 0.092 to 0.096 lb ai/A (~1x the maximum proposed seasonal rate of 0.09 lb ai/A for cotton). Application was made using ground equipment in ~10-20 gal/A of water, with an adjuvant added to the spray solution. Samples of mature cotton were harvested 6 to 8 days posttreatment from each test location using either stripper or picker harvest equipment. Samples were then ginned to yield fuzzy seed (undelinted cottonseed) and gin trash (gin byproducts). These cotton commodities were analyzed for residues of flumiclorac pentyl using a GC/NPD method (RM-29-2a) with a validated LOQ of 0.02 ppm. This method is adequate for data collection based on acceptable method recoveries.

The maximum storage intervals of samples, from harvest to analysis, were 119 days (3.9 months) for cottonseed and 142 days (4.7 months) for gin byproducts. Supporting storage stability data were included in the residue field studies; refer to the 860.1380 DER for MRIDs 46082808 and 46102801. These data indicate that residues of flumiclorac pentyl are stable under frozen conditions in/on cotton undelinted seed for up to ~2 months and in/on gin byproducts for up to ~4 months.

The results of the cotton field trials are summarized in Table 7. The maximum residues of flumiclorac pentyl in/on treated samples harvested by stripper equipment were 0.11 ppm for undelinted cottonseed and 0.83 ppm for cotton gin byproducts. The maximum residues of flumiclorac pentyl in/on treated samples harvested by picker equipment were 0.06 ppm for undelinted cottonseed and 2.2 ppm for cotton gin byproduct.

TABLE 7. Summary of Residue Data from Cotton Field Trials with Flumiclorac Pentyl.

Cotton Matrix [Harvest Equipment]	Total Applic. Rate (lb ai/A)	PHI (days)	Residue Levels (ppm) [1]						
			n	Min.	Max.	HAFT[2]	Median (STMdR[3])	Mean (STMR[4])	Std. Dev.
Undelinted cottonseed [stripper]	0.094-0.096	7-8	12	0.02	0.11	0.10	0.03	0.04	0.03
Cotton, gin byproducts [stripper]	0.094-0.096	7-8	12	0.17	0.83	0.77	0.43	0.45	0.26
Undelinted cottonseed [picker]	0.092-0.096	6-7	14	<0.02	0.06	0.05	0.01	0.02	0.02
Cotton, gin byproducts [picker]	0.092-0.096	6-7	14	0.03	2.2	2.1	0.66	0.74	0.72

[1] For calculation of the minimum, maximum, and HAFT residues, the LOQ (0.02 ppm) was used for residues reported below the LOQ in Table C.3. of the DER; for calculation of the median, mean, and standard deviation, half the LOQ (0.01 ppm, equivalent to the LOD) was used for residues reported below the LOQ.

[2] HAFT = Highest Average Field Trial.

[3] STMdR = Supervised Trial Median Residue.

[4] STMR = Supervised Trial Mean Residue.

860.1520 Processed Food and Feed

Processing studies were conducted with soybean and field corn treated at 5.0x the maximum application rate. Flumiclorac pentyl residues were not detected in the RACs. In the processed fractions, flumiclorac pentyl residues were detected in soybean hulls at 0.01 ppm (processing factor of 1x) and in crude oil from corn at 0.02 ppm (wet milled) to 0.08 ppm (dry milled). Crude oil, however, is not considered a regulated commodity of commerce. A tolerance level of 0.02 ppm is appropriate to cover the residues found in soybean hulls.

A processing study with cottonseed has been submitted. Residues of flumiclorac pentyl were 0.02-0.03 ppm in/on undelinted cottonseed treated with an EC formulation at ~1x. Residues of flumiclorac pentyl did not concentrate (0.3x processing factors) in the processed commodities of cottonseed (meal, hulls, and refined oil).

No tolerances are required for any of the processed commodities of field corn or cotton. The Executive Summary of the cotton processing study DER is provided below.

Cotton

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Valent U.S.A. Corporation has submitted a cottonseed processing study with flumiclorac pentyl. In a trial conducted in TX, mature cotton was harvested 7 seven days following a single postemergence foliar application of Resource Herbicide®, an emulsifiable concentrate (EC) formulation containing 0.86 lb ai/gal of flumiclorac pentyl, at 0.096 lb ai/A (~1x the maximum

proposed seasonal rate). Cottonseed was ginned and processed into meal, hulls, and refined oil using small-scale processing procedures.

Samples of undelinted cottonseed and its processed commodities were analyzed for residues of flumiclorac pentyl using GC/NPD method RM-29-2a, with a validated LOQ of 0.02 ppm for all cotton matrices. This method is adequate for data collection based on acceptable concurrent method recovery data.

The maximum storage intervals of processing study samples from harvest to analysis were 104 days (3.4 months) for cottonseed, and 11 days (<1 month) for processed meal, hulls, and refined oil. The petitioner submitted storage stability data (MRIDs 46082808 and 46102801) in conjunction with the cotton field trial data; these data indicate that residues of flumiclorac pentyl are stable under frozen conditions in/on undelinted cottonseed for up to ~2 months and cotton gin byproducts for up to ~4 months. The available storage stability data support the storage conditions and intervals of RAC samples from the submitted cotton processing study, and storage stability data are not required for the processed commodities because they were analyzed within 30 days of collection.

The results of the cottonseed processing study are presented in Table 8. Residues of flumiclorac pentyl were 0.02-0.03 ppm in/on undelinted cottonseed (RAC) treated with the 0.86 lb/gal EC formulation at 0.096 lb ai/A. Residues of flumiclorac pentyl did not appear to concentrate (0.3x processing factors) in the processed commodities of cottonseed; residues were at or below the LOD (0.01 ppm) in all samples of meal, hulls, and refined oil processed from treated cottonseed. The observed processing factor of 0.3x from the current study does not exceed the theoretical concentration factors of 3.8x for hulls, 2.2x for meal, and 6.3x for refined oil (Table 3 of OPPTS 860.1520).

TABLE 8. Residue Data from Cottonseed Processing Study with Flumiclorac Pentyl.

RAC	Processed Commodity	Total Rate (lb ai/A)	PHI (days)	Flumiclorac Pentyl Residues (ppm) [1]	Processing Factor
Cottonseed	undelinted (ginned) seed (RAC)	0.096	7	0.02, 0.03	--
	meal (solvent extracted)			<0.01, <0.01	<0.3x
	hulls			<0.01, <0.01	<0.3x
	refined oil			<0.01, 0.01	≤0.3x

[1] Results are for duplicate analyses of a single sample.

860.1650 Submittal of Analytical Reference Standards

As of 8/28/04, an analytical reference standard for flumiclorac pentyl is available in the National Pesticide Standards Repository. Analytical reference standards of flumiclorac pentyl must be supplied and supplies replenished as requested by the Repository. The reference standards should be sent to the Analytical Chemistry Lab, which is located at Fort Meade, to the attention of either Theresa Cole or Frederic Siegelman at the following address:

USEPA
National Pesticide Standards Repository/Analytical Chemistry Branch/OPP
701 Mapes Road
Fort George G. Meade, MD 20755-5350
(Note that the mail will be returned if the extended zip code is not used.)

860.1850 Confined Accumulation in Rotational Crops

In the available confined rotational crop study, flumiclorac pentyl, uniformly labeled with ^{14}C in the phenyl ring or at positions 1 and 2 of the tetrahydrophthalamide ring, was applied to sandy loam soil in greenhouse pots at a rate equivalent to 48 g ai/A (0.11 lb ai/A), the maximum seasonal use rate. After intervals of 30, 120, or 360 days, the pots were planted with carrots, lettuce, or wheat.

After a normal growing interval, the plants were harvested. Lettuce, carrot roots and foliage, and wheat forage samples were extracted with acetone:0.1 N HCl (90:10, v:v), filtered, and partitioned with methylene chloride. Aliquots of the extracts and residues were analyzed for radioactivity by liquid scintillation counting.

Total residues greater than 0.01 ppm were found only in wheat grain (0.14 ppm), wheat chaff (0.026 ppm), and wheat straw (0.048 ppm) planted 30 days after the soil treatment. All other RAC's at all planting intervals had residues ranging from 0.0 to 12.6 ppb. Due to the low levels in the samples it was not possible to characterize the nature of the residue.

The available metabolism studies for flumiclorac pentyl all show extensive metabolism of the parent compound to yield a variety of compounds, all at low levels in the various matrices studied. The submitted confined accumulation in rotational crops study shows low levels of residue uptake. Therefore, a plant back interval (PBI) of 30 days is appropriate for all rotational crops except for cotton, field corn, and soybean [no restriction necessary for labeled crops]. However, if future uses of flumiclorac pentyl result in an increase in the maximum seasonal use rate of 0.11 lb ai/A, a new confined rotational crop study should be submitted and decisions regarding the PBI should be based on the results of the new study, which should characterize and identify the residues found.

860.1900 Field Accumulation in Rotational Crops

A field accumulation study in rotational crops has not been submitted due to the low concentrations recovered from the confined accumulation study.

TOLERANCE REASSESSMENT SUMMARY

Tolerance Reassessment for Flumiclorac Pentyl

Permanent tolerances are established for residues of flumiclorac pentyl, including all the metabolites of flumiclorac pentyl. The tolerance level is expressed in terms of the parent only, which serves as an indicator of the use of flumiclorac pentyl, in/on field corn grain, forage, and fodder at 0.01 ppm; soybean seed at 0.01 ppm, and soybean hulls at 0.02 ppm [40 CFR §180.477]. HED recommends that the tolerance expression be revised to only include residues of flumiclorac pentyl *per se*. There are currently no tolerances for flumiclorac pentyl residues in livestock commodities or for inadvertent residues in rotational crops.

Adequate magnitude of the residue data are available to reassess the tolerances listed in 40 CFR §180.477. The available data indicate that residues of flumiclorac pentyl were consistently below the LOQ of 0.01 ppm in/on samples of soybean seed and field corn grain, forage, and fodder treated according to the maximum use patterns for each crop. The tolerances for soybean seed and hulls are reassessed at 0.01 and 0.02 ppm, respectively. The tolerances for field corn RACs are reassessed at 0.01 ppm each.

Although the available residue data for soybean hay and forage indicate that residues of flumiclorac pentyl residues were detected above the LOQ, no tolerances are needed for these soybean RACs because the registered end-use products contain adequate label restrictions which prohibit the feeding and grazing of livestock animals on treated soybean fields.

The requirements for residue data on the aspirated grain fractions may be waived since residues in/on samples of field corn grain and soybean seed, following treatment at 1x, were below the LOQ. In addition, one field corn trial conducted at an exaggerated rate of 5x also showed flumiclorac pentyl residue levels below LOQ in corn grain. Based on these findings, a tolerance for aspirated grain fractions need not be established.

A summary of flumiclorac pentyl tolerance reassessment is presented in Table 9.

Proposed Tolerances

Valent U.S.A. has submitted an amended registration application and a tolerance petition (PP#3F6767) for the use of flumiclorac pentyl on cotton as a harvest aid (desiccant). The petitioner proposes the establishment of tolerances for residues of flumiclorac pentyl *per se* in/on undelinted cottonseed at 0.1 ppm and cotton gin byproducts at 2.0 ppm.

Adequate residue data have been submitted to support the proposed uses on cotton pending submission of a revised Section F to reflect appropriate tolerance levels. The petitioner needs to submit a revised Section F to increase the proposed tolerance levels on: (i) undelinted cottonseed from 0.1 ppm to 0.20 ppm; and (ii) cotton gin byproducts from 2.0 ppm to 3.0 ppm.

TABLE 9. Tolerance Reassessment Summary for Flumiclorac Pentyl.			
Commodity	Current Tolerance (ppm)	Tolerance Reassessment (ppm)	Comments
Tolerances Listed in 40 CFR §180.477			
Corn, field, grain	0.01	0.01	
Corn, field, forage	0.01	0.01	
Corn, field, stover	0.01	0.01	
Soybean, hulls	0.02	0.02	
Soybean, seed	0.01	0.01	
Tolerances Proposed in PP#3F6767			
Cotton, seed undelinted	0.1 (proposed)	0.20	Cotton, undelinted seed
Cotton gin byproducts	2.0 (proposed)	3.0	Cotton, gin byproducts

Codex/International Harmonization

There are no Codex maximum residue limits (MRLs) for flumiclorac pentyl; therefore, no questions of compatibility with U.S. tolerances exist.

Attachments:
International Residue Limit Status sheet
Appendix 1 - Chemical Name and Structure Table
46082803.der
46082804.der
46082805.der
46082806.der
46082808.de1
46082808.de2
46102801.der

Template Version November 2003

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42825845 Kurtz, A. (1992) Magnitude of the Residue of V-23031 in Soybean Forage, Hay and Seed from 1991 Soybean Trials: Lab Project Number: 3944-91-0178-CR-001. Unpublished study prepared by Ricerca, Inc. 931 p.

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42825849 Crawford, C.; Dillon, K. (1992) Stability of V-23031 in Corn Processing Fractions--1991: Lab Project Number: 3717-91-0197-CR-001: V-23031. Unpublished study prepared by Ricerca, Inc. 108 p.

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43439901 Fujie, G. (1994) Determination of Residues of Flumiclorac Pentyl Ester in Soybean and its Processing Fractions: Lab Project Number: RM-29-2. Unpublished study prepared by Valent U.S.A. Corp. 17 p.

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46082803 Panthani, A.; Kaman, R. (2002) A Study to Determine the Nature of the Residue in Milk, Meat and Tissue From Lactating Goats Dosed with (Phenyl-(Carbon 14)) S-23031. Project Number: 3790/90/0513/EF/001, S/23031. Unpublished study prepared by Ricerca, Inc. 275 p.

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46082805 Huhtanen, K. (1992) A Study to Determine the Nature of the Residue in Poultry and Egg From Chickens Dosed with (Phenyl-(Carbon 14)) S-23031 Analytical Phase of Study. Project Number: 90/0497, 3789/90/0049/EF/002, (CARBON 14)S/23031. Unpublished study prepared by Ricerca, Inc. 153 p.

46082806 Huhtanen, K. (1992) A Study to Determine the Nature of the Residue in Poultry and Egg From Chickens Dosed with (THP-(Carbon 14)) S-23031 Analytical Phase of Study. Project Number: 90/0511, 3789/90/0511/EF/001. Unpublished study prepared by Ricerca, Inc. 161 p.

46082808 Stearns, J. (2003) Magnitude of the Residues of Flumiclorac Pentyl Ester on Cotton, Undelinted Seed and Cotton Gin Byproducts. Project Number: 24838, V/02/24838. Unpublished study prepared by Sumitomo Chemical Co., Ltd. 184 p.

46102801 Green, C. (1998) Magnitude of the Residues of Flumiclorac Pentyl Ester on Cotton and Cotton Processing Fractions. Project Number: V/97/11707, V/11707/A, V/11707/B. Unpublished study prepared by Valent U.S.A. Corporation. 475 p.

Agency Memoranda Citations

Agency Memoranda Citations.						
Date	**DP Barcode**	**CB No.**	**From**	**To**	**MRID Nos.**	**Subject**
7/28/92	D174474	9352	J. Garbus	J. Miller/ D. Kenny and A. Kocialski	42187400 thru 42187405, 42169849 thru 42169859, 42187407 thru 42187408	PP#2G4078: New Chemical EUP: V-23031, Flumiclorac pentyl on Field Corn and Soybeans. Evaluation of Analytical Methods and of Residue Data.
3/21/94	D194610, D194615, D197255, & D198102	—	A. Abramovitch	Unknown	—	EFOWB review
5/25/94	D195861, 195864, 195822, 195816, 197257	12902, 12644, 12645, 12646, 12647	J. Garbus	J. Miller/ D. Kenny and A. Kocialski	42825840 thru 42825850, 42883907, 42883908, 43002301	PP#s 3F4234/3H5682 Flumiclorac pentyl (V-23031, Resource) on Field Corn and Soybeans. Evaluation of Analytical Methods and of Residue Data.
7/27/94	—	—	R. Loranger	HED Metabolism Committee	—	HED Metabolism Committee Meeting of 7/13/94. Flumiclorac Pentyl (Resource ®)
8/2/94	D198103	13034	J. Garbus	J. Miller and D. Kenny	42942900, 42942901	PP#s 3F4234/3H5682 V-23031, Flumiclorac pentyl (V-23031, Resource) on Field Corn and Soybeans. Additional Field Trial Data for Corn RAC's.
10/18/94	—	—	J. Garbus	J. Miller/ D. Kenny and A. Kocialski	—	PP#s 2G4078/3F4234: New Chemical EUP and Permanent Tolerances: V-23031, Flumiclorac pentyl on Field Corn and Soybeans. Results of Method Validation Request for Parent in/on Corn Grain and Corn Fodder.

Agency Memoranda Citations.						
Date	**DP Barcode**	**CB No.**	**From**	**To**	**MRID Nos.**	**Subject**
10/18/94	—	—	J. Garbus	J. Miller/ D. Kenny and A. Kocialski	—	PP#s 2G4078/3F4234: New Chemical EUP and Permanent Tolerances: V-23031, Flumiclorac-Pentyl on Field Corn and Soybeans. Results of Method Validation Request for Parent in/on Corn Grain and Corn Fodder.
10/19/94	D205338	14055	J. Garbus	J. Miller/ D. Kenny and A. Kocialski	None	PP's #3F4234/3H5682: Flumiclorac Pentyl Ester (V-23031, Resource) on Field Corn and Soybeans. Revised Section F.
10/27/94	—	—	G.F. Kramer	J. Miller/ D. Kenny and A. Kocialski	—	PP#s 2G4078/3F4234: New Chemical EUP and Permanent Tolerances: V-23031, Flumiclorac pentyl on Field Corn and Soybeans. Results of Method Validation Request for Parent in/on Soybean Seed and Hulls.
11/9/94	D209204	14651	J. Garbus	J. Miller/ D. Kenny and A. Kocialski	43439901 and 43439902	PP's# 3F234/3H5682: Flumiclorac Pentyl Ester (Resource) on Field Corn and Soybeans. Revised Section F's and Revised Enforcement Analytical Methods. Amendment of November 1, 1994.
12/6/94	—	—	M. Bradley	A. Marcotte	—	PAM II Method to FDA

INTERNATIONAL RESIDUE LIMIT STATUS

Chemical Name: Pentyl[2-chloro-4-fluoro-5-(1,3,4,5,6,7- hexahydro-1,3-dioxo-2H-isoindol-2-yl) phenoxy]acetate	Common Name: Flumiclorac pentyl	X Proposed tolerance ☐ Reevaluated tolerance ☐ Other	Date: 1/26/05

Codex Status (Maximum Residue Limits)	U. S. Tolerances
X No Codex proposal step 6 or above ☐ No Codex proposal step 6 or above for the crops requested	Petition Number: PP3F6767 DP Barcode: D302003 Other Identifier:
Residue definition (step 8/CXL): N/A	Reviewer/Branch: RRB3
	Residue definition of established tolerances in 40 CFR §180.477: Flumiclorac pentyl including all of its metabolites. Residue definition of tolerances proposed in PP33F6767: Flumiclorac pentyl *per se*

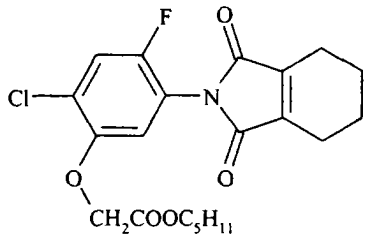
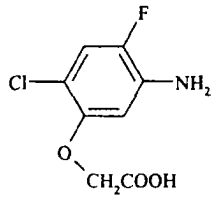
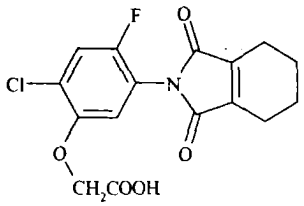
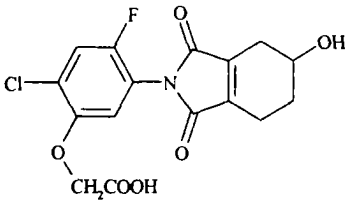
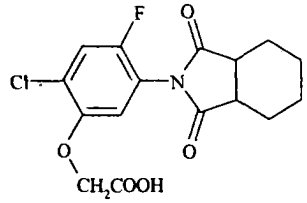
Crop (s)	MRL (mg/kg)	Crop(s)	Tolerances (ppm)
		Cotton, seed undelinted	0.1
		Cotton gin byproducts	2.0

Limits for Canada	Limits for Mexico
X No Limits ☐ No Limits for the crops requested	X No Limits ☐ No Limits for the crops requested
Residue definition: N/A	Residue definition: N/A

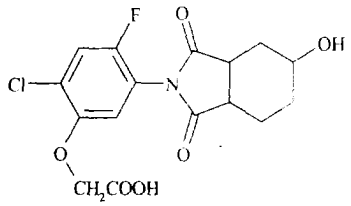
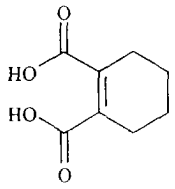
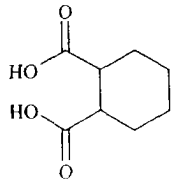
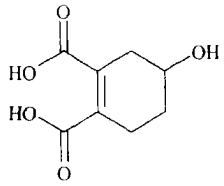
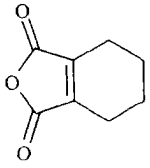
Crop(s)	MRL (mg/kg)	Crop(s)	MRL (mg/kg)

Notes/Special Instructions:

Appendix I. Chemical Name and Structure of Flumiclorac Pentyl and Its Transformation Products.

Company Name	Chemical Name	Structure
Flumiclorac pentyl; S-23031 or V-23031	Pentyl[2-chloro-4-fluoro-5-(1,3,4,5,6,7-hexahydro-1,3-dioxo-2H-isoindol-2-yl)phenoxy]acetate or Acetic acid, {2-chloro-4-fluoro-5-(1,3,4,5,6,7-hexahydro-1,3-dioxo-2H-isoindol-2-yl)phenoxy}-,pentyl ester or 2-chloro-4-fluoro-5-(1,3,4,5,6,7-hexahydro-1,3-dioxo-2H-isoindol-2-yl)phenoxy]acetic acid, pentyl ester	
AFCA	5-amino-2-chloro-4-fluorophenoxyacetic acid	
IMCA	2-chloro-4-fluoro-5-(3,4,5,6-tetrahydrophthalimido)phenoxyacetic acid	
4-OH-IMCA	2-chloro-4-fluoro-5-(4-hydroxy-3,4,5,6-tetrahydrophthalimido) phenoxyacetate	
SAT-IMCA	2-chloro-4-fluoro-5-(cyclohexane-1,2-dicarboximido)phenoxyacetate	

Appendix I. Chemical Name and Structure of Flumiclorac Pentyl and Its Transformation Products.

Company Name	Chemical Name	Structure
SAT-4-OH-IMCA	2-chloro-4-fluoro-5-(4-hydroxy-1,2,-cyclohexanedicarboximido) phenoxyacetate	
THPA	3,4,5,6-tetrahydrophthalic acid	
HPA	(±)trans-1,2-cyclohexanedicarboxylic acid	
4-OH-THPA	4-hydroxy-1-cyclohexene-1,2-dicarboxylate	
Δ^1-TPA	3,4,5,6-tetrahydrophthalic anhydride	

Flumiclorac pentyl/PC Code 128724/Valent U.S.A. Corporation
OPPTS 860.1300
Nature of the Residues in Livestock - Goat

Primary Evaluator William H. Donovan
William H. Donovan, Ph.D.
Chemist
HED/RRB3
Date: 6/24/05

Approved by
for Catherine Eiden
Branch Chief
HED/RRB3
Date: 6/24/05

This DER was originally prepared under contract by Dynamac Corporation (20440 Century Boulevard, Suite 100; Germantown, MD 20874; submitted 01/26/2005). The DER has been reviewed by the Health Effects Division (HED) and revised to reflect current Office of Pesticide Programs (OPP) policies.

STUDY REPORT:

46082803 Panthani, A.; and Kaman, R. (2002) A Study to Determine the Nature of the Residue in Milk, Meat and Tissue From Lactating Goats Dosed with [Phenyl-^{14}C]S-23031. Laboratory Project Identification Number: 3790-90-0513-EF-001. Unpublished study prepared by Ricerca, Inc (Painesville, OH) and submitted by Valent USA Corp. (Walnut Creek, CA). 275 p.

EXECUTIVE SUMMARY:

Valent U.S.A. Corporation has submitted a study investigating the metabolism of [phenyl-U-^{14}C]flumiclorac pentyl in lactating goats. Information concerning the in-life phase of this study was previously submitted in MRID 42169852 and reviewed (DP Barcode D174474, 7/28/92, J. Garbus) in conjunction with PP#2G4078. The current submission reports the identification/characterization of radioactive residues in goat milk and tissues.

The test substance, [phenyl-U-^{14}C]flumiclorac pentyl, was administered orally to two goats at 20 ppm in the diet. The goats were dosed once per day for five consecutive days. Milk was collected twice daily and composited each day, and tissues (kidney, liver, muscle, and fat) were collected at sacrifice. The in-life phase of the study was conducted by ABC Laboratories (Columbia, MO), and the analytical phase was conducted by Ricerca, Inc. (Painsville, OH).

Radioactivity was low in all goat matrices, with the highest levels observed in kidney and liver. Total radioactive residues were 0.006-0.016 ppm in milk, 0.0291-0.0451 ppm in kidney, 0.0310-0.088 ppm in liver, <0.0007-0.0009 ppm in fat (perirenal and omental), and 0.0013 ppm in muscle (loin and leg) from goats dosed with [phenyl-U-^{14}C]flumiclorac pentyl. Residues appear to remain fairly consistent in milk throughout the study period; approximately 3% of the milk radioactivity was determined to represent butterfat. The study reported that a large portion of the administered dose was excreted, with urine accounting for 27-30% and feces accounting for 29-36% of the administered dose.

Because of low radioactivity, residue characterization of fat and muscle samples was not conducted. The majority of the radioactivity (~74-99% TRR) in milk, kidney, and liver was extractable with organic solvents; nonextractable residues accounted only for 1-13% of TRR. Adequate storage stability data were submitted for milk, kidney, and liver, demonstrating the stability of the metabolite profile in these matrices for ~8-9 months. The parent compound significantly declined in the stored kidney sample.

Radioactive residues in milk, kidney, and liver were initially characterized by various chromatographic techniques (HPLC, TLC, and LC/MS); the identification of residues was confirmed by GC/MS analysis. Approximately 48-89% of the TRR in milk, kidney and liver were identified. The parent was only detected in the kidney of one goat at 23.0% TRR (0.011 ppm). A later re-analysis showed that most of the parent compound was degraded during freezer storage. Several metabolites were identified including: AFCA, IMCA, 4-OH-IMCA, SAT-IMCA, and SAT-4-OH-IMCA; the chemical names and structures of these metabolites are listed in Table C.3.1. Although certain of these metabolites represent a high percentage of the TRR in some analyzed goat matrices, the identified metabolites were detected at low absolute levels ($\leq$0.056 ppm). In milk, the metabolite AFCA was the principal residue component accounting for 56.0-64.6% TRR. The metabolite IMCA was detected in all samples except liver, even though it was not a major metabolite.

Based on the results of this study, the petitioner proposed that flumiclorac pentyl is rapidly metabolized and excreted in goats. Initial hydrolysis of the pentyl ester of flumiclorac pentyl yields IMCA. No significant metabolites with the intact pentyl ester group were detected in goat matrices. IMCA is further metabolized by cleavage of the imide ring to AFCA, which is readily excreted. The major residue in goat liver and kidney, SAT-IMCA is formed by a reduction process, where IMCA is further metabolized by gut microflora.

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the goat metabolism data are classified as scientifically acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document DP Barcode D308674.

COMPLIANCE:

A signed and dated compliance statement was provided. The study was conducted and reported in compliance with Good Laboratory Practice Regulations with the exception of the reference standards that were supplied and characterized by Sumitomo Chemical Company, Ltd. The characterizations of the identity of these substances were not done entirely under GLP procedures.

A. BACKGROUND INFORMATION

Flumiclorac pentyl is an N-phenylphthalimide derivative herbicide used for the control of broadleaf weeds. Its mode of action is through the accumulation of porphyrins in susceptible plants; the photosensitizing action of accumulated porphyrins may cause membrane lipid peroxidation which leads to irreversible damage of membrane function and structure in the plant. Flumiclorac pentyl is registered for postemergence application to field corn and soybeans; registration for use on cotton as a defoliant is pending. The PC code and nomenclature of flumiclorac pentyl are listed below in Table 1. The physicochemical properties of flumiclorac pentyl are listed in Table 2.

TABLE 1. Flumiclorac Pentyl Nomenclature

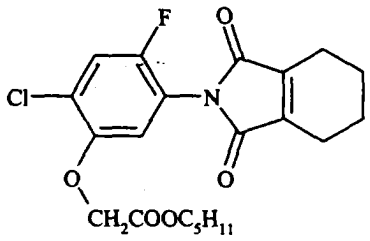
Chemical Structure	
Common name	Flumiclorac pentyl
Company experimental name	S-23031 or V-23031
Molecular Formula	$C_{21}H_{23}ClFNO_5$
Molecular Weight	423.9
IUPAC name	Pentyl (2-chloro-5 (cyclohex-1-ene-1,2-dicarboximido)-4-fluorophenoxy) acetate
CAS name	Pentyl[2-chloro-4-fluoro-5-(1,3,4,5,6,7- hexahydro-1,3-dioxo-2H-isoindol-2-yl)phenoxy]acetate
CAS #	87546-18-7
PC Code	128724

TABLE 2. Physicochemical Properties of Flumiclorac Pentyl

Parameter	Value	Reference
Melting point	88.9-90.1 °C	PP#2G4078; D174474, 7/28/92, J. Garbus
pH	6.03 at 25 °C	
Density, bulk density, or specific gravity	1.3316 g/mL at 20 °C	
Water solubility	0.189 mg/L at 25 °C	
Solvent solubility	g/100 mL at 25 °C: hexane 0.328 n-octanol 1.60 methanol 4.78 Solvesso 150 27.1 acetonitrile 58.9 acetone 59.0 tetrahydrofuran 69.7 N-methyl 2-pyrrolidinone 134.0 methylene chloride 288.0	

TABLE 2. Physicochemical Properties of Flumiclorac Pentyl		
Parameter	Value	Reference
Vapor pressure	$<1 \times 10^{-7}$ mm Hg at 22.4 °C	
Dissociation constant, pK_a	No dissociation at pH ≤7; flumiclorac pentyl decomposes at pH ≥9.	
Octanol/water partition coefficient	Log P_{ow} = 4.99 at 19.7-21.0 °C	
UV/visible absorption spectrum	Not available	

B. EXPERIMENTAL DESIGN

Information concerning the in-life phase of this study, including TRR determinations, was previously submitted in MRID 42169852 and reviewed (DP Barcode D174474, 7/28/92, J. Garbus) in conjunction with PP#2G4078. This information is re-presented herein with the supplemental residue characterization data.

B.1. Livestock

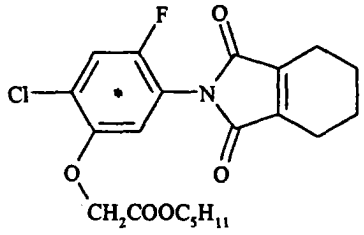
TABLE B.1.1. General Test Animal Information.					
Species	Breed	Age	Weight at study initiation (kg)	Health Status	Description of housing/holding area
Lactating goats	LaMancha or Toggenburg	2-6 years	45-53	Good	Individual metabolism stalls, maintained indoors at ABC Laboratories (Columbia, MO). Temperatures ranged 18-26 °C, with a humidity of 45-82% Rh.

Two goats (Goats #2 and #11) were treated, and a third goat received placebo doses as a control.

TABLE B.1.2. Test Animal Dietary Regime.				
Composition of Diet	Feed consumption (average kg/day)	Water	Acclimation period	Predosing
Dairy ration and alfalfa cubes, mixed at 0.4 kg grain + 0.6 kg roughage for a total of 1 kg, fed twice per day.	1.976-2.000	County public water, *ad libitum*	Nine days	None

TABLE B.1.3. Test Animal Dosing Regime			
Treatment Type	Feeding Level (ppm test material in food)	Vehicle	Timing/Duration
Oral via a bolus gun	20 ppm	Gelatin capsule	Once per day, after the morning milking, for five consecutive days.

B.2. Test Materials

TABLE B.2.1. Test Material Characteristics.	
Chemical structure	
Radiolabel position	Uniformly labeled in the phenyl ring
Lot No.	C-90-064 (isotopically diluted)
Purity	>97%
Specific activity of diluted test substance	95,100 dpm/µg

B.3. Sampling Information

TABLE B.3.1. Sample Collection Information			
Milk collected	Urine, feces and cage wash collected	Interval from last dose to sacrifice	Tissues harvested and analyzed
Milk was collected twice daily; p.m. samples were composited with the following a.m. sample. Each test goat yielded about 1 liter of milk per day.	Feces and urine were collected daily through Day 3; an aqueous cage wash was collected after removing goats for sacrifice.	within 4 hours	Omental fat, perirenal fat, kidneys, liver, loin muscle, and rear leg muscle.

B.4. Identification/Characterization of Residues

B.4.1. Sample Handling and Preparation

Daily (p.m. and following a.m.) milk samples were composited. Tissue samples, collected after goat sacrifice, were homogenized in a food grinder. Subsamples of milk and tissue samples were used for radioassay, and the remaining sample was frozen. Butterfat was separated from a subsample of Day 2 and 4 milk for percent content and radioassay. Frozen milk and tissue samples were shipped to Ricerca, Inc. (Painsville, OH) for residue extraction and characterization/identification. Because of low radioactivity, muscle and fat samples were not further extracted.

Days 2 and 4 milk samples were extracted with ethanol and filtered. The filter cake was rinsed with ethanol and 80% aqueous ethanol. The filtrate and rinsates were combined, concentrated and partitioned (2x) with hexane. The aqueous fraction was concentrated almost to dryness and centrifuged with 50% aqueous ethanol. The supernatant was concentrated, redissolved in acetonitrile (ACN):water (1:1, v:v) with 1% acetic acid for HPLC and TLC analysis. The solids remaining after centrifugation were mixed with 1 M NaOH and heated in a boiling water bath for 1 hour; an aliquot was reserved for LSC analysis.

Kidney and liver samples were extracted (2x) with ACN in a blender and filtered; the filter cake was rinsed with additional ACN. The filtrates and rinsates were combined. The nonextractable residues were further extracted (2x) with ACN:water (1:1, v:v) containing 1% acetic acid and then centrifuged. The supernatants were filtered and combined. The ACN and ACN/water extracts were separately concentrated almost to dryness and redissolved in the respective solvent for HPLC and TLC analysis.

B.4.2. Analytical Methodology

Total radioactive residues were determined in samples of milk by direct LSC and in tissue samples by combustion/LSC (triplicate aliquots) at ABC Laboratories. TRRs in the petroleum ether fraction of butterfat samples were determined in triplicate by LSC using the Babcock Method. TRR was also determined for selected milk and tissue samples at the analytical laboratory (Ricerca, Painesville, OH) using combustion/LSC. Extracts and hydrolysates were radioassayed by LSC, and nonextractable residues were radioassayed by combustion/LSC. For determinations made at ABC Laboratories, the minimum quantifiable limits were 0.0005 ppm for milk, 0.0004 ppm for butterfat, and 0.0005-0.0008 ppm for tissues.

Milk, kidney, and liver extracts and/or hydrolysates were analyzed by HPLC using a C18 or C8 column, UV detection, radiodetection, and a gradient mobile phase of 1% acetic acid, ACN and/or methanol. Metabolites were identified by co-chromatography or comparison of retention times with those of the reference standards (see Appendix 1). Metabolites were isolated and purified using preparative HPLC. Isolated peaks from multiple runs were combined for further analysis by TLC or with standards by HPLC.

TLC analyses were also conducted for metabolite quantitation; however, attempts were unsuccessful for milk extracts and inconclusive for kidney and liver extracts due to matrix interferences. TLC analyses for metabolite confirmation of isolated residues, were conducted using a silica gel 60 F254 or 60 CF254 plate and a solvent system of toluene:ethyl acetate:acetic acid (5:7:1 or 8:2:1, v:v:v).

The major metabolite identified in Day 4 milk was confirmed as AFCA by HPLC co-chromatography with reference standard. Part of the identified AFCA residue was conjugated and eluted earlier with HPLC analysis. The isolated polar material was hydrolyzed with 0.1 M HCl and completely converted to AFCA. Hydrolysis of the same isolated peak with 0.1 M NaOH and HPLC analysis of the aqueous hydrolysate also determined the residue as AFCA. Radiolabeled IMCA was also subjected to acid and base hydrolysis to confirm that the conjugated AFCA metabolite identified in milk was not released as a result of hydrolytic cleavage of the tetrahydrophthalimide ring. Identification of metabolite IMCA in milk was also confirmed by HPLC co-chromatography with reference standard. Further confirmation of AFCA and IMCA in milk was conducted by TLC analysis of the pooled HPLC fraction.

Flumiclorac pentyl was confirmed in the goat #2 kidney sample by HPLC co-chromatography with reference standard. Identification of metabolite AFCA in kidney extracts was confirmed by TLC and HPLC co-chromatography of the isolated fraction with reference standard.

HPLC fractions of kidney and liver extracts containing Metabolites IMCA and SAT-IMCA, combined with the respective fractions of kidney and liver extracts from goats treated with [THP-^{14}C]flumiclorac pentyl (refer to the DER for MRID 46082804), were purified by open column chromatography on C18 silica. HPLC analysis of the purified fraction yielded IMCA, Metabolite SAT-IMCA, and Metabolite L (mostly present in liver). The IMCA and SAT-IMCA regions were further purified by HPLC and converted to the methyl derivatives with diisopropylethylamine and dimethyl sulfate, or with ethereal diazomethane in ACN/water. The methylated metabolites were analyzed by HPLC with methylated standards. Methylated IMCA was confirmed by TLC and GC/MS (electron impact) analysis of the derivatized residues.

Metabolite L, isolated from the combined kidney and liver fractions, was further purified by HPLC and converted to its methyl ester (as described above) for LC/MS analysis with methylated SAT-4-OH-IMCA standard. The metabolite was further confirmed as SAT-4-OH-IMCA following methylation and TLC and HPLC co-chromatography with methylated standard.

To demonstrate the extraction efficiency of the procedures used in the metabolism study, samples of untreated milk, liver, kidney, and loin muscle were fortified with [phenyl-^{14}C]flumiclorac pentyl and extracted as described under Section B.4.1 (above). The concentrated extracts were analyzed by HPLC and TLC. The petitioner also conducted radiovalidation of the residue analytical method, entitled, "Residue Method for the Determination of Residues of S-23031 in Chicken Eggs, Muscle, and Tissue, and Goat Milk, Muscle and Tissue" (Ricerca number 3789-92-0194-MD-001) using milk, kidney, and liver samples from [phenyl-^{14}C]flumiclorac pentyl treated goat.

C. RESULTS AND DISCUSSION

The storage intervals and conditions for the goat metabolism study are presented in Table C.1. The petitioner provided the dates of initial and final sample extraction; initial HPLC analysis dates were determined from representative chromatograms. Comparison of the chromatograms of initial and final analyses indicated that the metabolite profiles were generally stable for the duration of the study, except for the parent compound, which significantly declined in the stored kidney sample. Flumiclorac pentyl was shown to extensively degrade under frozen conditions when untreated kidney and liver samples were fortified with flumiclorac pentyl and stored under similar conditions for ca. 6 months.

Total radioactive residues (TRR) in goat milk and tissues are reported in Table C.2.1. TRR were 0.006-0.013 ppm in milk, 0.0291-0.0451 ppm in kidney, 0.0310-0.088 ppm in liver, <MQL (<0.0007)-0.0009 ppm in perirenal and omental fat, and <LOD-0.0013 ppm in loin and leg muscle from goats dosed orally with [phenyl-U-^{14}C]flumiclorac pentyl at 20 ppm in the diet for 5 consecutive days. Radioactivity was low in all goat matrices, with the highest levels in kidney

and liver. Residues appear to remain fairly consistent in milk throughout the study period; approximately 3% of the milk radioactivity was determined to represent butterfat. A large portion of the administered dose was excreted, with urine accounting for 27-30% and feces accounting for 29-36% of the administered dose.

The distribution of the radioactivity in goat matrices is presented in Tables C.2.2.1 (Goat #2) and C.2.2.2 (Goat #11). Because of low radioactivity, fat and muscle samples were not extracted. The majority of the radioactivity (~74-99% TRR) in milk, kidney, and liver was extractable (using ethanol for milk, and ACN and ACN/water for kidney and liver); we note that the petitioner did not report the %TRR or ppm levels in the individual fractions through the extraction/cleanup steps, and only reported the total extractable residues even though the ACN and ACN/water extracts of kidney and liver were analyzed separately. Nonextractable residues accounted for 1-13% TRR (≤0.009 ppm) in milk, kidney, and liver; accountabilities were 100% because extractable and nonextractable residues were normalized, but actual recoveries were 85-106%. Residues were characterized primarily by HPLC analysis, using TLC, LC/MS, and GC/MS analyses for confirmation of metabolite identifications. These methods successfully identified the predominant residues in goat matrices.

The characterization and identification of residues in goat matrices is summarized in Tables C.2.3.1 (Goat #2) and C.2.3.2 (Goat #11). Approximately 48-89% of the TRR in milk, kidney and liver were identified. The parent was only detected in the kidney of one goat at 23.0% TRR (0.011 ppm). The major metabolite in milk was AFCA accounting for 56.0-64.6% TRR; AFCA was also identified in kidney at 11.5 or 22.6% TRR. The metabolite IMCA was identified in milk at 5.6-12.7% TRR and in kidney at 10.3-19.0% TRR. SAT-IMCA was a major metabolite identified in kidney at 19.4-28.0% TRR and in liver at 28.9-60.3% TRR. SAT-IMCA was also identified in milk from one goat at 3.4-6.8% TRR. SAT-4-OH-IMCA was not detected in milk or kidney but was a major residue component in liver at 19.1-28.6% TRR. The metabolite 4-OH-IMCA was identified in milk of one goat at 6.9-9.7% TRR. Additional residues, each present at <10% TRR were characterized as polar or other unknowns in milk, kidney, and liver. Solids precipitated from the concentration of the milk extract accounted for 13.3-23.5% TRR.

Analysis of samples of untreated milk, liver, kidney, and loin muscle fortified with [phenyl-^{14}C]flumiclorac pentyl demonstrated good extraction efficiency of the procedures used in the goat metabolism study; the major component recovered was flumiclorac pentyl, with little or no degration of the parent in milk samples. Minor degradation of the parent compound was observed in muscle, but 20-50% of the parent compound degraded in fortified liver and kidney samples. Representative chromatograms were included, but actual data were not provided. Radiovalidation of the residue analytical method, entitled, "Residue Method for the Determination of Residues of S-23031 in Chicken Eggs, Muscle, and Tissue, and Goat Milk, Muscle and Tissue" (Ricerca number 3789-92-0194-MD-001) using milk, kidney, and liver samples from [phenyl-^{14}C]flumiclorac pentyl treated goat demonstrated that flumiclorac pentyl residues were below the limit of detection (0.01 ppm) of the residue method.

C.1. Storage Stability

Samples of goat matrices were placed in frozen storage after collection. Milk samples were initially extracted 156-158 days after collection, and kidney and liver samples were initially extracted 71-98 days after collection. Initial HPLC analyses were conducted within 187 (milk) or 207 (kidney and liver) days of collection, and further analysis of isolated metabolites was conducted within 318 days of collection based on representative chromatogram dates. To demonstrate storage stability, samples of milk, kidney and liver were re-extracted 82 (milk) or 178-205 (kidney and liver) days after the initial extraction and profiled for comparison with the earlier samples. The samples were extracted using procedures similar to those used for initial extractions, and the resulting HPLC profiles indicated that the metabolite profiles in milk, kidney, and liver did not change significantly during storage. However, the parent compound, identified in the initial analysis of a single goat kidney extract, was detected at much lower levels (5.1% TRR vs. 23.0% TRR) in the stored sample. Flumiclorac pentyl was shown to extensively degrade under frozen conditions when untreated kidney and liver samples were fortified with flumiclorac pentyl and stored under similar conditions for ca. 6 months.

The petitioner did not provide the actual dates of final analysis for any sample; dates of analysis were determined by the study reviewer from the representative chromatograms. The petitioner should note that for future submissions, the dates of all extraction and analyses should be reported. Because the storage stability sample extractions and analyses were conducted near the completion of the study, HED concludes that the submitted storage stability data are adequate to support the goat metabolism study.

TABLE C.1. Summary of Storage Conditions

Matrix	Storage Temp. (°C)	Actual Storage Duration [1]	Interval of Demonstrated Storage Stability [2]
Milk	-20 °C	187 days (6.2 months)	238 days (7.8 months)
Kidney and liver		207 days (6.8 months)	276 days (9.1 months)

[1] Actual final analysis dates were not provided; the storage duration from sampling to analysis was determined by the study reviewer from representative chromatogram dates.
[2] Interval from collection to second extraction date.

C.2. Identification, Characterization, and Distribution of Residues

TABLE C.2.1. Total Radioactive Residues (TRR) in Milk, Tissue and Excreta

Matrix	Collection Timing	[Phenyl U-^{14}C]Flumiclorac Pentyl [1]		
		Goat #2, ppm	Goat #11, ppm	% Administered Dose
Urine and cage wash	Study duration	--	--	26.55-30.31
Feces	Study duration	--	--	29.46-35.52
Milk [2]	Day 1	0.006	0.013	0.031-0.050
	Day 2	0.008 (0.010)	0.016 (0.016)	
	Day 3	0.007	0.015	
	Day 4	0.010 (0.010)	0.015 (0.016)	
Milk, butterfat [3]	Day 2	0.0014	0.0016	--

TABLE C.2.1. Total Radioactive Residues (TRR) in Milk, Tissue and Excreta

Matrix	Collection Timing	[Phenyl U-^{14}C]Flumiclorac Pentyl [1]		
		Goat #2, ppm	Goat #11, ppm	% Administered Dose
	Day 4	0.0016	0.0028	--
Kidney	Sacrifice	0.0451 (0.0451)	0.0291 (0.0296)	<0.001-0.002
Liver	Sacrifice	0.0850 (0.088)	0.0311 (0.0310)	0.018-0.055
Perirenal fat	Sacrifice	0.0009	<MQL	<0.001
Omental fat	Sacrifice	<MQL	<MQL	<0.001
Loin muscle	Sacrifice	0.0013 (<LOD)	<LOD	<0.001
Leg muscle	Sacrifice	<LOD	<LOD	<0.001
Intestinal contents	Sacrifice	3.8320	3.3370	1.84-3.84
Other (heart, blood)	Sacrifice	--	--	0.01
Total				63.73-63.99

[1] MQL = minimum quantitation limit (<0.0006 perirenal fat, <0.0007 omental fat, <0.0005 ppm loin muscle, and <0.0008 ppm leg muscle) and LOD = limit of detection (2x background dpm). Values presented in parentheses are TRR determinations made at the analytical laboratory; all other values were determined at the test site by ABC Laboratories.

[2] Milk samples were not collected on the last day of dosing because of the short interval between dosing and sacrifice; we note that the petitioner identified the milk samples as Day 0-3. The study reviewer re-named Day 0-3 as Day 1-4 to reflect correct chronology of milk sampling.

[3] Based on determined TRR, milk contained 3.0-3.2% butterfat.

FIGURE C.2.1. Pharmacokinetics of Flumiclorac Pentyl in Milk of Lactating Goat.

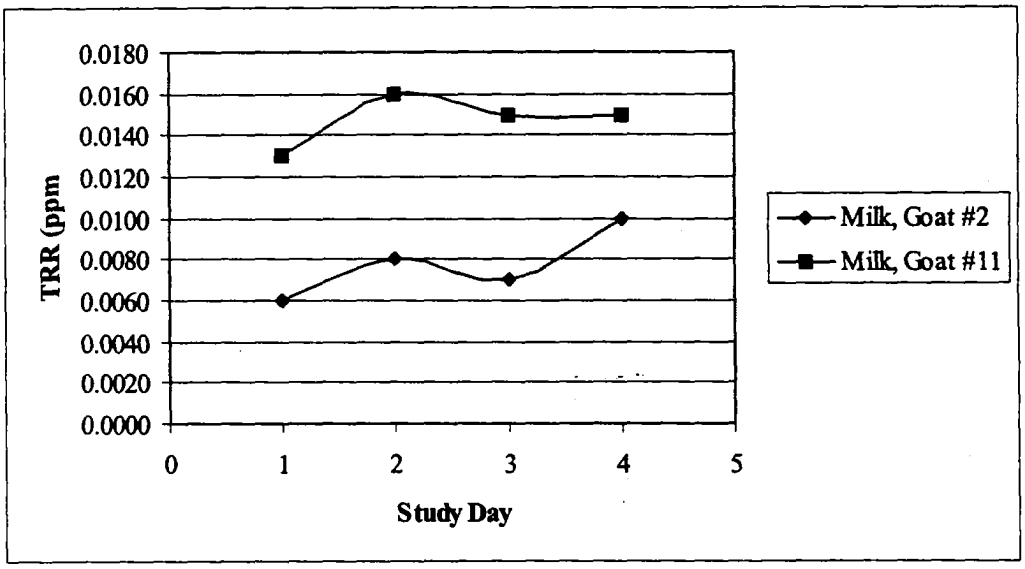


TABLE C.2.2.1. Distribution of the Parent and the Metabolites in Lactating Goat (#2) Matrices Following Dosing with [Phenyl-U-^{14}C]Flumiclorac Pentyl.

Metabolite Fraction	Milk, Day 2		Milk, Day 4		Kidney		Liver	
	TRR = 0.010 ppm		TRR = 0.010 ppm		TRR = 0.045 ppm		TRR = 0.088 ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Extractable [1]	96.0	0.008	99.0	0.010	87.0	0.041	90.8	0.085
Flumiclorac pentyl	–	–	–	–	23.0	0.011	–	–
AFCA	64.6	0.006	62.2	0.006	11.5	0.005	–	–
IMCA	8.4	0.001	5.6	0.001	19.0	0.009	–	–
4-OH-IMCA	9.7	0.001	6.9	0.001	–	–	–	–
SAT-IMCA	–	–	–	–	28.0	0.013	60.3	0.056
SAT-4-OH-IMCA	–	–	–	–	–	–	28.6	0.027
Polar unknowns	<0.1	<0.001	8.4	0.001	–	–	–	–
Other unknowns (each <10% TRR)	–	–	–	–	5.6	0.003	1.9	0.002
Solids precipitated with concentration	13.3	0.001	15.9	0.002	–	–	–	–
Nonextractable [1]	4.0	<0.001	1.0	<0.001	13.0	0.006	9.2	0.009

[1] Percent TRR was normalized to sum of extractable and nonextractable residues.

TABLE C.2.2.2. Distribution of the Parent and the Metabolites in Lactating Goat (#11) Matrices Following Dosing with [Phenyl-U-^{14}C]Flumiclorac Pentyl.

Metabolite Fraction	Milk, Day 2		Milk, Day 4		Kidney		Liver	
	TRR = 0.016 ppm		TRR = 0.016 ppm		TRR = 0.030 ppm		TRR = 0.031 ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Extractable [1]	98.6	0.016	99.3	0.015	75.5	0.020	73.7	0.020
Flumiclorac pentyl	–	–	–	–	–	–	–	–
AFCA	56.0	0.009	61.8	0.010	22.6	0.006	--	--
IMCA	12.7	0.002	10.1	0.002	10.3	0.003	--	--
4-OH-IMCA	–	–	–	–	–	–	–	–
SAT-IMCA	3.4	0.001	6.8	0.001	19.4	0.005	28.9	0.008
SAT-4-OH-IMCA	–	–	–	–	–	–	19.1	0.005
Polar unknowns	3.0	<0.001	--	--	9.1	0.002	18.3	0.005
Other unknowns (each <10% TRR)	--	--	--	--	14.1	0.004	7.5	0.002
Solids precipitated with concentration	23.5	0.004	20.5	0.003	--	--	--	--
Nonextractable [1]	1.4	<0.001	0.7	<0.001	24.5	0.006	26.3	0.007

[1] Percent TRR was normalized to sum of extractable and nonextractable residues.

TABLE C.2.3.1. Summary of Characterization and Identification of Radioactive Residues in Lactating Goat (#2) Matrices Following Dosing with [Phenyl-U-^{14}C]Flumiclorac Pentyl at 20 ppm.

Compound	Milk, Day 2		Milk, Day 4		Kidney		Liver	
	TRR = 0.010 ppm		TRR = 0.010 ppm		TRR = 0.045 ppm		TRR = 0.088 ppm	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
Flumiclorac pentyl	–	–	–	–	23.0	0.011	--	--
AFCA	64.6	0.006	62.2	0.006	11.5	0.005	--	--
IMCA	8.4	0.001	5.6	0.001	19.0	0.009	--	--
4-OH-IMCA	9.7	0.001	6.9	0.001	--	--	--	--
SAT-IMCA	–	–	–	–	28.0	0.013	60.3	0.056
SAT-4-OH-IMCA	–	–	–	–	–	–	28.6	0.027
Polar unknowns	<0.1	<0.001	8.4	0.001	--	--	--	--
Other unknowns (each <10% TRR)	--	--	--	--	5.6	0.003	1.9	0.002
Solids precipitated with concentration	13.3	0.001	15.9	0.002	--	--	--	--
Total identified	82.7	0.008	74.7	0.008	81.5	0.038	88.9	0.083
Total characterized	13.3	0.001	24.3	0.003	5.6	0.003	1.9	0.002
Total extractable	96.0	0.008	99.0	0.010	87.0	0.041	90.8	0.085
Unextractable (PES)[1]	4.0	<0.001	1.0	<0.001	13.0	0.006	9.2	0.009
Accountability[2]	100		100		100		100	

[1] Residues remaining after exhaustive extractions.

[2] Accountability was 100% because extractable and nonextractable residues were normalized; actual recoveries reported by the petitioner were 91-106%.

TABLE C.2.3.2. Summary of Characterization and Identification of Radioactive Residues in Lactating Goat (#11) Matrices Following Dosing with [Phenyl-U-^{14}C]Flumiclorac Pentyl at 20 ppm.

Compound	Milk, Day 2		Milk, Day 4		Kidney		Liver	
	TRR = 0.016 ppm		TRR = 0.016 ppm		TRR = 0.030 ppm		TRR = 0.031 ppm	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
Flumiclorac pentyl	--	--	--	--	--	--	--	--
AFCA	56.0	0.009	61.8	0.010	22.6	0.006	--	--
IMCA	12.7	0.002	10.1	0.002	10.3	0.003	--	--
4-OH-IMCA	--	--	--	--	--	--	--	--
SAT-IMCA	3.4	0.001	6.8	0.001	19.4	0.005	28.9	0.008
SAT-4-OH-IMCA	--	--	--	--	--	--	19.1	0.005
Polar unknowns	3.0	<0.001	--	--	9.1	0.002	18.3	0.005
Other unknowns (each <10% TRR)	--	--	--	--	14.1	0.004	7.5	0.002
Solids precipitated with concentration	23.5	0.004	20.5	0.003	--	--	--	--
Total identified	72.1	0.012	78.7	0.013	52.3	0.014	48.0	0.013
Total characterized	26.5	0.004	20.5	0.003	23.2	0.006	25.8	0.007
Total extractable	98.6	0.016	99.3	0.015	75.5	0.020	73.7	0.020
Unextractable (PES)[1]	1.4	<0.001	0.7	<0.001	24.5	0.006	26.3	0.007
Accountability[2]	100		100		100		100	

[1] Residues remaining after exhaustive extractions.
[2] Accountability was 100% because extractable and nonextractable residues were normalized; actual recoveries reported by the petitioner were 85-98%.

C.3. Proposed Metabolic Profile

FIGURE C.3.1. Proposed Metabolic Profile of Flumiclorac Pentyl in Lactating Goat.

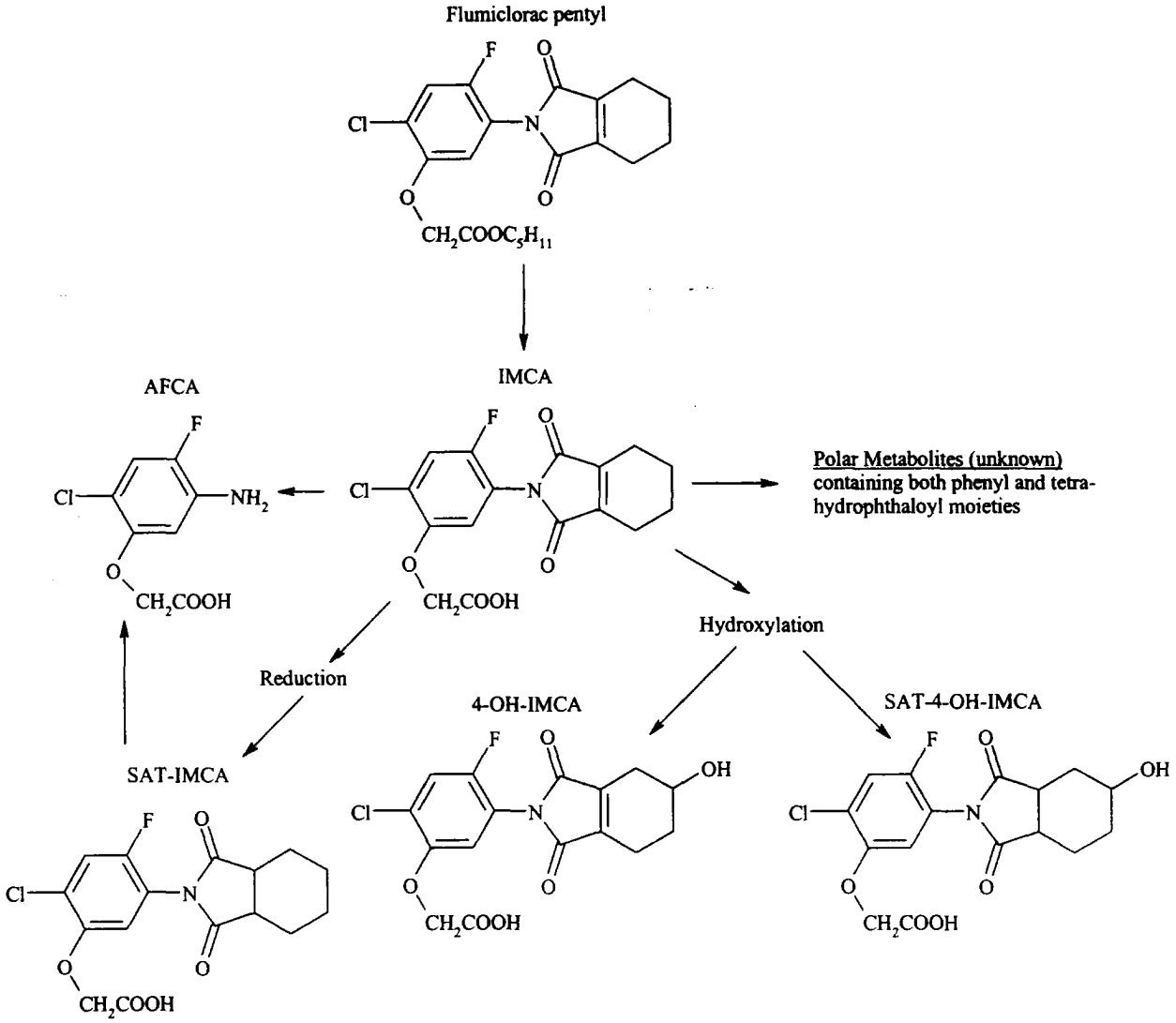


TABLE C.3.1. Identification of Compounds from Metabolism Study

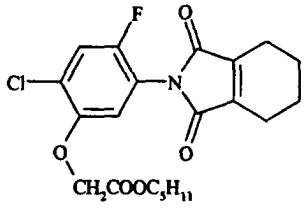
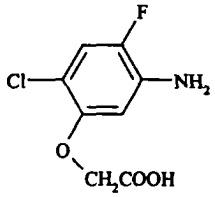
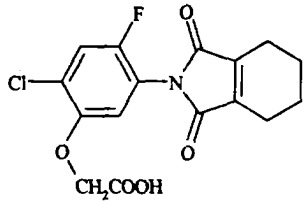
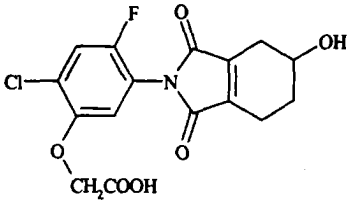
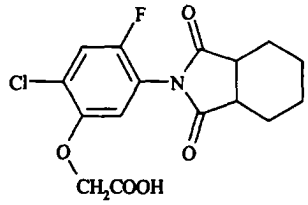
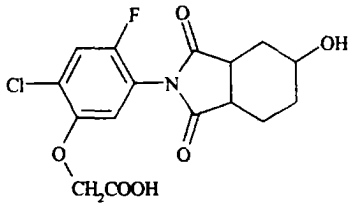
Common name/code Figure C.3.1 ID No.	Chemical name	Chemical structure
Flumiclorac pentyl; S-23031	Acetic acid, {2-chloro-4-fluoro-5-(1,3,4,5,6,7-hexahydro-1,3-dioxo-2H-isoindol-2-yl)phenoxy}-,pentyl ester or 2-chloro-4-fluoro-5-(1,3,4,5,6,7-hexahydro-1,3-dioxo-2H-isoindol-2-yl)phenoxy]acetic acid, pentyl ester	
AFCA	5-amino-2-chloro-4-fluorophenoxyacetic acid	
IMCA	2-chloro-4-fluoro-5-(3,4,5,6-tetrahydrophthalimido)phenoxyacetic acid	
4-OH-IMCA	2-chloro-4-fluoro-5-(4-hydroxy-3,4,5,6-tetrahydrophthalimido)phenoxyacetate	
SAT-IMCA	2-chloro-4-fluoro-5-(cyclohexane-1,2-dicarboximido)phenoxyacetate	

TABLE C.3.1. Identification of Compounds from Metabolism Study		
Common name/code Figure C.3.1 ID No.	Chemical name	Chemical structure
SAT-4-OH-IMCA	2-chloro-4-fluoro-5-(4-hydroxy-1,2,-cyclohexanedicarboximido)phenoxyacetate	

D. CONCLUSION

Total radioactive residues were 0.006-0.013 ppm in milk, 0.0291-0.0451 ppm in kidney, 0.0310-0.088 ppm in liver, <0.0007-0.0009 ppm in perirenal and omental fat, and up to 0.0013 ppm in loin and leg muscle from goats dosed orally with [phenyl-U-^{14}C]flumiclorac pentyl at 20 ppm in the diet for 5 consecutive days. A large portion of the administered dose was excreted, with urine accounting for 27-30% and feces accounting for 29-36% of the administered dose.

The majority of the radioactivity (~74-99% TRR) was extractable (using ethanol for milk, and ACN and ACN/water for kidney and liver). Nonextractable residues accounted for <0.01 ppm in milk, kidney, and liver; accountabilities were 100% because extractable and nonextractable residues were normalized, but actual recoveries were 85-106%. Fat and muscle samples were not extracted due to low TRR.

Approximately 48-89% of the TRR in milk, kidney and liver were identified. The parent was only found in the kidney of one goat at 23.0% TRR (0.011 ppm). The major metabolite in milk was AFCA; AFCA was also identified in kidney at lower but significant levels. The metabolite IMCA was identified as a significant residue in milk and kidney. SAT-IMCA was a major metabolite identified in kidney and liver; SAT-IMCA was also identified in milk from one goat at <10% TRR. SAT-4-OH-IMCA was also a major metabolite in liver, but was not detected in milk or kidney. The metabolite 4-OH-IMCA was identified in milk of one goat at minor levels. Additional residues, each present at <10% TRR were characterized as polar or other unknowns in milk, kidney, and liver.

Based on the results of this study, the petitioner proposed that flumiclorac pentyl is rapidly metabolized and excreted in goats. Initial hydrolysis of the pentyl ester of flumiclorac pentyl yields IMCA; no significant metabolites with the intact pentyl ester group were detected in goat matrices. IMCA is further metabolized by cleavage of the imide ring to AFCA (the major metabolic pathway in goats), which is readily excreted. The major residue in goat liver and kidney, SAT-IMCA is formed by a reduction process, where IMCA is further metabolized by gut microflora.

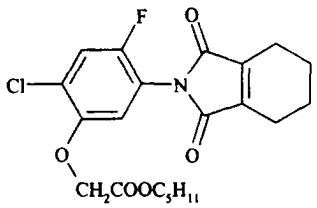
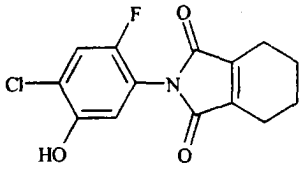
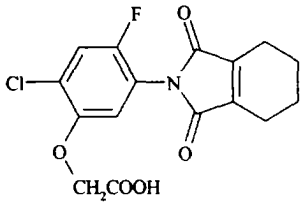
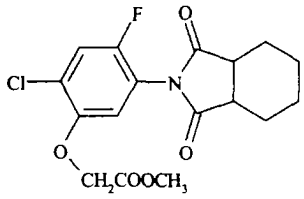
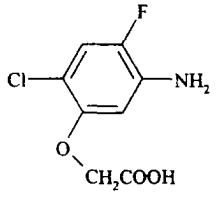
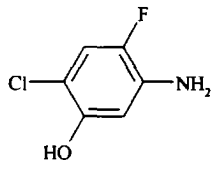
E. REFERENCES

DP Barcode: D174474
Subject: PP#2G4078: New Chemical EUP: V-23031, Flumiclorac-Pentyl on Field Corn and Soybeans. Evaluation of Analytical Methods and of Residue Data.
From: J. Garbus
To: J. Miller and A. Kocialski
Dated: 7/28/92
MRIDs: 42187400-42187405, 42169849-42169859, and 42187407-42187408.

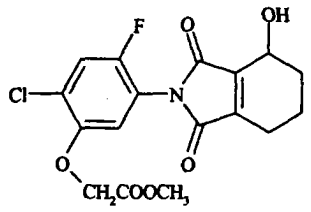
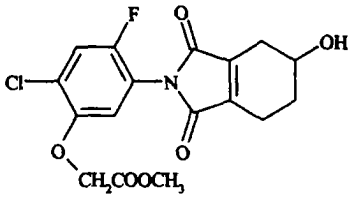
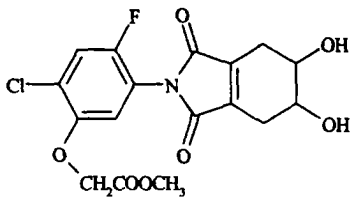
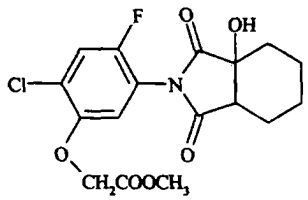
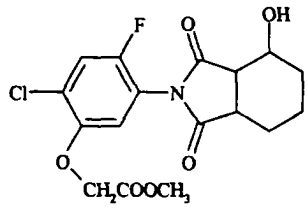
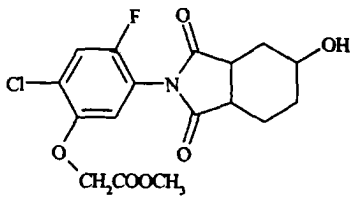
F. DOCUMENT TRACKING

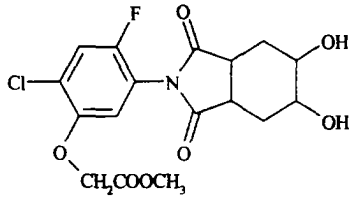
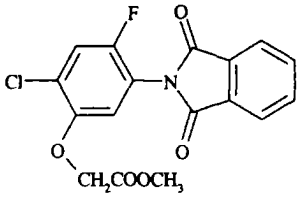
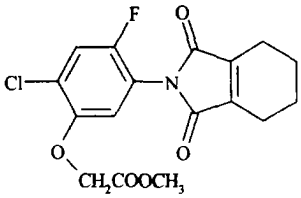
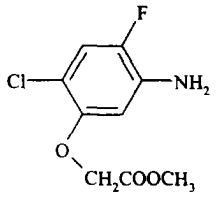
RDI: C. Eiden, (24-JUN-2005)
Petition Number(s): PP#3F6767
DP Barcode(s): D308674
PC Code: 128724

Template Version September 2003

APPENDIX I. Chemical Names and Structures of Reference Standards Used in Goat Metabolism Study.		
Common name/code Figure C.3.1 ID No.	Chemical name	Chemical structure
Flumiclorac pentyl; S-23031	Acetic acid, {2-chloro-4-fluoro-5-(1,3,4,5,6,7-hexahydro-1,3-dioxo-2H-isoindol-2-yl)phenoxy}-,pentyl ester or 2-chloro-4-fluoro-5-(1,3,4,5,6,7-hexahydro-1,3-dioxo-2H-isoindol-2-yl)phenoxy]acetic acid, pentyl ester	
IMFP	N-(4-chloro-2-fluoro-5-hydroxyphenyl)-3,4,5,6-tetrahydrophthalimide	
IMCA	2-chloro-4-fluoro-5-(3,4,5,6-tetrahydrophthalimido)phenoxyacetic acid	
SAT-IMCA-ME	methyl 2-chloro-4-fluoro-5-(cyclohexane-1,2-dicarboximido)phenoxyacetate	
AFCA	5-amino-2-chloro-4-fluorophenoxyacetic acid	
AMFP	5-amino-2-4-fluorophenol	

APPENDIX I. Chemical Names and Structures of Reference Standards Used in Goat Metabolism Study.

Common name/code Figure C.3.1 ID No.	Chemical name	Chemical structure
3-OH-IMCA-ME	methyl 2-chloro-4-fluoro-5-(3-hydroxy-3,4,5,6-tetrahydrophthalimido)phenoxyacetate	
4-OH-IMCA-ME	methyl 2-chloro-4-fluoro-5-(4-hydroxy-3,4,5,6-tetrahydrophthalimido)phenoxyacetate	
4,5-OH-IMCA-ME	methyl 2-chloro-4-fluoro-5-(4,5-dihydroxy-3,4,5,6-tetrahydrophthalimido)phenoxyacetate	
SAT-1-OH-IMCA-ME	methyl 2-chloro-4-fluoro-5-(1-hydroxy-1,2-cyclohexanedicarboximido)phenoxyacetate	
SAT-3-OH-IMCA-ME	methyl 2-chloro-4-fluoro-5-(3-hydroxy-1,2-cyclohexanedicarboximido)phenoxyacetate	
SAT-4-OH-IMCA-ME	methyl 2-chloro-4-fluoro-5-(4-hydroxy-1,2,-cyclohexanedicarboximido)phenoxyacetate	

APPENDIX I. Chemical Names and Structures of Reference Standards Used in Goat Metabolism Study.		
Common name/code Figure C.3.1 ID No.	Chemical name	Chemical structure
SAT-4,5-OH-IMCA-ME	methyl 2-chloro-4-fluoro-5-(4,5-dihydroxy-1,2,-cyclohexanedicarboximido)phenoxyacetate	
AR-IMCA-ME	methyl 2-chloro-4-fluoro-5-phthalimidophenoxyacetate	
IMCA-ME	methyl 2-chloro-4-fluoro-5-(3,4,5,6-tetrahydrophthalimido)phenoxyacetate	
AFCA-ME	methyl 5-amino-2-chloro-4-fluorophenoxyacetate	

Flumiclorac pentyl/PC Code 128724/Valent U.S.A. Corporation
OPPTS 860.1300
Nature of the Residues in Livestock - Goat

Primary Evaluator William H. Donovan Date: 6/24/05
William H. Donovan, Ph.D.
Chemist
HED/RRB3

Approved by for Catherine Eiden Date: 6/24/05
Catherine Eiden
Branch Chief
HED/RRB3

This DER was originally prepared under contract by Dynamac Corporation (20440 Century Boulevard, Suite 100; Germantown, MD 20874; submitted 01/26/2005). The DER has been reviewed by the Health Effects Division (HED) and revised to reflect current Office of Pesticide Programs (OPP) policies.

STUDY REPORT:

46082804 Panthani, A.; Kaman, R. (2002) A Study to Determine the Nature of the Residue in Milk, Meat and Tissue From Lactating Goats Dosed with [THP-^{14}C]S-23031. Laboratory Project Identification Number: 3790-90-0499-EF-001. Unpublished study prepared by Ricerca, Inc. (Painesville, OH) and Analytical Biochemistry Labs (Columbia, MO) and submitted by Valent USA Corp. 349 p.

EXECUTIVE SUMMARY:

Valent U.S.A. Corporation has submitted a study investigating the metabolism of [tetrahydrophthaloyl-1,2-^{14}C]flumiclorac pentyl in lactating goats. Information concerning the in-life phase of this study was previously submitted in MRID 42169851 and reviewed (DP Barcode D174474, 7/28/92, J. Garbus) in conjunction with PP#2G4078. The current submission reports the identification/characterization of radioactive residues in goat milk and tissues.

The test substance, [THP-1,2-^{14}C]flumiclorac pentyl, was administered orally to two goats at 20 ppm in the diet. The goats were dosed once per day for five consecutive days. Milk was collected twice daily and composited each day, and tissues (kidney, liver, muscle, and fat) were collected at sacrifice. The in-life phase of the study was conducted by ABC Laboratories (Columbia, MO), and the analytical phase was conducted by Ricerca, Inc. (Painsville, OH).

Total radioactive residues were 0.0049-0.0234 ppm in milk, 0.157-0.192 ppm in kidney, 0.137-0.208 ppm in liver, 0.017-0.021 ppm in perirenal fat, 0.007-0.011 ppm in omental fat, and 0.005-0.006 ppm in muscle (loin and leg) from goats dosed with [THP-1,2-^{14}C]flumiclorac pentyl. Radioactivity was lowest in muscle and highest in kidney and liver. Residues appear to remain fairly consistent in milk throughout the study period; approximately 3% of the milk radioactivity was determined to represent butterfat. The study reported that a large portion of the administered dose was excreted, with urine accounting for 22-29% and feces accounting for 37-39% of the administered dose.

Because of low radioactivity, residue characterization in omental fat and muscle samples was not conducted. The majority of the radioactivity (~64-93% TRR) in milk, perirenal fat, kidney, and liver was extractable with organic solvents. Protease hydrolysis released additional radioactivity (9.8-29.0% TRR) from the nonextractable solids of kidney and liver. Nonextractable residues remaining after solvent extraction and/or enzyme hydrolysis accounted for 5.1-13.5% TRR in milk, perirenal fat, kidney, and liver. Adequate storage stability data were submitted for milk, fat, kidney, and liver, demonstrating the stability of the metabolite profile in these matrices for ~8-9 months. The parent compound significantly declined in the stored kidney sample.

Approximately 64-89% of the TRR in milk, perirenal fat, kidney, and liver were identified. Residues were characterized primarily by HPLC analysis; confirmatory analyses utilized various TLC, LC/MS, and GC/MS techniques. The parent was only found in the kidney of one goat at 10.3% TRR (0.018 ppm). A later re-analysis showed that most of the parent compound was degraded during freezer storage. Several metabolites were identified including: THPA, IMCA, HPA, 4-OH-THPA, 4-OH-IMCA, SAT-IMCA, and SAT-4-OH-IMCA; the chemical names and structures of these metabolites are listed in Table C.3.1. Although certain of these metabolites represent a high percentage of the TRR in some analyzed goat matrices, the identified metabolites were detected at low absolute levels (≤0.036 ppm). In milk, the metabolite THPA was the principal residue component accounting for 23.3-40.1% TRR. The metabolite IMCA was detected in all samples except in perirenal fat, even though it was not a major metabolite.

Based on the results of this study, the petitioner proposed that flumiclorac pentyl is rapidly metabolized and excreted in goats. Initial hydrolysis of the pentyl ester of flumiclorac pentyl yields IMCA. No significant metabolites with the intact pentyl ester group were detected in goat matrices. IMCA is further metabolized by cleavage of the imide ring to THPA which is readily excreted. A major residue in goat liver and kidney, SAT-IMCA, is formed by a reduction process, where IMCA is further metabolized by gut microflora. Hydrolysis of SAT-IMCA likely forms HPA in kidney, urine, and feces of goat.

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the goat metabolism data are classified as scientifically acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document DP Barcode D308674.

COMPLIANCE:

A signed and dated compliance statement was provided. The study was conducted and reported in compliance with Good Laboratory Practice Regulations with the exception of the reference standards that were supplied and characterized by Sumitomo Chemical Company, Ltd. The characterizations of the identity of these substances were not done entirely under GLP procedures.

A. BACKGROUND INFORMATION

Flumiclorac pentyl is an N-phenylphthalimide derivative herbicide used for the control of broadleaf weeds. Its mode of action is through the accumulation of porphyrins in susceptible plants; the photosensitizing action of accumulated porphyrins may cause membrane lipid peroxidation which leads to irreversible damage of membrane function and structure in the plant. Flumiclorac pentyl is registered for postemergence application to field corn and soybeans; registration for use on cotton as a defoliant is pending. The PC code and nomenclature of flumiclorac pentyl are listed below in Table 1. The physicochemical properties of flumiclorac pentyl are listed in Table 2.

TABLE 1. Flumiclorac Pentyl Nomenclature

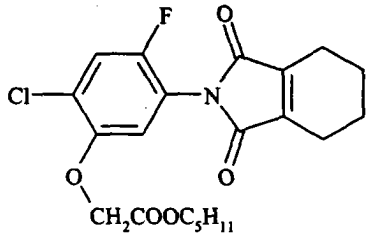
Chemical Structure	
Common name	Flumiclorac pentyl
Company experimental name	S-23031 or V-23031
Molecular Formula	$C_{21}H_{23}ClFNO_5$
Molecular Weight	423.9
IUPAC name	Pentyl (2-chloro-5 (cyclohex-1-ene-1,2-dicarboximido)-4-fluorophenoxy) acetate
CAS names	Pentyl[2-chloro-4-fluoro-5-(1,3,4,5,6,7- hexahydro-1,3-dioxo-2H-isoindol-2-yl)phenoxy]acetate
CAS #	87546-18-7
PC Code	128724

TABLE 2. Physicochemical Properties of Flumiclorac Pentyl

Parameter	Value	Reference
Melting point	88.9-90.1 °C	PP#2G4078; D174474, 7/28/92, J. Garbus
pH	6.03 at 25 °C	
Density, bulk density, or specific gravity	1.3316 g/mL at 20 °C	
Water solubility	0.189 mg/L at 25 °C	

TABLE 2. Physicochemical Properties of Flumiclorac Pentyl		
Parameter	Value	Reference
Solvent solubility	g/100 mL at 25 °C: hexane 0.328 n-octanol 1.60 methanol 4.78 Solvesso 150 27.1 acetonitrile 58.9 acetone 59.0 tetrahydrofuran 69.7 N-methyl 2-pyrrolidinone 134.0 methylene chloride 288.0	
Vapor pressure	$<1 \times 10^{-7}$ mm Hg at 22.4 °C	
Dissociation constant, pK_a	No dissociation at pH ≤7; flumiclorac pentyl decomposes at pH ≥9.	
Octanol/water partition coefficient	Log P_{OW} = 4.99 at 19.7-21.0 °C	
UV/visible absorption spectrum	Not available	

B. EXPERIMENTAL DESIGN

Information concerning the in-life phase of this study, including TRR determinations, was previously submitted in MRID 42169851 and reviewed (DP Barcode D174474, 7/28/92, J. Garbus) in conjunction with PP#2G4078. This information is re-presented herein with the supplemental characterization data.

B.1. Livestock

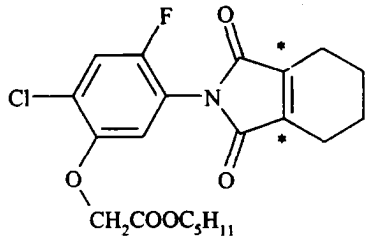
TABLE B.1.1. General Test Animal Information.					
Species	Breed	Age	Weight at study initiation (kg)	Health Status	Description of housing/holding area
Lactating goats	Saanen, Nubian, or Alpine	4-5 years	39-53	Good	Individual metabolism stalls, maintained indoors at ABC Laboratories (Columbia, MO). Temperatures ranged 18-26 °C, with a humidity of 45-82% Rh.

Two goats (Goats # 7 and #13) were treated, and a third goat received placebo doses as a control.

TABLE B.1.2. Test Animal Dietary Regime.				
Composition of Diet	Feed consumption (average kg/day)	Water	Acclimation period	Predosing
Dairy ration and alfalfa cubes, mixed at 0.4 kg grain + 0.6 kg roughage for a total of 1 kg, fed twice per day.	1.924-2.000	County public water, *ad libitum*	Seven days	None

TABLE B.1.3. Test Animal Dosing Regime			
Treatment Type	Feeding Level (ppm test material in food)	Vehicle	Timing/Duration
Oral via a bolus gun	20 ppm	Gelatin capsule	Once per day, after the morning milking, for five consecutive days.

B.2. Test Materials

TABLE B.2.1. Test Material Characteristics.	
Chemical structure	
Radiolabel position	Labeled on the 1 and 2 carbon of the phthalamide ring
Lot No.	C-90-009 (isotopically diluted)
Purity	>97%
Specific activity	89,200 dpm/µg

B.3. Sampling Information

TABLE B.3.1. Sample Collection Information			
Milk collected	Urine, feces and cage wash collected	Interval from last dose to sacrifice	Tissues collected and analyzed
Milk was collected twice daily; p.m. samples were composited with the following a.m. sample. Each test goat yielded about 1 liter of milk per day.	Feces and urine were collected daily through Study Day 4. An aqueous cage wash was collected after removing goats for sacrifice.	within 4 hours	Omental fat, perirenal fat, kidneys, liver, loin muscle, and rear leg muscle.

B.4. Identification/Characterization of Residues

B.4.1. Sample Handling and Preparation

Daily (p.m. and following a.m.) milk samples were composited. Tissue samples, collected after goat sacrifice, were homogenized in a food grinder. Subsample of milk and tissue samples were taken for radioassay, and the remaining sample was frozen. Butterfat was separated from a subsample of Days 2 and 4 milk for percent content and radioassay. Frozen milk and tissue samples were shipped to Ricerca, Inc. (Painsville, OH) for extraction and characterization/identification of residues. Because of low radioactivity, muscle and omental fat samples were not further extracted.

Days 2 and 4 milk samples were extracted with ethanol and then filtered. The filter cake was rinsed with ethanol and 80% aqueous ethanol. The filtrate and rinsates were combined, concentrated and partitioned (2x) with hexane. The aqueous fraction was concentrated almost to dryness and centrifuged with 50% aqueous ethanol. The supernatant was concentrated, redissolved in acetonitrile (ACN):water (1:1, v:v) with 1% acetic acid for HPLC and TLC

analysis. The solids remaining after centrifugation were mixed with 1 M NaOH and heated in a boiling water bath for 1 hour; an aliquot was reserved for LSC analysis.

Kidney and liver samples were extracted (2x) with ACN in a blender and then filtered; the filter cake was rinsed with additional ACN. The filtrates and rinsates were combined. The nonextractable residues were further extracted (2x) with ACN:water (1:1, v:v) with 1% acetic acid and then centrifuged. The supernatants were filtered and combined. The ACN and ACN/water extracts were separately concentrated almost to dryness and redissolved in the respective solvent for HPLC and TLC analysis.

Separate subsamples of liver's nonextractable residues from one treated goat (#13) were subjected to acid (0.1 M HCl at 37-40 °C for 20 hours), base (0.1 M NaOH at 37-40 °C for 20 hours), or enzyme (protease in potassium phosphate buffer pH 7.7 at 37-40 °C for 20 hours) hydrolysis. The hydrolysates were radioassayed to determine which hydrolysis released the greatest amount of radioactivity. Another subsample of liver's and kidney's nonextractable residues from both treated goats was then hydrolyzed with protease (at 40 °C for 16 hours, then at room temperature for 4 hours). The aqueous hydrolysate was adjusted to pH 3 with 1 M HCl and partitioned with ethyl acetate. The organic and aqueous phases were reserved for TLC and HPLC analysis.

Perirenal fat samples were extracted (2x) with hexane in a blender and then filtered; the hexane extract was discarded. The remaining solids were then extracted (1-2x) with ACN:water (1:1, v:v) with 1% acetic acid and centrifuged. The ACN/water extract(s) were concentrated for HPLC analysis.

B.4.2. Analytical Methodology

Total radioactive residues were determined in samples of milk by direct LSC and in tissue samples by combustion/LSC (triplicate aliquots) at ABC Laboratories. TRR in the petroleum ether fraction of butterfat samples were determined in triplicate by LSC using the Babcock Method. TRR was also determined for selected milk and tissue samples at the analytical laboratory (Ricerca, Painesville, OH) using combustion/LSC. Extracts and hydrolysates were radioassayed by LSC, and nonextractable residues were radioassayed by combustion/LSC. For determinations made at ABC Laboratories, the minimum quantifiable limits were 0.0006 ppm for milk, 0.0004 ppm for butterfat, and 0.0005-0.0007 ppm for tissues. The limit of detection for combustion/LSC analyses conducted by Ricerca was 0.002 ppm for milk and tissues.

Milk, kidney, liver, and perirenal fat extracts and/or hydrolysates were analyzed by HPLC using a C18 or C8 column, UV detection, radiodetection, and a gradient mobile phase of 1% acetic acid, ACN methanol, and/or 0.1% phosphoric acid in ACN. Metabolites were identified by co-chromatography or comparison of retention times with those of the reference standards (see Appendix 1). Metabolites were isolated and purified using preparative HPLC. Isolated peaks from multiple runs were combined for further analysis by TLC or with standards by HPLC.

TLC analyses were also conducted for metabolite quantitation. However, attempts were unsuccessful for milk extracts and inconclusive for kidney and liver extracts due to matrix interferences; radioactivity in fat extracts remained at the origin with TLC analysis. TLC analyses for metabolite confirmation of isolated residues, were conducted using a silica gel 60 F254 or 60 CF254 plate and a solvent system of toluene:ethyl acetate:acetic acid (5:7:1 or 8:2:1, v:v:v).

Extracts of milk from treated goat #7, which contained higher residue levels, were used for identification. Individual peak fractions were collected and analyzed by HPLC with co-injected standards. The identities of metabolites THPA and IMCA were confirmed by TLC. The 4-OH-IMCA metabolite fraction was isolated and converted to the methyl derivative with diazomethane. HPLC and TLC analysis of the methylated fraction was identified as 4-OH-IMCA by co-chromatography with 4-OH-IMCA-ME standard.

The polar, water-soluble metabolite eluting at the solvent front of the HPLC analysis of milk, was tentatively identified as 4-OH-THPA by comparison with similar peaks in kidney, urine, and feces; identification in milk was not feasible because of low concentration and large amounts of early eluting matrix.

Flumiclorac pentyl was confirmed in the goat #7 kidney sample by HPLC co-chromatography with reference standard. Identification of metabolites IMCA, SAT-IMCA, and HPA in kidney extracts were confirmed by MS of the isolated fraction following derivatization. The isolated HPA fraction of kidney was combined with the respective fraction from urine and feces extracts. The combined fractions were converted to the di-p-bromophenacyl ester by treatment with p-bromophenacyl-8 (at room temperature for 1 hour followed by heating at 80 °C for 1 hour). The resulting derivative was analyzed by TLC and HPLC co-chromatography with the same derivative prepared from trans-cyclohexane-1,2,dicarboxylic acid. The identification of the di-bromophenacyl ester of HPA was confirmed by LC/MS (positive ion) and direct probe CI/MS.

HPLC fractions of kidney and liver extracts containing Metabolites IMCA and SAT-IMCA, combined with the respective fractions of kidney and liver extracts from goats treated with [phenyl-U-^{14}C]flumiclorac pentyl (refer to the DER for MRID 46082803), were purified by open column chromatography on C18 silica. HPLC analysis of the purified fraction yielded IMCA, Metabolite SAT-IMCA, and Metabolite L (mostly present in liver). The IMCA and SAT-IMCA regions were further purified by HPLC and converted to the methyl derivatives with diisopropylethylamine and dimethyl sulfate, or with diazomethane in ACN/water. The methylated SAT-IMCA metabolite was identified by HPLC and TLC analyses with methylated standard. Direct probe CI and GC/MS (electron impact) also confirmed the methyl ester of SAT-IMCA in kidney and liver. The methylated IMCA fraction was identified by GC/MS analysis with IMCA-ME standard. IMCA in kidney and liver was also confirmed by TLC and HPLC analysis of the isolated residue from the respective matrix.

The radioactivity in the kidney's ACN/water extract, which eluted at the solvent front, was isolated and identified as 4-OH-THPA following derivatization with diazomethane. The methyl

ester derivative was analyzed by HPLC and TLC with 4-OH-THPA-DME standard, confirming the early eluting residue as 4-OH-THPA. The petitioner noted that only about 40-50% of the residue was converted to the dimethyl derivative, most likely due to solubility problems and matrix interference.

Metabolite L isolated from the combined kidney and liver fractions was further purified by HPLC and converted to its methyl ester (as described above) for LC/MS analysis with methylated SAT-4-OH-IMCA standard. The metabolite was further confirmed as SAT-4-OH-IMCA following methylation, and TLC and HPLC co-chromatography with SAT-4-OH-IMCA-ME standard.

THPA was identified in perirenal fat by HPLC co-chromatography with standard. TLC and HPLC analysis of the aqueous extract after partitioning with ethyl acetate confirmed the residue identification as THPA. An early eluting component in fat was tentatively identified as 4-OH-THPA by comparison to similar components in kidney, urine and feces.

To demonstrate extraction efficiency of the procedures used in the metabolism study, samples of untreated milk, liver, kidney, and loin muscle were fortified with [THP-^{14}C]flumiclorac pentyl and extracted as described under Section B.4.1 (above). The concentrated extracts were analyzed by HPLC and TLC. The petitioner also conducted radiovalidation of the residue analytical method, entitled, "Residue Method for the Determination of Residues of S-23031 in Chicken Eggs, Muscle, and Tissue, and Goat Milk, Muscle and Tissue" (Ricerca number 3789-92-0194-MD-001) using milk, kidney, and loin muscle samples from [THP-^{14}C]flumiclorac pentyl treated goat.

C. RESULTS AND DISCUSSION

The storage intervals and conditions for the goat metabolism study are presented in Table C.1. The petitioner provided the dates of initial and final sample extraction; initial HPLC analysis dates were determined from representative chromatograms. Comparison of the chromatograms of initial and final analyses indicated that the metabolite profiles were generally stable for the duration of the study, except for the parent compound, which significantly declined in the stored kidney sample. Flumiclorac pentyl was shown to extensively degrade under frozen conditions when untreated kidney and liver samples were fortified with flumiclorac pentyl and stored under similar conditions for ca. 1.5 months.

Total radioactive residues (TRR) in goat milk and tissues are reported in Table C.2.1. TRR were 0.0049-0.0234 ppm in milk, 0.157-0.192 ppm in kidney, 0.137-0.208 ppm in liver, 0.017-0.021 ppm in perirenal fat, 0.007-0.011 ppm in omental fat, and 0.005-0.006 ppm in loin and leg muscle from goats dosed orally with [THP-1,2-^{14}C]flumiclorac pentyl at 20 ppm in the diet for 5 consecutive days. Radioactivity was lowest in muscle and highest in kidney and liver. Residues appear to remain fairly consistent in milk throughout the study period; approximately 3% of the milk radioactivity was determined to represent butterfat. A large portion of the administered

dose was excreted, with urine accounting for 22-29% and feces accounting for 37-39% of the administered dose.

The distribution of the radioactivity in goat matrices is presented in Tables C.2.2.1 (Goat #7) and C.2.2.2 (Goat #13). Because of low radioactivity, omental fat and muscle samples were not extracted. The majority of the radioactivity (~64-93% TRR) in milk, perirenal fat, kidney, and liver was extractable (using ethanol for milk, and ACN and acidic ACN/water for kidney and liver, and acidic ACN/water for fat); we note that the petitioner did not report the %TRR or ppm levels in the individual fractions through the extraction/cleanup steps, and only reported the total extractable residues even though the ACN and ACN/water extracts of kidney and liver were analyzed separately. Protease hydrolysis released additional radioactivity (9.8-29.0% TRR, 0.013-0.044 ppm) from the nonextractable solids of kidney and liver. Nonextractable residues remaining after solvent extraction and/or enzyme hydrolysis accounted for 5.1-13.5% TRR (≤0.012 ppm) in milk, perirenal fat, kidney, and liver; accountabilities were 100% because extractable and nonextractable residues were normalized, but actual recoveries were 85-111% (69% in fat). Residues were characterized primarily by HPLC analysis, using TLC, LC/MS, and GC/MS analyses for confirmation of metabolite identifications. These methods successfully identified the predominant residues in goat matrices.

The characterization and identification of residues in goat matrices is summarized in Tables C.2.3.1 (Goat #7) and C.2.3.2 (Goat #13). Approximately 64-89% of the TRR in milk, perirenal fat, kidney, and liver were identified. The parent was only found in the kidney of one goat at 10.3% TRR (0.018 ppm). The major metabolite in milk and perirenal fat was THPA accounting for 23.3-40.1% TRR (0.001-0.006 ppm) in milk and 44.1-54.2% TRR (0.008 ppm) in fat; THPA was not detected in kidney or liver. The metabolite IMCA was identified in all matrices except fat, accounting for 8.4-25.0% TRR (<0.001-0.005 ppm) in milk, 14.0-20.5% TRR (0.019-0.036 ppm) in kidney, and 3.8-11.3% TRR (0.006-0.021 ppm) in liver. 4-OH-THPA and 4-OH-IMCA were also significant metabolites identified in milk at 11.8-16.2% TRR (0.001-0.002 ppm) and 17.8-18.7% TRR (0.001-0.004 ppm), respectively; 4-OH-THPA was also identified in kidney at 6.8-12.7% TRR (0.012-0.017 ppm) and fat at 10.5-32.1% TRR (0.001-0.006 ppm). HPA was a major metabolite identified in kidney at 15.2-24.9% TRR (0.027-0.034 ppm) and a minor metabolite identified in liver at up to 3.1% TRR (0.006 ppm). SAT-IMCA and SAT-4-OH-IMCA were identified in kidney and liver at significant levels; SAT-IMCA accounted for 18.6-21.2% (0.029-0.033 ppm) in kidney and 37.6-41.4% TRR (0.063-0.070 ppm) in liver, and SAT-4-OH-IMCA accounted for 2.8% TRR (0.005 ppm) in kidney and 18.5-18.7% TRR (0.028-0.034 ppm) in liver. SAT-IMCA was identified in milk at 6.2% TRR (<0.001 ppm). Metabolites THPA and IMCA were also identified, each at ≤0.005 ppm, in the protease hydrolysate of kidney and liver. Additional residues, each present at <5% TRR, were characterized as polar or other unknowns in milk, perirenal fat, kidney, and liver.

Analysis of samples of untreated milk, liver, kidney, and loin muscle fortified with [THP-^{14}C]flumiclorac pentyl demonstrated good extraction efficiency of the procedures used in the goat metabolism study; the major component recovered was flumiclorac pentyl, with little or no degradation of the parent in milk samples. Minor degradation of the parent compound was

observed in tissue samples. Representative chromatograms were included, but actual data were not provided. Radiovalidation of the residue analytical method, entitled, "Residue Method for the Determination of Residues of S-23031 in Chicken Eggs, Muscle, and Tissue, and Goat Milk, Muscle and Tissue" (Ricerca number 3789-92-0194-MD-001) using milk, kidney, and loin muscle samples from [THP-^{14}C]flumiclorac pentyl treated goat demonstrated that flumiclorac pentyl residues were below the limit of detection (0.01 ppm) of the residue method.

C.1. Storage Stability

Samples of goat matrices were placed in frozen storage after collection. Milk samples were initially extracted 164-167 days after collection, and kidney and liver samples were initially extracted 85-93 days after collection. Initial HPLC analyses were conducted within 207 days of collection, and further analysis of isolated metabolites was conducted within 329 days of collection based on representative chromatogram dates. To demonstrate storage stability, samples of milk, kidney and liver were re-extracted 74 (milk) or 170-188 (kidney and liver) days after the initial extraction and profiled for comparison with the earlier samples. The samples were extracted using the same procedures used for initial extractions. The resulting HPLC profiles indicated that the metabolite profiles in milk, kidney, and liver did not change significantly during storage. However, the parent compound, identified in the initial analysis of a single goat kidney extract, completely degraded in the stored sample. Flumiclorac pentyl was shown to extensively degrade under frozen conditions when untreated kidney and liver samples were fortified with flumiclorac pentyl and stored under similar conditions for ca. 1.5 months.

The petitioner did not provide the actual dates of final analysis for any sample (dates of analysis were determined by the study reviewer from the representative chromatograms). The petitioner should note that for future submissions, the dates of all extraction and analyses should be reported. However, because the storage stability sample extractions and analyses were conducted near the completion of the study, HED concludes that the submitted storage stability data are adequate to support the goat metabolism study.

TABLE C.1. Summary of Storage Conditions

Matrix	Storage Temp. (°C)	Actual Storage Duration [1]	Interval of Demonstrated Storage Stability [2]
Milk	-20 °C	176-207 days (5.8-6.8 months)	241 days (7.9 months)
Kidney and liver		92-206 days (3.0-6.8 months)	273 days (9.0 months)

[1] Actual final analysis dates were not provided; the storage duration from sampling to analysis was estimated by the study reviewer from representative chromatogram dates.
[2] Interval from collection to second extraction date.

C.2. Identification, Characterization, and Distribution of Residues

TABLE C.2.1. Total Radioactive Residues (TRR) in Milk, Tissue and Excreta				
Matrix	Collection Timing	[THP-1,2-^{14}C]Flumiclorac Pentyl [1]		
		Goat #7, ppm	Goat #13, ppm	% Administered Dose
Urine and cage wash	Study duration	--	--	25.6-29.2
Feces	Study duration	--	--	36.7-38.9
Milk [2]	Day 1	0.0177	0.0068	0.03-0.06
	Day 2	0.0179 (0.017)	0.0066 (0.007)	
	Day 3	0.0234	0.0075	
	Day 4	0.0229 (0.022)	0.0049 (0.004)	
Milk, butterfat [3]	Day 2	0.0023	0.0010	--
	Day 4	0.0030	0.0009	--
Kidney	Sacrifice	0.186 (0.192)	0.157 (0.163)	0.01-0.02
Liver	Sacrifice	0.202 (0.208)	0.137 (0.139)	0.08-0.10
Perirenal fat	Sacrifice	0.017 (0.020)	0.017 (0.021)	<0.01
Omental fat	Sacrifice	0.007	0.011	<0.01
Loin muscle	Sacrifice	0.006	0.005	<0.01
Leg muscle	Sacrifice	0.005	0.005	<0.01
Intestinal contents	Sacrifice	3.350	2.393	1.71-2.81
Other (heart, blood)	Sacrifice	--	--	0.04
Total				66.4-68.9

[1] Values presented in parentheses are TRR determinations made at the analytical laboratory; all other values were determined at the test site by ABC Laboratories.

[2] Milk samples were not collected after the last dose because of the short interval between dosing and sacrifice. We note that the petitioner labeled the collected milk samples as Day 0-3. The study reviewer re-named Day 0-3 as Day 1-4 to reflect correct chronology of milk sampling.

[3] Based on determined TRR, milk contained 2.9-3.1% butterfat.

FIGURE C.2.1. Pharmacokinetics of Flumiclorac Pentyl in Milk of Lactating Goat.

TABLE C.2.2.2. Distribution of the Parent and the Metabolites in Lactating Goat (#13) Matrices Following Dosing with [THP-^{14}C]Flumiclorac Pentyl. [1]

Metabolite Fraction	Milk, Study day 2		Milk, Study day 4		Kidney		Liver		Fat, Perirenal	
	TRR=0.007 ppm		TRR=0.004 ppm		TRR=0.163 ppm		TRR=0.139 ppm		TRR=0.021 ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Extractable [2]	88.6	0.006	92.6	0.004	85.4	0.118	63.9	0.097	89.5	0.016
Flumiclorac pentyl	--	--	--	--	--	--	--	--	--	--
THPA	40.1	0.002	30.7	0.001	--	--	--	--	44.1	0.008
IMCA	8.4	<0.001	14.2	0.001	14.0	0.019	3.8	0.006	--	--
HPA	--	--	--	--	24.9	0.034	--	--	--	--
4-OH-THPA	16.2	0.001	--	--	12.7	0.017	--	--	32.1	0.006
4-OH-IMCA	17.9	0.001	18.7	0.001	--	--	--	--	--	--
SAT-IMCA	6.2	<0.001	--	--	21.2	0.029	41.4	0.063	--	--
SAT-4-OH-IMCA	--	--	--	--	--	--	18.7	0.028	--	--
Polar unknowns	--	--	29.0	0.001	9.5	0.013	--	--	--	--
Other unknowns (each <5% TRR)	--	--	--	--	3.2	0.004	--	--	13.3	0.002
Nonextractable [2]	11.4	0.001	7.4	<0.001	14.6	0.020	36.1	0.055	10.5	0.002
Protease hydrolysate [3]					9.8	0.013	29.0	0.044		
Organosoluble [3,4]					3.8	0.010	12.1	0.018		
Aqueous soluble					not reported		not reported			
Post-hydrolysis solids [5]					5.2	0.007	7.7	0.012		

[1] Shading indicates that the extraction/hydrolysis step or analysis was not conducted for that matrix/sample.
[2] Percent TRR was normalized to sum of extractable and nonextractable residues.
[3] %TRR were calculated by the study reviewer from % of fraction released.
[4] TLC analysis identified THPA and IMCA at 0.003 and 0.002 ppm, respectively, in kidney and 0.003 and 0.001 ppm, respectively, in liver; the remaining residue consisted of 3-4 minor components.
[5] Calculated by the study reviewer from the DPM remaining in the fraction.

TABLE C.2.3.1. Summary of Characterization and Identification of Radioactive Residues in Lactating Goat (#7) Matrices Following Dosing with [THP-^{14}C]Flumiclorac Pentyl at 20 ppm.

Compound	Milk, Study day 2		Milk, Study day 4		Kidney		Liver		Fat, Perirenal	
	TRR=0.017 ppm		TRR=0.022 ppm		TRR=0.192 ppm		TRR=0.208 ppm		TRR=0.020 ppm	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	%TRR	ppm	% TRR	ppm
Flumiclorac pentyl	–	–	–	–	10.3	0.018	--	--	--	--
THPA	23.3	0.004	29.4	0.006	--	--	--	--	54.2	0.008
IMCA	25.0	0.004	24.6	0.005	20.5	0.036	11.3	0.021	--	--
HPA	–	--	–	--	15.2	0.027	3.1	0.006	--	--
4-OH-THPA	14.1	0.002	11.8	0.002	6.8	0.012	--	--	10.5	0.001
4-OH-IMCA	17.8	0.003	17.8	0.004	--	--	--	--	--	--
SAT-IMCA	–	–	–	–	18.6	0.033	37.6	0.070	--	--
SAT-4-OH-IMCA	–	–	–	–	2.8	0.005	18.5	0.034	--	--
Polar unknowns	6.4	0.001	3.0	0.001	6.5	0.011	8.5	0.016	15.1	0.002
Other unknowns	--	--	--	--	3.4	0.006	0.8	0.001	13.1	0.002
Protease hydrolysate	--	--	--	--	10.1	0.018	13.3	0.025	--	--
Total identified	80.2	0.013	83.6	0.017	74.2	0.131 [1]	70.5	0.131 [2]	64.7	0.009
Total characterized	6.4	0.001	3.0	0.001	20.0	0.035	22.6	0.042	28.2	0.004
Total extractable	86.5	0.014	86.6	0.018	94.1	0.165	93.1	0.174	93.0	0.013
Unextractable (PES)[3]	13.5	0.002	13.4	0.003	5.7	0.010	5.1	0.010	7.0	0.001
Accountability[4]	100		100		100		100		100	

[1] Does not include the THPA and IMCA tentatively identified in the organosoluble fraction of the protease hydrolysate, each at ≤0.002 ppm.

[2] Does not include the THPA and IMCA tentatively identified in the organosoluble fraction of the protease hydrolysate, each at ≤0.005 ppm.

[3] Residues remaining after exhaustive extractions.

[4] Accountability was 100% because extractable and nonextractable residues were normalized; actual recoveries reported by the petitioner were 90-96% (69% in fat).

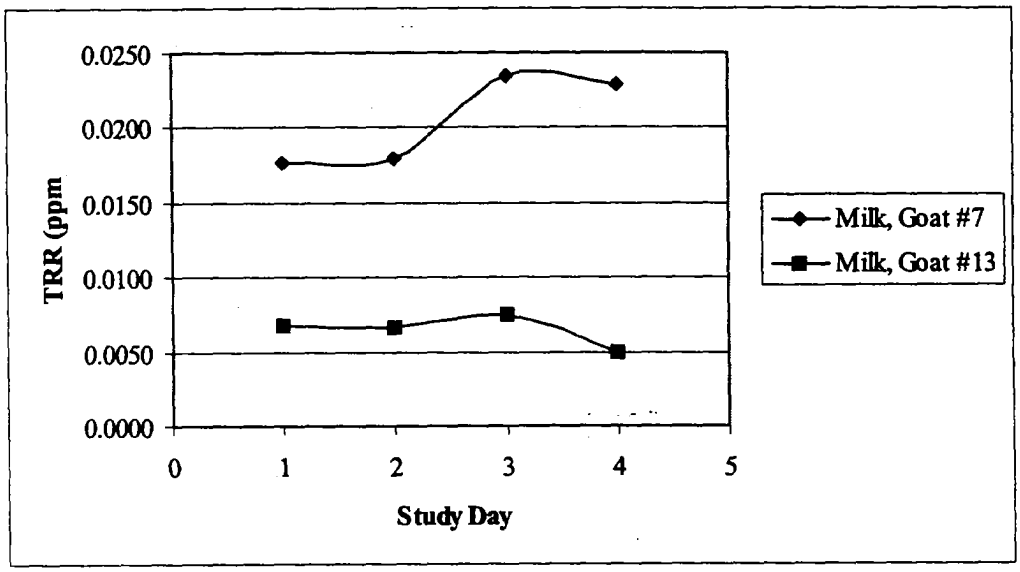

0.0250
0.0200
0.0150
0.0100
0.0050
0.0000
TRR (ppm
0
1
2
3
4
5
Study Day
Milk, Goat #7
Milk, Goat #13

TABLE C.2.2.1. Distribution of the Parent and the Metabolites in Lactating Goat (#7) Matrices Following Dosing with [THP-^{14}C]Flumiclorac Pentyl. [1]

Metabolite Fraction	Milk, Study day 2		Milk, Study day 4		Kidney		Liver		Fat, Perirenal	
	TRR=0.017 ppm		TRR=0.022 ppm		TRR=0.192 ppm		TRR=0.208 ppm		TRR=0.020 ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Extractable [2]	86.5	0.014	86.6	0.018	84.0	0.147	79.8	0.149	93.0	0.013
Flumiclorac pentyl	--	--	--	--	10.3	0.018	--	--	--	--
THPA	23.3	0.004	29.4	0.006	--	--	--	--	54.2	0.008
IMCA	25.0	0.004	24.6	0.005	20.5	0.036	11.3	0.021	--	--
HPA	--	--	--	--	15.2	0.027	3.1	0.006	--	--
4-OH-THPA	14.1	0.002	11.8	0.002	6.8	0.012	--	--	10.5	0.001
4-OH-IMCA	17.8	0.003	17.8	0.004	--	--	--	--	--	--
SAT-IMCA	--	--	--	--	18.6	0.033	37.6	0.070	--	--
SAT-4-OH-IMCA	--	--	--	--	2.8	0.005	18.5	0.034	--	--
Polar unknowns	6.4	0.001	3.0	0.001	6.5	0.011	8.5	0.016	15.1	0.002
Other unknowns	--	--	--	--	3.4	0.006	0.8	0.001	13.1	0.002
Nonextractable [2]	13.5	0.002	13.4	0.003	16.0	0.028	20.2	0.038	7.0	0.001
Protease hydrolysate [3]					10.1	0.018	13.3	0.025		
Organosoluble [3,4]					3.8	0.007	5.8	0.016		
Aqueous soluble					not reported		not reported			
Post-hydrolysis solids [5]					5.7	0.010	5.1	0.010		

[1] Shading indicates that the extraction/hydrolysis step or analysis was not conducted for that matrix/sample.
[2] Percent TRR was normalized to sum of extractable and nonextractable residues.
[3] %TRR were calculated by the study reviewer from % of fraction released.
[4] TLC analysis identified THPA and IMCA at 0.002 and 0.001 ppm, respectively, in kidney and 0.005 and 0.003 ppm, respectively, in liver; the remaining residue consisted of 3-4 minor components.
[5] Calculated by the study reviewer from the DPM remaining in the fraction.

TABLE C.2.3.2. Summary of Characterization and Identification of Radioactive Residues in Lactating Goat (#13) Matrices Following Dosing with [THP-^{14}C]Flumiclorac Pentyl at 20 ppm.

Compound	Milk, Study day 2		Milk, Study day 4		Kidney		Liver		Fat, Perirenal	
	TRR=0.007 ppm		TRR=0.004 ppm		TRR=0.163 ppm		TRR=0.139 ppm		TRR=0.021 ppm	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	%TRR	ppm	% TRR	ppm
Flumiclorac pentyl	–	–	–	–	–	–	–	–	–	–
THPA	40.1	0.002	30.7	0.001	–	–	–	–	44.1	0.008
IMCA	8.4	<0.001	14.2	0.001	14.0	0.019	3.8	0.006	–	–
HPA	–	–	–	–	24.9	0.034	–	–	–	–
4-OH-THPA	16.2	0.001	–	–	12.7	0.017	–	–	32.1	0.006
4-OH-IMCA	17.9	0.001	18.7	0.001	–	–	–	–	–	–
SAT-IMCA	6.2	<0.001	–	–	21.2	0.029	41.4	0.063	–	–
SAT-4-OH-IMCA	–	–	–	–	–	–	18.7	0.028	–	–
Polar unknowns	–	–	29.0	0.001	9.5	0.013	–	–	–	–
Other unknowns	–	–	–	–	3.2	0.004	–	–	13.3	0.002
Protease hydrolysate	–	–	–	–	9.8	0.013	29.0	0.044	–	–
Total identified	88.8	<0.006	63.6	0.003	72.8	0.099	63.9	0.097	76.2	0.014
Total characterized	–	–	29.0	0.001	22.5	0.030 [1]	29.0	0.044 [1]	13.3	0.002
Total extractable	88.6	0.006	92.6	0.004	95.2	0.131	92.9	0.141	89.5	0.016
Unextractable (PES)[2]	11.4	0.001	7.4	<0.001	5.2	0.007	7.7	0.012	10.5	0.002
Accountability[3]	100		100		100		100		100	

[1] Does not include the THPA and IMCA tentatively identified in the organosoluble fraction of the protease hydrolysate, each at ≤0.003 ppm.

[3] Residues remaining after exhaustive extractions.

[4] Accountability was 100% because extractable and nonextractable residues were normalized; actual recoveries reported by the petitioner were 85-111%.

C.3. Proposed Metabolic Profile

FIGURE C.3.1. Proposed Metabolic Profile of Flumiclorac Pentyl in Lactating Goat.

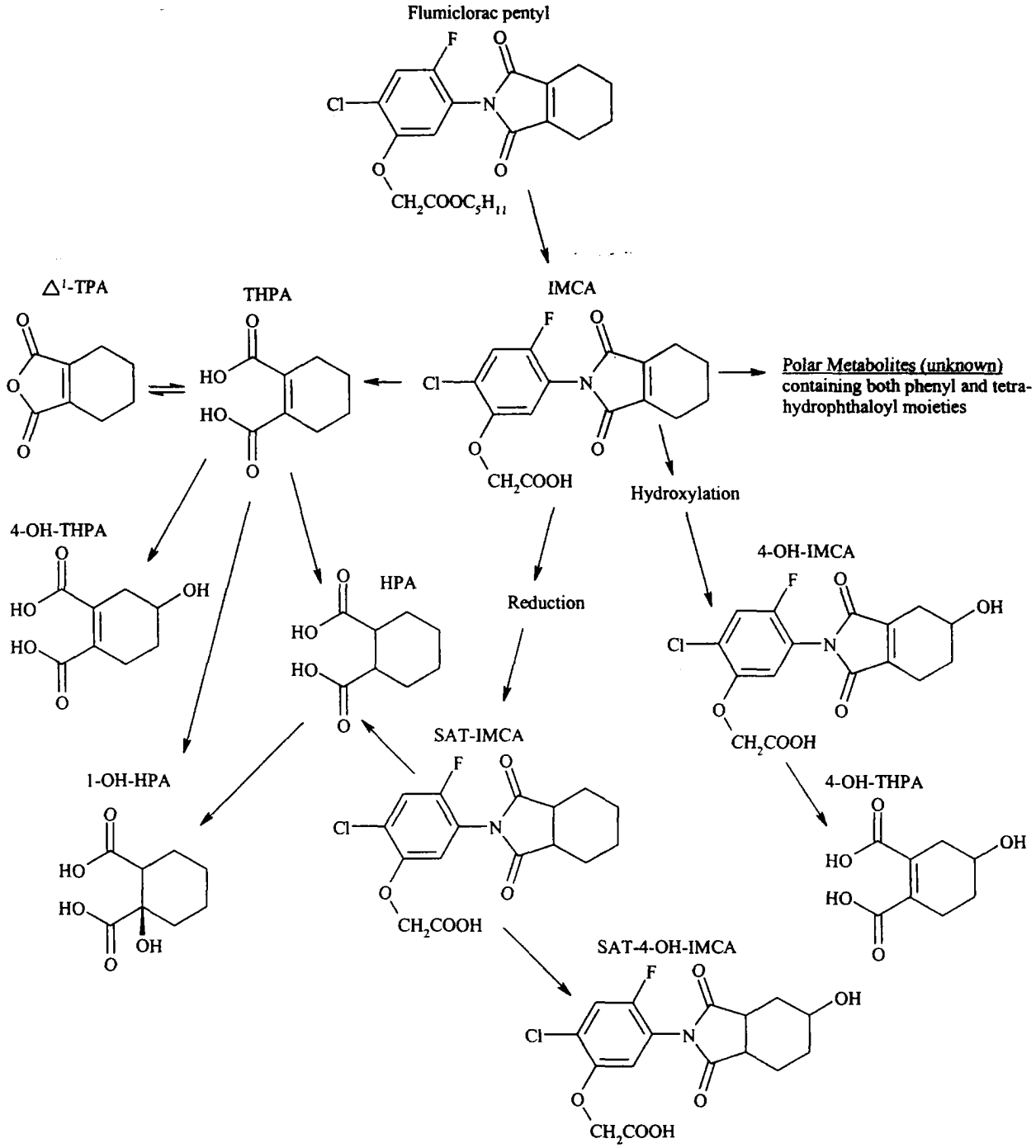


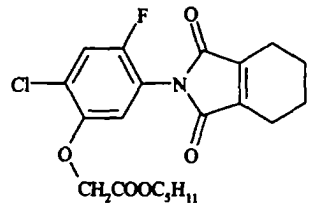
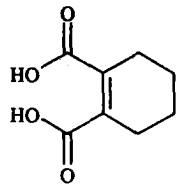
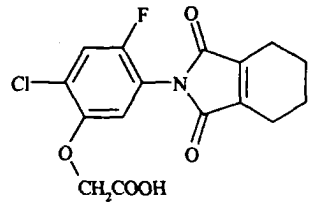
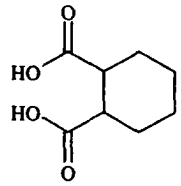
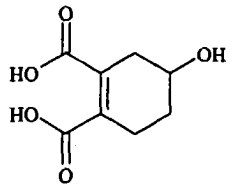
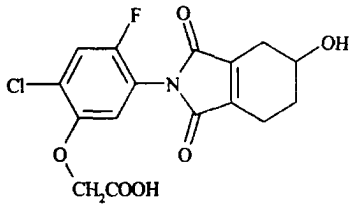
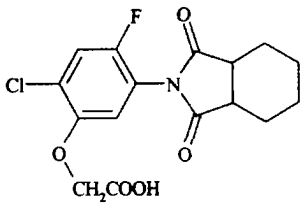
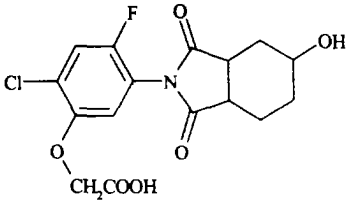
TABLE C.3.1. Identification of Compounds from Metabolism Study		
Common name/code Figure C.3.1 ID No.	Chemical name	Chemical structure
Flumiclorac pentyl; S-23031	Acetic acid, {2-chloro-4-fluoro-5-(1,3,4,5,6,7-hexahydro-1,3-dioxo-2H-isoindol-2-yl)phenoxy}-,pentyl ester or 2-chloro-4-fluoro-5-(1,3,4,5,6,7-hexahydro-1,3-dioxo-2H-isoindol-2-yl)phenoxy]acetic acid, pentyl ester	
THPA	3,4,5,6-tetrahydrophthalic acid	
IMCA	2-chloro-4-fluoro-5-(3,4,5,6-tetrahydrophthalimido)phenoxyacetic acid	
HPA	(±)trans-1,2-cyclohexanedicarboxylic acid	
4-OH-THPA	4-hydroxy-1-cyclohexene-1,2-dicarboxylate	

TABLE C.3.1. Identification of Compounds from Metabolism Study		
Common name/code Figure C.3.1 ID No.	Chemical name	Chemical structure
4-OH-IMCA	2-chloro-4-fluoro-5-(4-hydroxy-3,4,5,6-tetrahydrophthalimido)phenoxyacetate	
SAT-IMCA	2-chloro-4-fluoro-5-(cyclohexane-1,2-dicarboximido)phenoxyacetate	
SAT-4-OH-IMCA	2-chloro-4-fluoro-5-(4-hydroxy-1,2,-cyclohexanedicarboximido)phenoxyacetate	

D. CONCLUSION

Total radioactive residues were 0.0049-0.0234 ppm in milk, 0.157-0.192 ppm in kidney, 0.137-0.208 ppm in liver, 0.017-0.021 ppm in perirenal fat, 0.007-0.011 ppm in omental fat, and 0.005-0.006 ppm in loin and leg muscle from goats dosed orally with [THP-1,2-^{14}C]flumiclorac pentyl at 20 ppm in the diet for 5 consecutive days. A large portion of the administered dose was excreted, with urine accounting for 22-29% and feces accounting for 37-39% of the administered dose.

The majority of the radioactivity (~64-93% TRR) was extractable (using ethanol for milk, and ACN and acidic ACN/water for kidney and liver, and acidic ACN/water for perirenal fat). Protease hydrolysis released additional radioactivity (~10-29% TRR) from the nonextractable solids of kidney and liver. Nonextractable residues remaining after solvent extraction and/or enzyme hydrolysis accounted for ≤0.01 ppm in milk, perirenal fat, kidney, and liver; accountabilities were 100% because extractable and nonextractable residues were normalized, but actual recoveries were 85-111% (69% in fat). Omental fat and muscle samples were not extracted due to low TRR.

Approximately 64-89% of the TRR in milk, perirenal fat, kidney, and liver were identified. The parent was only found in the kidney of one goat at 10.3% TRR (0.018 ppm). The major metabolite in milk and perirenal fat was THPA; THPA was not detected in kidney or liver. The metabolite IMCA was identified at significant levels in all matrices except fat. 4-OH-THPA and 4-OH-IMCA were also significant metabolites identified in milk; 4-OH-THPA was also identified as a significant residue in kidney and fat. HPA was a major metabolite identified in kidney and a minor metabolite identified in liver. SAT-IMCA and SAT-4-OH-IMCA were identified in kidney and liver at significant levels. SAT-IMCA was also identified in milk at trace levels (<0.001 ppm). Metabolites THPA and IMCA were also identified, each at ≤0.005 ppm, in the protease hydrolysate of kidney and liver. Additional residues, each present at <5% TRR were characterized as polar or other unknowns in milk, perirenal fat, kidney, and liver.

Based on the results of this study, the petitioner proposed that flumiclorac pentyl is rapidly metabolized and excreted in goats. Initial hydrolysis of the pentyl ester of flumiclorac pentyl yields IMCA; no significant metabolites with the intact pentyl ester group were detected in goat matrices. IMCA is further metabolized by cleavage of the imide ring to THPA (the major metabolic pathway in goats), which is readily excreted. A major residue in goat liver and kidney, SAT-IMCA, is formed by a reduction process, where IMCA is further metabolized by gut microflora. Hydrolysis of SAT-IMCA likely forms HPA in kidney, urine, and feces of goat.

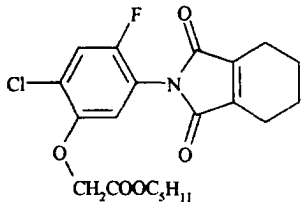
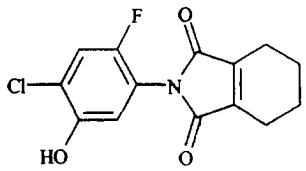
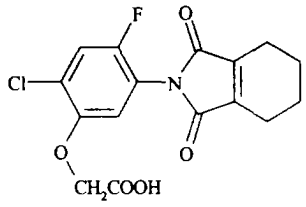
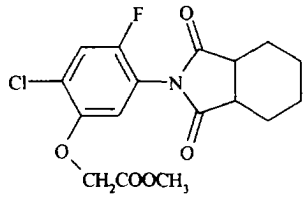
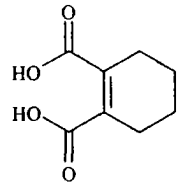
E. REFERENCES

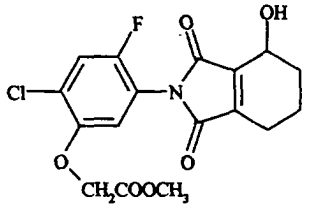
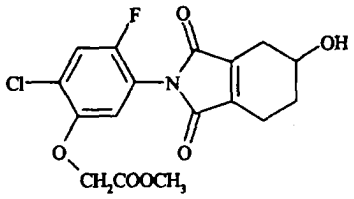
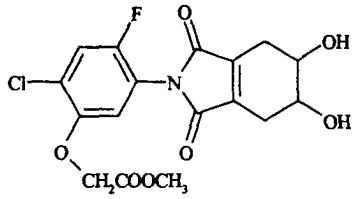
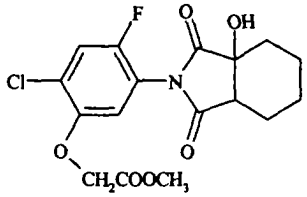
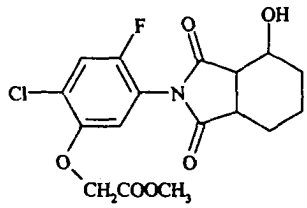
DP Barcode: D174474
Subject: PP#2G4078: New Chemical EUP: V-23031, Flumiclorac-Pentyl on Field Corn and Soybeans. Evaluation of Analytical Methods and of Residue Data.
From: J. Garbus
To: J. Miller and A. Kocialski
Dated: 7/28/92
MRIDs: 42187400-42187405, 42169849-42169859, and 42187407-42187408.

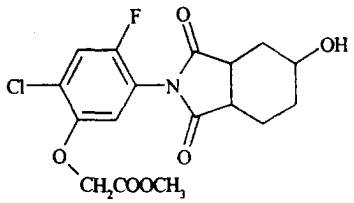
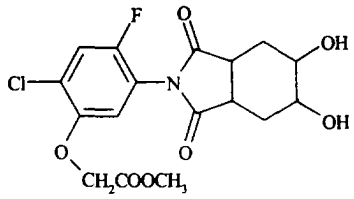
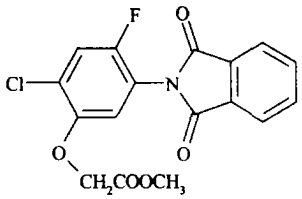
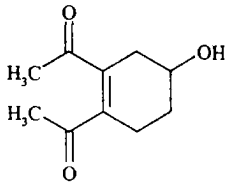
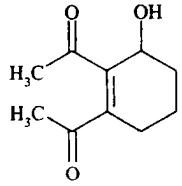
F. DOCUMENT TRACKING

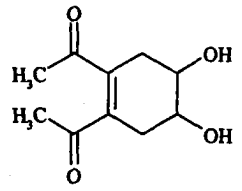
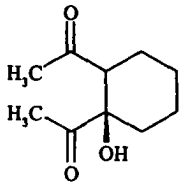
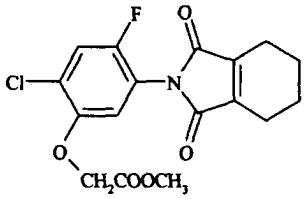
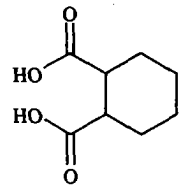
RDI: C. Eiden (24-JUN-2005)
Petition Number(s): PP#3F6767
DP Barcode(s): D308674
PC Code: 128724

Template Version September 2003

APPENDIX I. Chemical Names and Structures of Reference Standards Used in Goat Metabolism Study.		
Common name/code Figure C.3.1 ID No.	Chemical name	Chemical structure
Flumiclorac pentyl; S-23031	Acetic acid, {2-chloro-4-fluoro-5-(1,3,4,5,6,7-hexahydro-1,3-dioxo-2H-isoindol-2-yl)phenoxy}-,pentyl ester or 2-chloro-4-fluoro-5-(1,3,4,5,6,7-hexahydro-1,3-dioxo-2H-isoindol-2-yl)phenoxy]acetic acid, pentyl ester	
IMFP (or IMF)	N-(4-chloro-2-fluoro-5-hydroxyphenyl)-3,4,5,6-tetrahydrophthalimide	
IMCA	2-chloro-4-fluoro-5-(3,4,5,6-tetrahydrophthalimido)phenoxyacetic acid	
SAT-IMCA-ME	methyl 2-chloro-4-fluoro-5-(cis-1,2-cyclohexanedicarboximido)phenoxyacetate	
THPA	3,4,5,6-tetrahydrophthalic acid	

APPENDIX I. Chemical Names and Structures of Reference Standards Used in Goat Metabolism Study.		
Common name/code Figure C.3.1 ID No.	Chemical name	Chemical structure
3-OH-IMCA-ME	methyl 2-chloro-4-fluoro-5-(3-hydroxy-3,4,5,6-tetrahydrophthalimido)phenoxyacetate	
4-OH-IMCA-ME	methyl 2-chloro-4-fluoro-5-(4-hydroxy-3,4,5,6-tetrahydrophthalimido)phenoxyacetate	
4,5-OH-IMCA-ME	methyl 2-chloro-4-fluoro-5-(4,5-dihydroxy-3,4,5,6-tetrahydrophthalimido)phenoxyacetate	
SAT-1-OH-IMCA-ME	methyl 2-chloro-4-fluoro-5-(1-hydroxy-1,2-cyclohexanedicarboximido)phenoxyacetate	
SAT-3-OH-IMCA-ME	methyl 2-chloro-4-fluoro-5-(3-hydroxy-1,2-cyclohexanedicarboximido)phenoxyacetate	

APPENDIX I. Chemical Names and Structures of Reference Standards Used in Goat Metabolism Study.		
Common name/code Figure C.3.1 ID No.	Chemical name	Chemical structure
SAT-4-OH-IMCA-ME	methyl 2-chloro-4-fluoro-5-(4-hydroxy-1,2,-cyclohexanedicarboximido)phenoxyacetate	
SAT-4,5-OH-IMCA-ME	methyl 2-chloro-4-fluoro-5-(4,5-dihydroxy-1,2,-cyclohexanedicarboximido)phenoxyacetate	
AR-IMCA-ME	methyl 2-chloro-4-fluoro-5-phthalimidophenoxyacetate	
4-OH-THPA-DME	dimethyl 4-hydroxy-1-cyclohexene-1,2-dicarboxylate	
3-OH-THPA-DME	dimethyl 3-hydroxy-1-cyclohexene-1,2-dicarboxylate	

APPENDIX I. Chemical Names and Structures of Reference Standards Used in Goat Metabolism Study.		
Common name/code Figure C.3.1 ID No.	Chemical name	Chemical structure
4,5-OH-THPA-DME	dimethyl 4,5-dihydroxy-1-cyclohexene-1,2-dicarboxylate	
1-OH-HPA-DME-1	dimethyl 1-hydroxy-trans-1,2-cyclohexanedicarboxylate	
IMCA-ME	methyl 2-chloro-4-fluoro-5-(3,4,5,6-tetrahydrophthalimido)phenoxyacetate	
HPA	(±)trans-1,2-cyclohexanedicarboxylic acid	

Flumiclorac pentyl/PC Code 128724/Valent U.S.A. Corporation
OPPTS 860.1300
Nature of the Residues in Livestock - Hen

Primary Evaluator William H. Donovan
William H. Donovan, Ph.D.
Chemist
HED/RRB3
Date: 6/24/05

Approved by for
Catherine Eiden
Branch Chief
HED/RRB3
Date: 6/24/05

This DER was originally prepared under contract by Dynamac Corporation (20440 Century Boulevard, Suite 100; Germantown, MD 20874; submitted 01/26/2005). The DER has been reviewed by the Health Effects Division (HED) and revised to reflect current Office of Pesticide Programs (OPP) policies.

STUDY REPORT:

46082806 Huhtanen, K. (1992) A Study to Determine the Nature of the Residue in Poultry and Egg From Chickens Dosed with [THP-^{14}C]S-23031 Analytical Phase of Study. Project Number: 90/0511, 3789/90/0511/EF/001. Unpublished study prepared by Ricerca, Inc. (Painesville, OH) and submitted by Valent U.S.A. Corp. 161 p.

EXECUTIVE SUMMARY:

Valent U.S.A. Corporation has submitted a study investigating the metabolism of [tetrahydrophthaloyl-1,2-^{14}C]flumiclorac pentyl in laying hens. Information concerning the in-life phase of this study was previously submitted in MRID 42169854 and reviewed (DP Barcode D174474, 7/28/92, J. Garbus) in conjunction with PP#2G4078. The current submission reports the characterization and identification of radioactive residues in poultry eggs and tissues.

The test substance, [THP-1,2-^{14}C]flumiclorac pentyl, was administered orally to ten hens at 10.5 ppm in the diet. The hens were dosed once per day for seven consecutive days. Eggs were collected twice daily, separated into whites and yolks, and composited for each study day. Hen tissues (gizzard, kidney, liver, muscle, skin, and fat) were collected at sacrifice. The in-life phase of the study was conducted by ABC Laboratories (Columbia, MO), and the analytical phase was conducted by Ricerca, Inc. (Painesville, OH).

Total radioactive residues, determined by the analytical laboratory, were 0.002 ppm in egg whites (Day 5), 0.027 ppm in egg yolk (Day 5), 0.008 ppm in fat, 0.009 ppm in thigh muscle, 0.036 ppm in skin, 0.079 ppm in liver, 0.312 ppm in kidney, and 1.586 ppm in gizzards from hens dosed with [THP-1,2-^{14}C]flumiclorac pentyl. Radioactivity was low in most hen matrices, with the highest levels observed in gizzards and kidney which are poultry matrices not typically regulated. The study reported that about 85% of the administered dose was excreted.

Because of low radioactivity, no residue characterization was conducted on egg white and breast muscle; the remainder of poultry matrices were subjected to residue extraction and characterization. The majority of the radioactivity (~44-95% TRR) in egg yolk, gizzards, fat, kidney, liver, thigh muscle, and skin was extractable with organic solvents. Protease hydrolysis released additional radioactivity (0.6-33.6% TRR) from the nonextractable solids of the above-listed matrices. Nonextractable residues remaining after solvent extraction and/or enzyme hydrolysis accounted for <10% TRR in all matrices. The collection, extraction, and analysis dates were not provided, and sample storage stability conditions and durations were not addressed in the study submission.

The parent was only identified in gizzards at 26.2% TRR. Several other metabolites were identified including: THPA, IMCA, 4-OH-IMCA, SAT-IMCA, Δ^1-TPA; the chemical names and structures of these metabolites are listed in Table C.3.1. The identified metabolites were detected at low absolute levels (<0.001-<0.008 ppm) in egg yolk, fat, liver, thigh muscle, and skin. Some metabolites were present at up to 0.416 ppm in gizzards and 0.02 ppm in kidney. The metabolite IMCA was detected in all poultry matrices analyzed.

The petitioner proposed that flumiclorac pentyl is rapidly metabolized and excreted in hens. Based on the phenyl- and THP-labeled hen metabolism studies, the proposed metabolic reactions in hens involve: (i) initial hydrolysis of the pentyl ester of flumiclorac pentyl to form IMCA; (ii) hydrolysis of the imide and subsequent formed amide; (iii) hydroxylation of the cyclohexane ring; and (iv) olefin reduction.

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the hen metabolism data are classified as scientifically unacceptable because information pertaining to sample storage conditions and intervals was not provided. The study may be upgraded if the petitioner submits the dates of hen sacrifice as well as the dates of initial and final analyses. Storage stability data are not normally required for samples analyzed within 4 to 6 months of collection, provided evidence is given that attempts were made to limit degradation of residues by appropriate storage of matrices and extracts during the analytical phase of the study. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document DP Barcode D308674.

COMPLIANCE:

A signed and dated compliance statement was provided. The study was conducted and reported in compliance with Good Laboratory Practice Regulations with the exception of the reference standards that were supplied and characterized by Sumitomo Chemical Company, Ltd. The characterizations of the identity of these substances were not done entirely under GLP procedures.

A. BACKGROUND INFORMATION

Flumiclorac pentyl is an N-phenylphthalimide derivative herbicide used for the control of broadleaf weeds. Its mode of action is through the accumulation of porphyrins in susceptible plants; the photosensitizing action of accumulated porphyrins may cause membrane lipid peroxidation which leads to irreversible damage of membrane function and structure in the plant. Flumiclorac pentyl is registered for postemergence application to field corn and soybeans; registration for use on cotton as a defoliant is pending. The PC code and nomenclature of flumiclorac pentyl are listed below in Table 1. The physicochemical properties of flumiclorac pentyl are listed in Table 2.

TABLE 1. Flumiclorac Pentyl Nomenclature

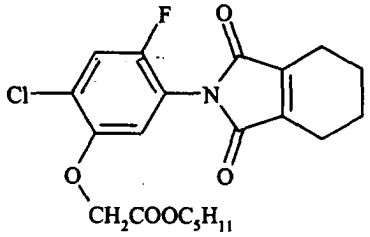
Chemical Structure	
Common name	Flumiclorac pentyl
Company experimental name	S-23031 or V-23031
Molecular Formula	$C_{21}H_{23}ClFNO_5$
Molecular Weight	423.9
IUPAC name	Pentyl (2-chloro-5 (cyclohex-1-ene-1,2-dicarboximido)-4-fluorophenoxy) acetate
CAS name	Pentyl[2-chloro-4-fluoro-5-(1,3,4,5,6,7- hexahydro-1,3-dioxo-2H-isoindol-2-yl)phenoxy]acetate
CAS #	87546-18-7
PC Code	128724

TABLE 2. Physicochemical Properties of Flumiclorac Pentyl

Parameter	Value	Reference
Melting point	88.9-90.1 °C	PP#2G4078; D174474, 7/28/92, J. Garbus
pH	6.03 at 25 °C	
Density, bulk density, or specific gravity	1.3316 g/mL at 20 °C	
Water solubility	0.189 mg/L at 25 °C	
Solvent solubility	g/100 mL at 25 °C: hexane 0.328 n-octanol 1.60 methanol 4.78 Solvesso 150 27.1 acetonitrile 58.9 acetone 59.0 tetrahydrofuran 69.7 N-methyl 2-pyrrolidinone 134.0 methylene chloride 288.0	

TABLE 2. Physicochemical Properties of Flumiclorac Pentyl		
Parameter	Value	Reference
Vapor pressure	$<1 \times 10^{-7}$ mm Hg at 22.4 °C	
Dissociation constant, pK_a	No dissociation at pH ≤7; flumiclorac pentyl decomposes at pH ≥9.	
Octanol/water partition coefficient	Log P_{ow} = 4.99 at 19.7-21.0 °C	
UV/visible absorption spectrum	Not available	

B. EXPERIMENTAL DESIGN

Information concerning the in-life phase of this study, including TRR determinations, was previously submitted in MRID 42169854 and reviewed (DP Barcode D174474, 7/28/92, J. Garbus) in conjunction with PP#2G4078.

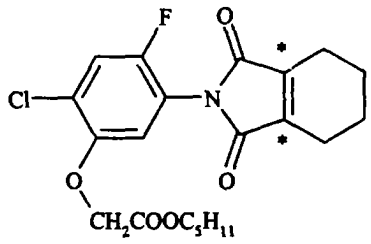
B.1. Livestock

TABLE B.1.1. General Test Animal Information.					
Species	Breed	Age	Weight at study initiation (kg)	Health Status	Description of housing/holding area
Laying hens	Leghorn	Not available from this submission			Not described in the study submission.

TABLE B.1.2. Test Animal Dietary Regime.				
Composition of Diet	Feed consumption (average kg/day)	Water	Acclimation period	Predosing
Not available from this submission				

TABLE B.1.3. Test Animal Dosing Regime			
Treatment Type	Feeding Level (ppm test material in food)	Vehicle	Timing/Duration
Oral	10.5 ppm	Gelatin capsule	Once per day for seven consecutive days.

B.2. Test Materials

TABLE B.2.1. Test Material Characteristics.	
Chemical structure	
Radiolabel position	Labeled on the 1 and 2 carbon of the phthalamide ring
Lot No.	C-90-009 (isotopically diluted)
Purity	>98%
Specific activity of isotopically diluted test material	89,200 dpm/µg

B.3. Sampling Information

TABLE B.3.1. Sample Collection Information			
Eggs collected	Urine, feces and cage wash collected	Interval from last dose to sacrifice	Tissues collected and analyzed
Eggs were collected twice daily. The eggs were then separated into whites and yolks, and then composited daily.	Excreta was collected daily.	within 4 hours	Gizzard, fat, kidney, liver, breast muscle, thigh muscle, and skin.

B.4. Identification/Characterization of Residues

B.4.1. Sample Handling and Preparation

Daily egg white and yolk samples were composited. Information pertaining to handling of the samples at the in-life facility is not available from this submission. It was, however, reported that frozen egg and tissue samples were received at Ricerca, Inc. (Painesville, OH) for extraction and characterization/identification of residues. Because of low radioactivity, egg white and breast muscle samples were not extracted.

Study Day 5 egg yolk samples were sequentially extracted with acetonitrile (ACN):1 M HCl (4:1, v:v), ACN:methylene chloride (1:1, v:v), and methylene chloride. Individual extracts were isolated by vacuum filtration and combined. The combined extract was diluted with 6% sodium chloride and extracted with methylene chloride. The phases were allowed to separate, and the aqueous phase was extracted again with methylene chloride. The combined methylene chloride phases were concentrated, and the oily residues were redissolved in hexane:methylene chloride (1:1, v:v) for gel permeation cleanup; residues were eluted with hexane/methylene chloride, collecting 6-minute fractions. Selected fractions were concentrated and diluted with ACN for

HPLC analysis. HPLC fractions were collected, and selected fractions were reserved for TLC analysis.

The nonextractable residues of egg yolk, which remained after the initial solvent extractions, were subjected to protease hydrolysis (in pH 7.5 0.1 M Tris buffer at 37 °C for 16 hours) and then centrifuged. The supernatant was acidified to pH 1 with 2 M HCl and cleaned up through a series of three C-18 cartridges; residues were eluted with ACN and then methanol. The combined ACN and methanol eluates were concentrated to an oily residue and sonicated with ACN:water (1:1, v:v) for HPLC analysis. Five-minute HPLC fractions were collected for subsequent TLC analysis of selected fractions.

Samples of tissues (gizzard, kidney, liver, or muscle) were extracted (3x) with 2% formic acid:ACN (7:3, v:v) and then centrifuged to precipitate solids. The first two filtrates were combined (the third extract did not contain significant radioactivity), concentrated, and the remaining aqueous solution was acidified to pH 2 with 3 M HCl for partitioning (2x) with diethyl ether. The organic phases were combined, concentrated, and the residues redissolved in 1% acetic acid in water:ACN (3:2, v:v) for HPLC analysis. The aqueous phase was concentrated, frozen, and lyophilized; resulting solids were extracted with methanol by sonification. The methanol extract was concentrated and residues redissolved in 1% acetic acid:ACN (3:2, v:v) for HPLC analysis. Five minute fractions of the HPLC eluent of the organic and aqueous phase analyses were collected, and selected fractions were reserved for TLC analysis.

Nonextractable residues of the initial tissue extraction were subjected to protease hydrolysis (in pH 7.5 0.1 M Tris buffer overnight at 37 °C) and then centrifuged. The supernatant was acidified to pH 2 with 3 M HCl and partitioned with ethyl acetate. The ethyl acetate phase was concentrated to near dryness, and residues were redissolved in 1% acetic acid:ACN (3:2, v:v) for HPLC analysis. HPLC fractions were collected for subsequent TLC analysis of selected fractions.

Fat and skin samples were extracted (3x) with ACN:0.1 M HCl (9:1, v:v) and then centrifuged. The respective combined extracts were partitioned (2x) with hexane:methylene chloride (2:1, v:v); a three-phase separation resulted. The ACN:aqueous acid phase was concentrated, the residue was solubilized in methylene chloride and concentrated to an oily residue. Fat residues were redissolved in ACN:water (1:1, v:v). Following centrifugation, the supernatant (ACN/water) was reserved for HPLC analysis. Skin residues were redissolved in methylene chloride, concentrated again, and redissolved in ACN:water (1:1, v:v); the precipitated oils were separated by centrifugation and extracted again with additional ACN/water. The resulting skin oils and extracts were combined for HPLC analysis. HPLC fractions were collected for subsequent TLC analysis of selected fractions.

Nonextractable residues remaining in the skin sample following solvent extraction were subjected to protease hydrolysis as described above for egg yolk.

B.4.2. Analytical Methodology

Total radioactive residues, initially determined by ABC Laboratories, were reported in MRID 42169854 (DP Barcode D174474, 7/28/92, J. Garbus). Following receipt of additional samples, TRRs were also determined for selected poultry matrices at the analytical laboratory (Ricerca, Painesville, OH). Extracts and hydrolysates were radioassayed by LSC, and nonextractable residues were radioassayed by combustion/LSC. For determinations made at Ricerca, the minimum quantifiable limit for tissues was dependent on the background levels and based on the normal background levels (10-30 dpm) was reported as 0.001 ppm.

The petitioner reported normalized results for the extractable and nonextractable residues in tissues with higher levels of radioactivity (gizzard, kidney, liver, and thigh muscle). But because lower recoveries were obtained from samples with higher lipid content, residue values were not normalized for egg yolk, fat and skin samples.

Extracts and/or hydrolysates were analyzed by HPLC using a C18 column, UV detection, radiodetection, and a gradient mobile phase of 1% acetic acid, ACN and/or methanol. HPLC fractions of individual metabolites with low radioactivity were collected for quantitative analysis, using combined HPLC and TLC. TLC analyses of isolated fractions were conducted using silica gel (K6F or F-254) plates and a solvent system of toluene:ethyl acetate:acetic acid (5:7:1, v:v:v). Metabolites were identified by co-chromatography or comparison of retention times with those of the reference standards (see Appendix 1). Non-labeled standards were detected using UV light, and radioactive standards or metabolites were detected with a linear analyzer imaging scanner.

Identifications of residues present at ≥0.01 ppm were confirmed by GC/MS analysis of the respective isolated component from excreta with standards or the methylated standard derivative. LC/MS (positive and negative ion) was used to analyze residues isolated through a C8 analytical column.

Residues present at <0.01 ppm were quantitated by the radioactivity found at the appropriate HPLC and TLC retention time; calculations based on HPLC and TLC results were normalized. The petitioner noted that TLC analyses of HPLC fractions contained numerous minor metabolites not seen with HPLC analysis.

The petitioner conducted radiovalidation of the residue analytical method, entitled, "Residue Method for the Determination of Residues of S-23031 in Chicken Eggs, Muscle, and Tissue, and Goat Milk, Muscle and Tissue" (Ricerca number 3789-92-0194-MD-001) using egg yolk, gizzard, and breast muscle samples from [THP-^{14}C]flumiclorac pentyl treated hens.

C. RESULTS AND DISCUSSION

Total radioactive residues in hen eggs and tissues are reported in Table C.2.1. TRR, determined by the analytical laboratory, were 0.002 ppm in egg whites (Day 5), 0.027 ppm in egg yolk (Day

5), 1.586 ppm in gizzards, 0.312 ppm in kidney, 0.079 ppm in liver, 0.009 ppm in thigh muscle, 0.008 ppm in fat, and 0.036 ppm in skin from hens dosed orally with [THP-1,2-^{14}C]flumiclorac pentyl at 10.5 ppm in the diet for 7 consecutive days. Radioactivity was low in most hen matrices, with the highest levels in gizzards and kidney (not typically matrices of concern for poultry). A large portion of the administered dose was excreted, accounting for 85% of the administered dose.

The distribution of the radioactivity in hen matrices is presented in Table C.2.2. Because of low radioactivity, residues in egg white and breast muscle samples were not extracted. The majority of the radioactivity (~44-95% TRR) in egg yolk, gizzards, fat, kidney, liver, thigh muscle, and skin was extractable (using acidic ACN, ACN, and/or methylene chloride). It is noted that the petitioner did not report the %TRR or ppm levels in the individual fractions through the extraction/cleanup steps, and only reported the total extractable residues. Protease hydrolysis released additional radioactivity (0.6-33.6% TRR, 0.001-0.090 ppm) from the nonextractable solids of egg yolk, gizzard, kidney, liver, and skin. Nonextractable residues remaining after solvent extraction and/or enzyme hydrolysis accounted for <10% TRR or <0.02 ppm in all matrices. Residues were characterized primarily by HPLC and TLC analysis. The identities of metabolites were confirmed using GC/MS and LC/MS analyses of isolated excreta residues.

The characterization and identification of residues in hen matrices is summarized in Table C.2.3. Approximately 4-13% of the TRR in egg yolk, fat, and skin, 17-25% TRR in kidney, liver, and thigh muscle, and 64% TRR in gizzard were identified. The parent was only identified in gizzard accounting for 26.2% TRR (0.416 ppm). IMCA was also identified as a major residue in gizzard accounting for 26.2% TRR (0.416 ppm). IMCA was also identified in all the other matrices (egg yolk, fat, kidney, liver, muscle, and skin) at lower levels (3.6-9.8% TRR, <0.001-0.020 ppm). The metabolite THPA was identified in gizzards at 10.2% TRR (0.161 ppm) and in muscle at 14.0% TRR (0.001 ppm); THPA was identified in fat, kidney, liver, and skin at low levels (0.3-6.4% TRR, <0.001-0.005 ppm). The metabolite 4-OH-IMCA was a minor metabolite identified in gizzards, fat, kidney, liver, and skin accounting for 0.8-6.4% TRR (<0.021-0.022 ppm). SAT-IMCA was identified as a minor metabolite in kidney and liver (3.8% TRR, ≤0.012 ppm). Δ^1-TPA was detected at trace levels (2.0% TRR, <0.001 ppm) in muscle only. The metabolites THPA and IMCA were also identified in the protease hydrolysates of nonextractable residues of gizzards, kidney, and liver (each <0.01 ppm). Additional residues, each present at <10% TRR or <0.01 ppm were characterized as polar or other unknowns in gizzards, kidney, liver, muscle, and skin. Solids which precipitated from the concentration of the gizzard and liver aqueous extract accounted for 4.8% TRR (0.076 ppm) and 36.7% TRR (0.029 ppm), respectively. Flumiclorac pentyl and IMCA were identified in the gizzard acid hydrolysate of the precipitated solids.

Radiovalidation of the residue analytical method, entitled, "Residue Method for the Determination of Residues of S-23031 in Chicken Eggs, Muscle, and Tissue, and Goat Milk, Muscle and Tissue" (Ricerca number 3789-92-0194-MD-001) using egg yolk, gizzard, and breast muscle samples from [phenyl-^{14}C]flumiclorac pentyl treated hens demonstrated that flumiclorac pentyl residues were below the limit of detection (0.02 ppm for eggs and 0.01 ppm for muscle) of the residue method in egg yolk and muscle. Residues of flumiclorac pentyl in gizzard were 0.148

ppm using the residue method and 0.416 ppm using the ^{14}C-analysis method. The petitioner stated that there was no apparent reason for the lower quantitation of residues using the residue method, but that since there is no expectation of the transmittal of detectable levels of flumiclorac pentyl to edible tissues of poultry from feed crops, the discrepancy between the methods was not further pursued.

C.1. Storage Stability

Samples of hen matrices were placed in frozen storage after collection. The dates of extraction and analysis were not provided for any of the samples. The petitioner did not address storage intervals, and representative chromatograms did not include analysis dates. The collection, extraction and analysis dates of each sample must be submitted to determine if storage stability data are required to support the storage conditions and duration of the samples from the hen metabolism study.

TABLE C.1. Summary of Storage Conditions

Matrix	Storage Temp. (°C)	Actual Storage Duration	Interval of Demonstrated Storage Stability
Egg yolk, gizzard, fat, kidney, liver, muscle, and skin	-20 °C	Extraction and analysis dates were not provided	None

C.2. Identification, Characterization, and Distribution of Residues

TABLE C.2.1. Total Radioactive Residues (TRR) in Eggs, Tissue and Excreta

Matrix	Collection Timing	[THP-1,2-^{14}C]Flumiclorac Pentyl		
		Ricerca, Inc. [1]	ABC Laboratories (in-life study)[2]	
		ppm	ppm	% Administered Dose
Excreta	Study Day 3	9.231	12.99	84.99
Egg, yolk	Study Day 5	0.027	0.009	0.015
Egg, white	Study Day 5	0.002	0.001	0.001
Gizzard	Sacrifice	1.586	1.564	0.423
Kidney	Sacrifice	0.312	0.309	0.043
Liver	Sacrifice	0.079	0.077	0.029
Breast muscle	Sacrifice	--	0.007	0.005
Thigh muscle	Sacrifice	0.009	0.010	0.007
Fat	Sacrifice	0.008	0.006	0.001
Skin	Sacrifice	0.036	0.036	0.005
Ovary contents	Sacrifice	0.029	0.032	0.032
Intestinal contents	Sacrifice	--	5.191	1.039
Total				86.59

[1] Combustion/LSC determinations made by Ricerca (analytical laboratory) prior to extraction.
[2] Values determined at ABC Laboratories and originally presented under DP Barcode D174474, 7/28/92, J. Garbus; these values are presented herein for informational purposes.

TABLE C.2.2. Distribution of the Parent and the Metabolites in Laying Hen Matrices Following Dosing with [THP-1,2-^{14}C]Flumiclorac Pentyl. [1]

Metabolite Fraction	Egg Yolk, Day 5		Gizzard		Fat		Kidney		Liver		Muscle, thigh		Skin	
	TRR = 0.027 ppm		TRR = 1.586 ppm		TRR = 0.008 ppm		TRR = 0.312 ppm		TRR = 0.079 ppm		TRR = 0.010 ppm		TRR = 0.036 ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Organic extract (nonpolar)	36.5	0.010	74.5	1.181	82.3	0.007	41.7	0.130	45.6	0.036	40.0	0.004	70.3	0.025
Flumiclorac pentyl	--	--	26.0	0.413	--	--	--	--	--	--	--	--	--	--
THPA	--	--	9.4	0.149	6.4	<0.001	--	--	6.3	0.005	14.0	0.001	5.0	0.002
IMCA	4.1	0.001	26.0	0.412	5.0	<0.001	4.8	0.015	8.9	0.007	8.0	<0.001	3.6	0.001
4-OH-IMCA	--	--	1.4	0.022	1.8	<0.001	6.4	0.020	5.1	0.004	--	--	0.8	<0.001
SAT-IMCA	--	--	--	--	--	--	3.8	0.012	3.8	0.003	--	--	--	--
Δ^1-TPA	--	--	--	--	--	--	--	--	--	--	2.0	<0.001	--	--
Unknown (LI-1 and LI-2, or TM-1 and TM-2)	--	--	--	--	--	--	--	--	8.9	0.007	6.0	<0.001	--	--
Aqueous extract (polar)	7.5	0.002	6.6	0.105			53.2	0.166	48.1	0.038	30.0	0.003		
Flumiclorac pentyl			0.2	0.003			--	--	--	--				
THPA			0.3	0.004			--	--	--	--				
IMCA			--	--			1.6	0.005	0.8	<0.001				
Unknowns (GI-1, GI-2, and GI-3 or KI-1, KI-2, and KI-3)			1.0	0.016			8.3	0.026	--	--				
Precipitated solids			*4.8*	0.076					*36.7*	0.029				
3N HCl hydrolysate			*2.6*	0.041										
Organic fraction [2]			2.0	0.031										
Nonextractable	45.3	0.012	18.9	0.300	0.0	0.0	5.1	0.016	6.3	0.005	30.0	0.003	41.5 (27.8) [3]	*0.015* (0.010)
Protease hydrolysate/organic phase	33.6	0.009	*5.7*	0.090			*0.6*	0.002	*1.3*	0.001			14.1	*0.005*
THPA	--	--	0.5	0.008			*0.3*	<0.001	0.1	<0.001			--	--
IMCA	--	--	0.2	0.004			--	--	0.1	<0.001			--	--
Unknowns (GI-4, GI-5, and GI-6, or LI-3, or polar skin fraction)	--	--	1.9	0.029			--	--	0.1	<0.001			*9.9*	*0.004*

TABLE C.2.2. Distribution of the Parent and the Metabolites in Laying Hen Matrices Following Dosing with [THP-1,2-^{14}C]Flumiclorac Pentyl. [1]

Metabolite Fraction	Egg Yolk, Day 5		Gizzard		Fat		Kidney		Liver		Muscle, thigh		Skin	
	TRR = 0.027 ppm		TRR = 1.586 ppm		TRR = 0.008 ppm		TRR = 0.312 ppm		TRR = 0.079 ppm		TRR = 0.010 ppm		TRR = 0.036 ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Nonextractable	not reported		*0.3*	0.004			not reported		not reported				Not reported	

[1] Shading indicates that the extraction/hydrolysis step or analysis was not conducted for that matrix/sample; *italicized* values were calculated by the study reviewer. The %TRR was normalized to the sum of extractable and nonextractable residues for gizzard, kidney, liver and muscle.
[2] HPLC analysis identified flumiclorac pentyl and IMCA (no quantitative data), confirming the precipitated solids contained the same residues as detected in the polar extract.
[3] The nonextractable residues (equivalent to 27.8% TRR) of a second skin extraction were reported by the petitioner, because nonextractable residues of the first sample extraction were not subjected to protease hydrolysis.

TABLE C.2.3. Summary of Characterization and Identification of Radioactive Residues in Laying Hen Matrices Following Dosing with [THP-1,2-^{14}C]Flumiclorac Pentyl at ~10 ppm.

Compound	Egg Yolk, Day 5		Gizzard		Fat		Kidney		Liver		Muscle, thigh		Skin	
	TRR = 0.027 ppm		TRR = 1.586 ppm		TRR = 0.008 ppm		TRR = 0.312 ppm		TRR = 0.079 ppm		TRR = 0.010 ppm		TRR = 0.036 ppm	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
Flumiclorac pentyl	--	--	26.2	0.416	--	--	--	--	--	--	--	--	--	--
THPA	--	--	10.2	0.161	6.4	<0.001	0.3	<0.001	6.4	0.005	14.0	0.001	5.0	0.002
IMCA	4.1	0.001	26.2	0.416	5.0	<0.001	6.4	0.020	9.8	<0.008	8.0	<0.001	3.6	0.001
4-OH-IMCA	--	--	1.4	0.022	1.8	<0.001	6.4	0.020	5.1	0.004	--	--	0.8	<0.001
SAT-IMCA	--	--	--	--	--	--	3.8	0.012	3.8	0.003	--	--	--	--
Δ^1-TPA	–	–	–	–	–	–	–	–	–	–	2.0	<0.001	--	--
Unknowns	--	--	2.9	0.045	--	--	8.3	0.026	9.0	0.007	6.0	<0.001	--	--
Aqueous extract	7.5	0.002	--	--	--	--	--	--	--	--	30.0	0.003	--	--
Protease hydrolysate	33.6	0.009	--	--	--	--	--	--	--	--	--	--	14.1	0.005
Precipitated solids	--	--	4.8 [1]	0.076	--	--	--	--	36.7	0.029	--	--	--	--
Total identified	4.1	0.001	64.0	1.015	13.2	0.001	16.9	<0.053	25.1	<0.020	24.0	<0.003	9.4	0.003
Total characterized	41.1	0.011	7.7	0.121	--	--	8.3	0.026	45.7	0.036	30.0	0.003	14.1	0.005
Total extractable	77.6	0.021	86.8	1.376	82.3	0.007	95.5	0.298	95.0	0.075	70.0	0.007	84.4	0.030
Unextractable (PES)[2]	NR	NR	0.3	0.004	0.0	0.0	NR	NR	NR	NR	30.0	0.003	NR	NR

TABLE C.2.3. Summary of Characterization and Identification of Radioactive Residues in Laying Hen Matrices Following Dosing with [THP-1,2-^{14}C]Flumiclorac Pentyl at ~10 ppm.

Compound	Egg Yolk, Day 5		Gizzard		Fat		Kidney		Liver		Muscle, thigh		Skin	
	TRR = 0.027 ppm		TRR = 1.586 ppm		TRR = 0.008 ppm		TRR = 0.312 ppm		TRR = 0.079 ppm		TRR = 0.010 ppm		TRR = 0.036 ppm	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
Accountability[3]	89.3		100		82.3		100		100		100		111.8	

[1] Solids precipitated during the preparation of the aqueous extract for analysis were subjected to acid hydrolysis; HPLC analysis identified flumiclorac pentyl and IMCA.
[2] Residues remaining after exhaustive extractions; not reported (NR) following protease hydrolysis of nonextractable residues of egg yolk, gizzards, kidney, liver, and skin.
[3] Accountability was 100% because extractable and nonextractable residues were normalized for gizzards, kidney, liver, and muscle; actual recoveries reported by the petitioner were ~91-109% for normalized matrices and as presented in the table for egg yolk, fat, and skin.

C.3. Proposed Metabolic Profile

FIGURE C.3.1. Proposed Metabolic Profile of Flumiclorac Pentyl in Laying Hens.

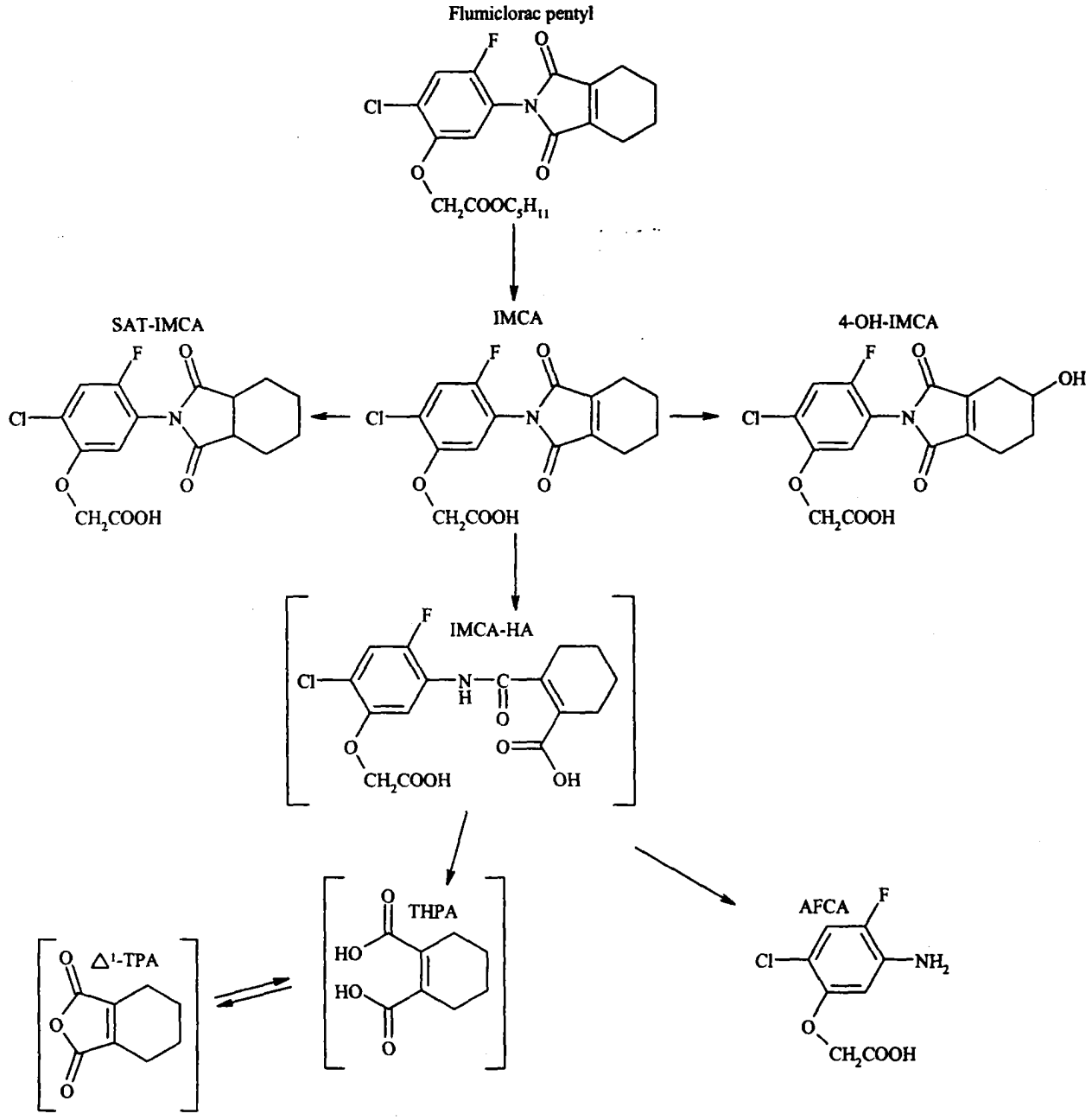


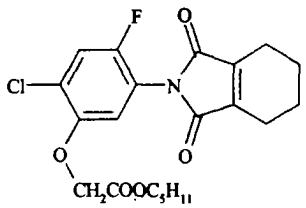
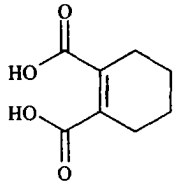
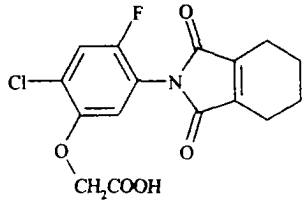
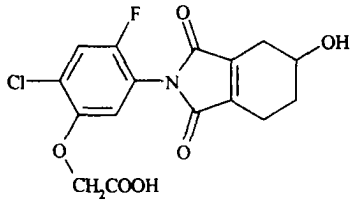
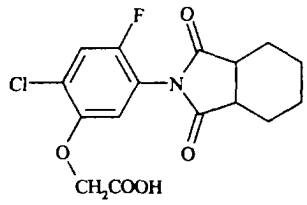
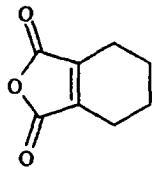
TABLE C.3.1. Identification of Compounds from Metabolism Study		
Common name/code Figure C.3.1 ID No.	Chemical name	Chemical structure
Flumiclorac pentyl; S-23031	Acetic acid, {2-chloro-4-fluoro-5-(1,3,4,5,6,7-hexahydro-1,3-dioxo-2H-isoindol-2-yl)phenoxy}-,pentyl ester or (2-chloro-4-fluoro-5-(1,3,4,5,6,7-hexahydro-1,3-dioxo-2H-isoindol-2-yl)phenoxy)acetic acid, pentyl ester	
THPA	3,4,5,6-tetrahydrophthalic acid	
IMCA	2-chloro-4-fluoro-5-(3,4,5,6-tetrahydrophthalimido)phenoxyacetic acid	
4-OH-IMCA	2-chloro-4-fluoro-5-(4-hydroxy-3,4,5,6-tetrahydrophthalimido)phenoxyacetate	
SAT-IMCA	2-chloro-4-fluoro-5-(cyclohexane-1,2-dicarboximido)phenoxyacetate	

TABLE C.3.1. Identification of Compounds from Metabolism Study		
Common name/code Figure C.3.1 ID No.	Chemical name	Chemical structure
Δ^1-TPA	3,4,5,6-tetrahydrophthalic anhydride	

D. CONCLUSION

Total radioactive residues, determined by the analytical laboratory, were 0.002 ppm in egg whites (Day 5), 0.027 ppm in egg yolk (Day 5), 1.586 ppm in gizzards, 0.312 ppm in kidney, 0.079 ppm in liver, 0.009 ppm in thigh muscle, 0.008 ppm in fat, and 0.036 ppm in skin from hens dosed orally with [THP-1,2-^{14}C]flumiclorac pentyl at ~10 ppm in the diet for 7 consecutive days. A large portion of the administered dose was excreted, accounting for 85% of the administered dose.

The majority of the radioactivity (~44-95% TRR) in egg yolk, gizzards, fat, kidney, liver, thigh muscle, and skin was extractable (using acidic ACN, ACN, and/or methylene chloride). Protease hydrolysis released additional radioactivity (0.6-33.6% TRR, 0.001-0.090 ppm) from the nonextractable solids of egg yolk, gizzard, kidney, liver, and skin. Nonextractable residues remaining after solvent extraction and/or enzyme hydrolysis accounted for <10% TRR or <0.02 ppm in all matrices. Extractable and nonextractable residues were normalized for gizzard, kidney, liver, and muscle. Egg white and breast muscle samples were not extracted because of low radioactivity.

Approximately 4-13% of the TRR in egg yolk, fat, and skin, 17-25% TRR in kidney, liver, and thigh muscle, and 64% TRR in gizzard were identified; all metabolites were identified at levels ≤0.01 ppm except in gizzards and kidney. The parent was only identified (as a major residue) in gizzard accounting for 26.2% TRR (0.416 ppm). IMCA was also identified as a major residue in gizzards; IMCA was also identified in all the other matrices (egg yolk, fat, kidney, liver, muscle, and skin) at lower levels (<10%TRR). The metabolite THPA was identified as a significant residue in gizzards and muscle, and at low levels in fat, kidney, liver, and skin. 4-OH-IMCA was a minor metabolite identified in gizzards, fat, kidney, liver, and skin; SAT-IMCA was identified as a minor metabolite in kidney and liver; and Δ^1-TPA was detected at trace levels in muscle only. The metabolites THPA and IMCA were also identified in the protease hydrolysates of nonextractable residues of gizzards, kidney, and liver. Additional residues, each present at <10% TRR or <0.01 ppm were characterized as polar or other unknowns in gizzards, kidney, liver, muscle, and skin. Flumiclorac pentyl and IMCA were identified in the gizzard acid hydrolysate of solids precipitated during the concentration of the aqueous extract.

The petitioner proposed that flumiclorac pentyl is rapidly metabolized and excreted in hens. Based on the phenyl- and THP-labeled hen metabolism studies the proposed metabolic reactions in hens involve: (i) initial hydrolysis of the pentyl ester of flumiclorac pentyl to form IMCA; (ii) hydrolysis of the imide and subsequent formed amide; (iii) hydroxylation of the cyclohexane ring; and (iv) olefin reduction.

E. REFERENCES

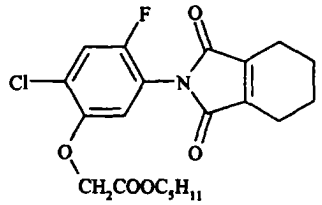
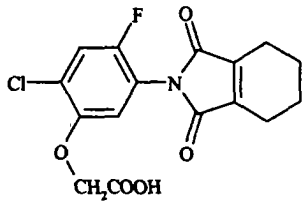
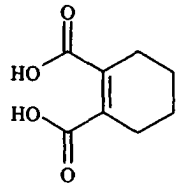
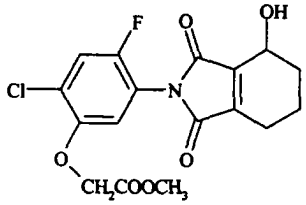
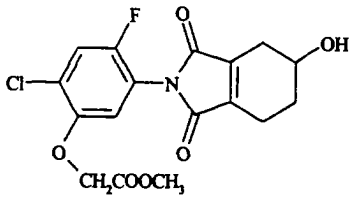
DP Barcode: D174474
Subject: PP#2G4078: New Chemical EUP: V-23031, Flumiclorac-Pentyl on Field Corn and Soybeans. Evaluation of Analytical Methods and of Residue Data.
From: J. Garbus
To: J. Miller and A. Kocialski
Dated: 7/28/92
MRIDs: 42187400-42187405, 42169849-42169859, and 42187407-42187408.

F. DOCUMENT TRACKING

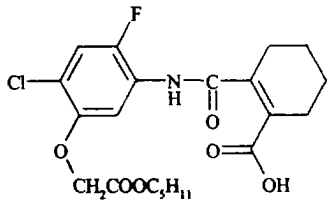
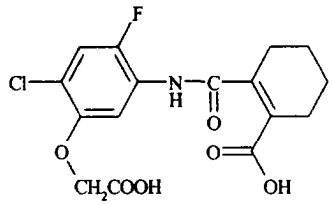
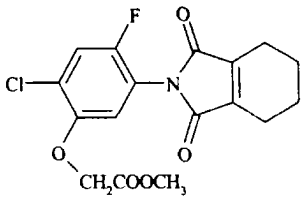
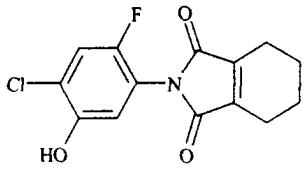
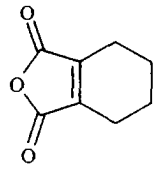
RDI: Catherine Eiden (24-JUN-2005)
Petition Number(s): PP#3F6767
DP Barcode(s): D308674
PC Code: 128724

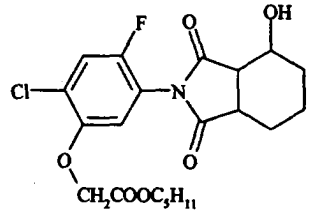
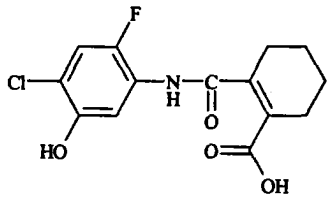
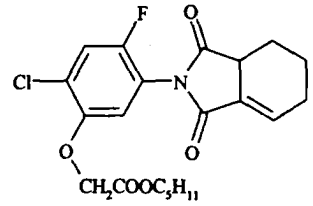
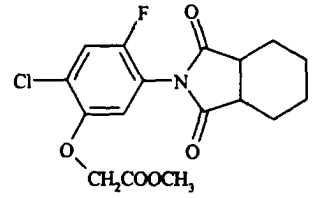
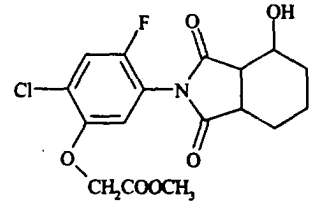
Template Version September 2003

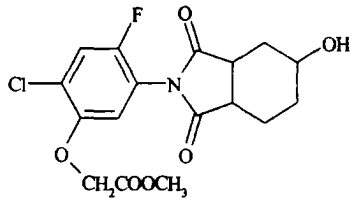
APPENDIX I. Chemical Names and Structures of Reference Standards Used in Hen Metabolism Study.

Common name/code Figure C.3.1 ID No.	Chemical name	Chemical structure
Flumiclorac pentyl; S-23031	acetic acid, {2-chloro-4-fluoro-5-(1,3,4,5,6,7-hexahydro-1,3-dioxo-2H-isoindol-2-yl)phenoxy}-,pentyl ester or (2-chloro-4-fluoro-5-(1,3,4,5,6,7-hexahydro-1,3-dioxo-2H-isoindol-2-yl)phenoxy)acetic acid, pentyl ester	
IMCA	2-chloro-4-fluoro-5-(3,4,5,6-tetrahydrophthalimido)phenoxyacetic acid	
THPA	3,4,5,6-tetrahydrophthalic acid	
3-OH-IMCA-ME	methyl 2-chloro-4-fluoro-5-(3-hydroxy-3,4,5,6-tetrahydrophthalimido)phenoxyacetate	
4-OH-IMCA-ME	methyl 2-chloro-4-fluoro-5-(4-hydroxy-3,4,5,6-tetrahydrophthalimido)phenoxyacetate	

APPENDIX I. Chemical Names and Structures of Reference Standards Used in Hen Metabolism Study.

Common name/code Figure C.3.1 ID No.	Chemical name	Chemical structure
031-HA	N-(4-chloro-2-fluoro-5-pentoxycarbonylmethoxyphenyl)-3,4,5,6-tetrahydrophthalamic acid	
IMCA-HA	N-(5-carboxymethoxy-4-chloro-2-fluorophenyl)-3,4,5,6-tetrahydrophthalamic acid	
IMCA-ME	methyl 2-chloro-4-fluoro-5-(3,4,5,6-tetrahydrophthalimido)phenoxyacetate	
IMFP (IMF in goats)	N-(4-chloro-2-fluoro-5-hydroxyphenyl)-3,4,5,6-tetrahydrophthalimide	
Δ^1-TPA	3,4,5,6-tetrahydrophthalic anhydride	

APPENDIX I. Chemical Names and Structures of Reference Standards Used in Hen Metabolism Study.		
Common name/code Figure C.3.1 ID No.	Chemical name	Chemical structure
031-SAT-3-OH	pentyl 2-chloro-4-fluoro-5-(3-hydroxy-1,2-cyclohexanedicarboximido	
IMFP-HA	N-(4-chloro-2-fluoro-5-hydroxyphenyl)-3,4,5,6-tetrahydrophthalamic acid	
031-Δ^2-ISO	pentyl 2-chloro-4-fluoro-5-(1,4,5,6-tetrahydrophthalimido) phenoxyacetate	
SAT-IMCA-ME	methyl-2-chloro-4-fluoro-5-(cyclohexane-1,2-dicarboximido)phenoxyacetate	
SAT-3-OH-IMCA-ME	methyl 2-chloro-4-fluoro-5-(3-hydroxy-1,2-cyclohexanedicarboximido)phenoxyacetate	

APPENDIX I. Chemical Names and Structures of Reference Standards Used in Hen Metabolism Study.		
Common name/code Figure C.3.1 ID No.	Chemical name	Chemical structure
SAT-4-OH-IMCA-ME	methyl 2-chloro-4-fluoro-5-(4-hydroxy-1,2,-cyclohexanedicarboximido)phenoxyacetate	

Flumiclorac pentyl/PC Code 128724/Valent U.S.A. Corporation
OPPTS 860.1300
Nature of the Residues in Livestock - Hen

Primary Evaluator William H. Donovan
William H. Donovan, Ph.D.
Chemist
HED/RRB3
Date: 6/24/05

Approved by for
Catherine Eiden
Branch Chief
HED/RRB3
Date: 6/24/05

This DER was originally prepared under contract by Dynamac Corporation (20440 Century Boulevard, Suite 100; Germantown, MD 20874; submitted 01/26/2005). The DER has been reviewed by the Health Effects Division (HED) and revised to reflect current Office of Pesticide Programs (OPP) policies.

STUDY REPORT:

46082805 Huhtanen, K. (1992) A Study to Determine the Nature of the Residue in Poultry and Egg From Chickens Dosed with [Phenyl-^{14}C]S-23031 Analytical Phase of Study. Laboratory Project ID 90-0497, Document No. 3789-90-00497-EF-002. Unpublished study prepared by Ricerca, Inc (Painesville, OH) and submitted by Valent U.S.A. Corp. 153 p.

EXECUTIVE SUMMARY:

Valent U.S.A. Corporation has submitted a study investigating the metabolism of [phenyl-U-^{14}C]flumiclorac pentyl in laying hens. Information concerning the in-life phase of this study was previously submitted in MRID 42169853 and reviewed (DP Barcode D174474, 7/28/92, J. Garbus) in conjunction with PP#2G4078. The current submission reports the characterization and identification of radioactive residues in hen eggs and tissues.

The test substance, [phenyl-U-^{14}C]flumiclorac pentyl, was administered orally to ten hens at 9.9 ppm in the diet. The hens were dosed once per day for seven consecutive days. During the study period, eggs were collected twice daily, separated into whites and yolks, and composited each day. Tissues (gizzard, kidney, liver, muscle, skin, and fat) were collected at hen sacrifice. The in-life phase of the study was conducted by ABC Laboratories (Columbia, MO), and the analytical phase was conducted by Ricerca, Inc. (Painesville, OH).

Total radioactive residues, determined by the analytical laboratory, were <0.001 ppm in egg whites (Day 4), 0.006 ppm in fat, 0.009 ppm in breast muscle, 0.015 ppm in egg yolk (Day 5), 0.026 ppm in skin, 0.056 ppm in liver, 0.223 ppm in kidney, and 1.634 ppm in gizzards from hens dosed with [phenyl-U-^{14}C]flumiclorac pentyl. Radioactivity was low in most hen matrices, with the highest levels in gizzards and kidney which are poultry matrices not typically regulated. The study reported that 78% of the administered dose was excreted.

Because of low radioactivity, no residue characterization was conducted on egg white samples; the remainder of poultry matrices were subjected to residue extraction and characterization. The majority of the radioactivity (~73-92% TRR) in egg yolk, gizzards, fat, kidney, liver, breast muscle, and skin was extractable with organic solvents. Protease hydrolysis released additional radioactivity (2.7-14.1% TRR) from the nonextractable solids of the above-listed matrices. Nonextractable residues remaining after solvent extraction and/or enzyme hydrolysis accounted for <10% TRR in all matrices. Information pertaining to the collection, extraction and analysis dates was not provided, and sample storage stability conditions and durations were not addressed.

The parent was identified as a major component in gizzard (29.1% TRR) but was a minor component in muscle and skin (1.1-9.1% TRR). Several other metabolites were identified including: AFCA, IMCA, 4-OH-IMCA, SAT-IMCA, and SAT-4-OH-IMCA; the chemical names and structures of these metabolites are listed in Table C.3.1. The identified metabolites were detected at low absolute levels (<0.001-0.008 ppm) in egg yolk, fat, liver, breast muscle, and skin. Some metabolites were present at up to 0.477 ppm in gizzards and 0.026 ppm in kidney. The metabolite IMCA was detected in all poultry matrices analyzed.

The petitioner proposed that flumiclorac pentyl is rapidly metabolized and excreted in hens. Based on the phenyl- and THP-labeled hen metabolism studies, the proposed metabolic reactions in hens involve: (i) initial hydrolysis of the pentyl ester of flumiclorac pentyl to form IMCA; (ii) hydrolysis of the imide and subsequent formed amide; (iii) hydroxylation of the cyclohexane ring; and (iv) olefin reduction.

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the hen metabolism data are classified as scientifically unacceptable because information pertaining to sample storage conditions and intervals was not provided. The study may be upgraded if the petitioner submits the dates of hen sacrifice as well as the dates of initial and final analyses. Storage stability data are not normally required for samples analyzed within 4 to 6 months of collection, provided evidence is given that attempts were made to limit degradation of residues by appropriate storage of matrices and extracts during the analytical phase of the study. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document DP Barcode D308674.

COMPLIANCE:

Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided. No deviations from regulatory requirements were reported which would impact the validity of the study.

A. BACKGROUND INFORMATION

Flumiclorac pentyl is an N-phenylphthalimide derivative herbicide used for the control of broadleaf weeds. Its mode of action is through the accumulation of porphyrins in susceptible plants; the photosensitizing action of accumulated porphyrins may cause membrane lipid peroxidation which leads to irreversible damage of membrane function and structure in the plant. Flumiclorac pentyl is registered for postemergence application to field corn and soybeans; registration for use on cotton as a defoliant is pending. The PC code and nomenclature of flumiclorac pentyl are listed below in Table 1. The physicochemical properties of flumiclorac pentyl are listed in Table 2.

TABLE 1. Flumiclorac Pentyl Nomenclature

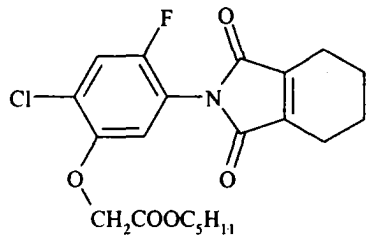
Chemical Structure	
Common name	Flumiclorac pentyl
Company experimental name	S-23031 or V-23031
Molecular Formula	$C_{21}H_{23}ClFNO_5$
Molecular Weight	423.9
IUPAC name	Pentyl (2-chloro-5 (cyclohex-1-ene-1,2-dicarboximido)-4-fluorophenoxy) acetate
CAS name	Pentyl[2-chloro-4-fluoro-5-(1,3,4,5,6,7- hexahydro-1,3-dioxo-2H-isoindol-2-yl)phenoxy]acetate
CAS #	87546-18-7
PC Code	128724

TABLE 2. Physicochemical Properties of Flumiclorac Pentyl

Parameter	Value	Reference
Melting point	88.9-90.1 °C	PP#2G4078; D174474, 7/28/92, J. Garbus
pH	6.03 at 25 °C	
Density, bulk density, or specific gravity	1.3316 g/mL at 20 °C	
Water solubility	0.189 mg/L at 25 °C	
Solvent solubility	g/100 mL at 25 °C: hexane 0.328 n-octanol 1.60 methanol 4.78 Solvesso 150 27.1 acetonitrile 58.9 acetone 59.0 tetrahydrofuran 69.7 N-methyl 2-pyrrolidinone 134.0 methylene chloride 288.0	

TABLE 2. Physicochemical Properties of Flumiclorac Pentyl		
Parameter	Value	Reference
Vapor pressure	$<1 \times 10^{-7}$ mm Hg at 22.4 °C	
Dissociation constant, pK_a	No dissociation at pH ≤7; flumiclorac pentyl decomposes at pH ≥9.	
Octanol/water partition coefficient	Log P_{OW} = 4.99 at 19.7-21.0 °C	
UV/visible absorption spectrum	Not available	

B. EXPERIMENTAL DESIGN

Information concerning the in-life phase of this study, including TRR determinations, was previously submitted in MRID 42169853 and reviewed (DP Barcode D174474, 7/28/92, J. Garbus) in conjunction with PP#2G4078.

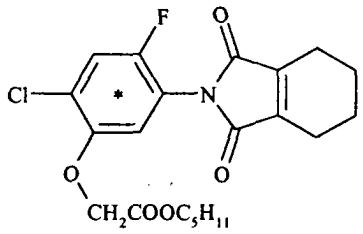
B.1. Livestock

TABLE B.1.1. General Test Animal Information.					
Species	Breed	Age	Weight at study initiation (kg)	Health Status	Description of housing/holding area
Laying hens	Leghorn	Not available from this submission			The biological phase of the study was performed at ABC Laboratories (Columbia, MO).

TABLE B.1.2. Test Animal Dietary Regime.				
Composition of Diet	Feed consumption (average kg/day)	Water	Acclimation period	Predosing
Not available from this submission.				

TABLE B.1.3. Test Animal Dosing Regime			
Treatment Type	Feeding Level (ppm test material in food)	Vehicle	Timing/Duration
Oral	9.9 ppm	Gelatin capsule	Once per day for seven consecutive days.

B.2. Test Materials

TABLE B.2.1. Test Material Characteristics.	
Chemical structure	
Radiolabel position	Uniformly labeled in the phenyl ring
Lot No.	C-90-064 (isotopically diluted)
Purity	>97%
Specific activity of isotopically diluted test material	95,100 dpm/µg

B.3. Sampling Information

TABLE B.3.1. Sample Collection Information			
Eggs collected	Urine, feces and cage wash collected	Interval from last dose to sacrifice	Tissues harvested and analyzed
Eggs were collected twice daily, separated into egg whites and yolks, and composited daily.	Excreta was collected daily.	within 4 hours	Gizzard, fat, kidney, liver, breast muscle, thigh muscle, and skin.

B.4. Identification/Characterization of Residues

B.4.1. Sample Handling and Preparation

Daily egg white and yolk samples were composited. Information pertaining to the handling of samples collected at the in-life facility was not available from this submission. However, it was reported that frozen egg and tissue samples were received at Ricerca, Inc. (Painsville, OH) for extraction and characterization/identification of residues. Because of low radioactivity, residues in egg white samples were not extracted.

Egg yolk (Day 5) samples were sequentially extracted with acetonitrile (ACN):1 M HCl (4:1, v:v), ACN:methylene chloride (1:1, v:v), and methylene chloride. Individual extracts were isolated by vacuum filtration and combined. The combined extract was diluted with 6% sodium chloride and re-extracted with methylene chloride. The phases were allowed to separate, and the aqueous phase was extracted again with methylene chloride. The combined methylene chloride phases were concentrated, and the oily residues were redissolved in hexane:methylene chloride (1:1, v:v) for gel permeation cleanup; residues were eluted with hexane/methylene chloride, collecting 6-minute fractions. Selected fractions were concentrated and diluted with ACN for HPLC analysis. HPLC fractions were collected, and selected fractions were reserved for TLC analysis.

The nonextractable residues of egg yolk, which remained after the initial solvent extractions, were subjected to protease hydrolysis (in pH 7.5 0.1 M Tris buffer at 37 °C for 16 hours) and then centrifuged. The supernatant was acidified to pH 1 with 2 M HCl and cleaned up through a series of three C-18 cartridges; residues were eluted with ACN and then methanol. The combined ACN and methanol eluates were concentrated to an oily residue and then sonicated with ACN:water (1:1, v:v) for HPLC analysis. Five-minute HPLC fractions were collected for subsequent TLC analysis of selected fractions.

Tissue (gizzards, kidney, liver, or muscle) samples were extracted (3x) with 2% formic acid:ACN (7:3, v:v) and then centrifuged to precipitate solids. The first two filtrates were combined (the third extract did not contain significant radioactivity), concentrated, and the remaining aqueous solution was acidified to pH 2 with 3 M HCl for partitioning (2x) with diethyl ether. The organic phases were combined, concentrated, and the residues redissolved in water:ACN (3:2, v:v) for HPLC analysis. The aqueous phase was concentrated, frozen, and lyophilized; resulting solids were extracted with methanol by sonification. The methanol extract was concentrated and residues redissolved in 1% acetic acid:ACN (3:2, v:v) for HPLC analysis. Five minute fractions of the HPLC eluent of the organic and aqueous phase analyses were collected and selected fractions were reserved for TLC analysis.

The nonextractable residues in hen tissues, which remained after initial extraction, were subjected to protease hydrolysis (in pH 7.5 0.1 M Tris buffer overnight at 37 °C) and then centrifuged. The supernatant was acidified to pH 2 with 3 M HCl and partitioned with ethyl acetate. The ethyl acetate phase was concentrated to near dryness, and residues were redissolved in acetic acid:ACN (3:2, v:v) for HPLC analysis. HPLC fractions were collected for subsequent TLC analysis of selected fractions.

Fat and skin samples were extracted (3x) with ACN:0.1 M HCl (9:1, v:v) and then centrifuged. The respective combined extracts were partitioned (2x) with hexane:methylene chloride (2:1, v:v); a three-phase separation resulted. The ACN:aqueous acid phase was concentrated, the residue solubilized in methylene chloride, and concentrated to an oily residue. Fat residues were redissolved in ACN:water (1:1, v:v). Following centrifugation, the supernatant (ACN/water) was reserved for HPLC analysis. Skin residues were redissolved in methylene chloride, concentrated again, and redissolved in ACN:water (1:1, v:v); the precipitated oils were separated by centrifugation and extracted again with additional ACN/water. The resulting skin oils and extracts were combined for HPLC analysis. HPLC fractions were collected for subsequent TLC analysis of selected fractions.

Nonextractable residues remaining in the skin sample following solvent extraction were subjected to protease hydrolysis as described above for egg yolk.

B.4.2. Analytical Methodology

Total radioactive residues, determined by ABC Laboratories, were previously reported (DP Barcode D174474, 7/28/92, J. Garbus). For residue characterization, TRR were re-determined at

the analytical laboratory (Ricerca, Painesville, OH) using combustion/LSC. Extracts and hydrolysates were radioassayed by LSC, and nonextractable residues were radioassayed by combustion/LSC. The minimum quantifiable limit for tissues was dependent on the background levels and based on the normal background levels (10-30 dpm) was reported as 0.001 ppm.

The petitioner reported normalized results for the extractable and nonextractable residues in tissues with higher levels of radioactivity (i.e., gizzard, kidney, liver, and breast muscle). But because lower recoveries were obtained from samples with higher lipid content, residue values were not normalized for egg yolk, fat and skin samples.

Extracts and/or hydrolysates were analyzed by HPLC using a C18 column, UV detection, radiodetection, and a gradient mobile phase of 1% acetic acid, ACN and/or methanol. HPLC fractions of individual metabolites with low radioactivity were collected for quantitative analysis, using combined HPLC and TLC. TLC analyses of isolated fractions were conducted using silica gel (K6F or F-254) plates and a solvent system of toluene:ethyl acetate:acetic acid (5:7:1, v:v:v). Metabolites were identified by co-chromatography or comparison of retention times with those of the reference standards (see Appendix 1). Non-labeled standards were detected using UV light and radioactive standards or metabolites were detected with a linear analyzer imaging scanner.

Identifications of residues present at ≥0.01 ppm were confirmed by GC/MS analysis of the respective isolated component from excreta with standards or the methylated standard derivative. LC/MS (positive and negative ion) was used to analyze residues isolated through a C8 analytical column.

Residues present at <0.01 ppm were quantitated by the radioactivity found at the appropriate HPLC and TLC retention time; calculations based on HPLC and TLC results were normalized. The petitioner noted that TLC analyses of HPLC fractions contained numerous minor metabolites not seen with HPLC analysis.

The petitioner conducted radiovalidation of the residue analytical method, entitled, "Residue Method for the Determination of Residues of S-23031 in Chicken Eggs, Muscle, and Tissue, and Goat Milk, Muscle and Tissue" (Ricerca number 3789-92-0194-MD-001) using egg yolk, gizzard, and breast muscle samples from [phenyl-^{14}C]flumiclorac pentyl treated hens.

C. RESULTS AND DISCUSSION

Total radioactive residues in hen eggs and tissues are reported in Table C.2.1. TRR, determined by the analytical laboratory, were <0.001 ppm in egg whites (Day 4), 0.015 ppm in egg yolk (Day 5), 1.634 ppm in gizzards, 0.223 ppm in kidney, 0.056 ppm in liver, 0.009 ppm in breast muscle, 0.006 ppm in fat, and 0.026 ppm in skin from hens dosed orally with [phenyl-U-^{14}C]flumiclorac pentyl at 9.9 ppm in the diet for 7 consecutive days. Radioactivity was low in most hen matrices, with the highest levels in gizzards and kidney (not typically matrices of concern for poultry). A large portion of the administered dose was excreted, accounting for 78% of the administered dose.

The distribution of the radioactivity in hen matrices is presented in Table C.2.2. Because of low radioactivity, egg white samples were not extracted. The majority of the radioactivity (~73-92% TRR) in egg yolk, gizzards, fat, kidney, liver, breast muscle, and skin was extractable (using acidic ACN, ACN, and/or methylene chloride); we note that the petitioner did not report the %TRR or ppm levels in the individual fractions through the extraction/cleanup steps, and only reported the total extractable residues. Protease hydrolysis released additional radioactivity (2.7-14.1% TRR) from the nonextractable solids of egg yolk, gizzard, kidney, liver, and skin. Nonextractable residues remaining after solvent extraction and/or enzyme hydrolysis accounted for <10% TRR or <0.01 ppm in all matrices; actual nonextractable residues were not reported following protease hydrolysis. Extractable and nonextractable residues were normalized for gizzard, kidney, liver, and muscle therefore accountabilities were 100%, but actual recoveries were 92-118% in all matrices. Residues were characterized primarily by HPLC and TLC analysis, using GC/MS and LC/MS analyses of isolated excreta residues for confirmation of metabolite identifications. These methods successfully identified the predominant residues in hen matrices.

The characterization/identification of residues in hen matrices is summarized in Table C.2.3. Approximately 4-13% of the TRR in egg yolk, fat, and skin, 27-38% TRR in kidney, liver, and breast muscle, and 70% TRR in gizzard were identified. The parent was identified as a major residue component in gizzard at 29.1% TRR but was detected at low levels in muscle and skin at 1.1-9.1% TRR (≤0.001 ppm). IMCA was also identified as a major residue in gizzard accounting for 29.2% TRR. IMCA was also identified in kidney, liver, muscle, and skin at fairly significant levels (10.2-18.2% TRR), but was detected in egg yolk and fat at low levels (4.0-4.8% TRR). The metabolite AFCA was identified in gizzards at 11.8% TRR, and in kidney and liver at 2.0-9.8% TRR. The metabolite 4-OH-IMCA was identified in kidney at 11.7% TRR; it was also identified in fat and liver at low levels (1.5-3.6% TRR). The metabolite SAT-IMCA was identified as a minor residue in kidney and liver (4.9-7.1% TRR). The metabolites AFCA and IMCA were also identified in the protease hydrolysates of nonextractable residues of gizzards, kidney, liver, and skin (each <0.02 ppm). Additional residues, each present at <10% TRR or <0.01 ppm were characterized as polar or other unknowns in gizzards, kidney, liver, muscle, and skin. Solids precipitated from the concentration of the gizzard and liver aqueous extract accounted for 7.6% TRR and 33.9% TRR, respectively. Flumiclorac pentyl and IMCA were identified (each <0.01 ppm) in the gizzard acid hydrolysate of the precipitated solids.

Radiovalidation of the residue analytical method, entitled, "Residue Method for the Determination of Residues of S-23031 in Chicken Eggs, Muscle, and Tissue, and Goat Milk, Muscle and Tissue" (Ricerca number 3789-92-0194-MD-001) using egg yolk, gizzard, and breast muscle samples from [phenyl-^{14}C]flumiclorac pentyl treated hens demonstrated that flumiclorac pentyl residues were below the limit of detection (0.02 ppm for eggs and 0.01 ppm for muscle) of the residue method in egg yolk and muscle. Residues of flumiclorac pentyl in gizzard were 0.159 ppm using the residue method and 0.472 ppm using the ^{14}C-analysis method. The petitioner stated that there was no apparent reason for the lower quantitation of residues using the residue method, but that since there is no expectation of the transmittal of detectable levels of

flumiclorac pentyl to edible tissues of poultry from feed crops, the discrepancy between the methods was not further pursued.

C.1. Storage Stability

Samples of hen matrices were placed in frozen storage after collection. The dates of extraction and analysis were not provided for any of the samples. The petitioner did not address storage intervals, and representative chromatograms did not include analysis dates. The collection, extraction and analysis dates of each sample must be submitted to determine if storage stability data are required to support the storage conditions and duration of the samples from the hen metabolism study.

TABLE C.1. Summary of Storage Conditions

Matrix	Storage Temp. (°C)	Actual Storage Duration	Interval of Demonstrated Storage Stability
Egg yolk, gizzard, fat, kidney, liver, muscle, and skin	-20 °C	Extraction and analysis dates were not provided	None

C.2. Identification, Characterization, and Distribution of Residues

TABLE C.2.1. Total Radioactive Residues (TRR) in Eggs, Tissue and Excreta

Matrix	Collection Timing	[Phenyl U-^{14}C]Flumiclorac Pentyl		
		Ricerca, Inc. [1]	ABC Laboratories (in-life study)[2]	
		ppm	ppm	% Administered Dose
Excreta	Study Day 3	8.868	10.59	77.7
Egg, yolk	Study Day 5	0.015	0.008	0.012
Egg, white	Study Day 4	<0.001	<MQL [3]	--
Gizzard	Sacrifice	1.634	1.71	0.493
Kidney	Sacrifice	0.223	0.201	0.032
Liver	Sacrifice	0.056	0.055	0.02
Breast muscle	Sacrifice	0.009	0.011	0.008
Thigh muscle	Sacrifice	--	0.007	0.005
Fat	Sacrifice	0.006	0.011	0.003
Skin	Sacrifice	0.026	0.024	0.004
Ovary contents	Sacrifice	0.018	0.16	0.017
Intestinal contents	Sacrifice	--	3.31	0.661
Total				79.0

[1] Combustion/LSC determinations made by Ricerca (analytical laboratory) prior to extraction.
[2] Values determined at ABC Laboratories and originally presented under DP Barcode D174474, 7/28/92, J. Garbus; these values are presented herein for informational purposes.
[3] MQL = minimum quantifiable limit, which ranged 4-8 x 10^{-4} ppm.

TABLE C.2.2. Distribution of the Parent and the Metabolites in Laying Hen Matrices Following Dosing with [Phenyl-U-^{14}C]Flumiclorac Pentyl. [1]

Metabolite Fraction	Egg Yolk, Day 5		Gizzard		Fat		Kidney		Liver		Muscle, breast		Skin	
	TRR = 0.015 ppm		TRR = 1.634 ppm		TRR = 0.006 ppm		TRR = 0.223 ppm		TRR = 0.056 ppm		TRR = 0.011 ppm		TRR = 0.026 ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Organic extract (nonpolar)	79.6	0.012	74.8	1.222	88.5	0.005	45.3	0.101	48.2	0.027	54.5	0.006	83.3	0.022
Flumiclorac pentyl	--	--	28.1	0.459	--	--			–	–	9.1	0.001	1.1	<0.001
AFCA	–	--	10.5	0.172	--	--	7.2	0.016	1.6	<0.001	--	--	1.6	<0.001
IMCA	4.0	<0.001	27.6	0.451	4.8	<0.001	11.7	0.026	8.9	0.005	18.2	0.002	9.6	0.003
4-OH-IMCA	–	--	--	--	1.5	<0.001	11.7	0.026	3.6	0.002	--	--	--	–
SAT-IMCA	–	--	--	--	–	--	4.9	0.011	7.1	0.004	--	--	--	–
Unknown (LI-1 or SK-1)	–	--	--	--	–	--	--	--	1.8	0.001	--	--	1.5	<0.001
Aqueous extract (polar)	2.8	<0.001	9.1	0.149			47.1	0.105	42.9	0.024	18.2	0.002		
Flumiclorac pentyl	--	--	1.0	0.017			--	--	--	--				
AFCA	--	--	0.2	0.004			2.2	0.005	--	--				
IMCA	--	--	0.5	0.008			--	--	3.6	0.002				
Unknowns (GI-1 and GI-2, or KI-2)	--	--	0.3	0.005			4.5	0.010	--	--				
Precipitated solids	--	--	*7.6*	0.124					*33.9*	0.019				
3N HCl hydrolysate	--	--	*6.2*	0.102										
Organic fraction [2]	--	--	*3.7*	0.060										
Nonextractable	35.1	0.005	16.1	0.263	3.0	<0.001	8.9	0.017	8.9	0.005	27.3	0.003	19.6 (28.1 [3])	0.005 (0.007)
Protease hydrolysate/organic phase	14.1	0.002	*8.6*	0.141			*2.7*	0.006	*3.6*	0.002			12.6	0.003
AFCA	--	--	*1.1*	0.018			0.4	0.001	0.4	<0.001			--	--
IMCA	--	--	*1.1*	0.018			--	--	1.4	<0.001			0.6	<0.001
Unknowns (GI-3, GI-4)	--	--	*1.0*	0.017			--	--	--	--			--	--
Nonextractable	not reported		not reported				not reported		not reported				Not reported	

[1] Shading indicates that the extraction/hydrolysis step or analysis was not conducted for that matrix/sample; *italicized* values were calculated by the study reviewer. The %TRR was normalized to the sum of extractable and nonextractable residues for gizzard, kidney, liver and muscle.

[2] HPLC analysis identified flumiclorac pentyl (0.007 ppm) and IMCA (0.005 ppm), confirming the precipitated solids contained the same residues as detected in the polar extract.

[3] The nonextractable residues (equivalent to 28.1% TRR) of a second skin extraction were reported by the petitioner, because nonextractable residues of the first sample

extraction were not subjected to protease hydrolysis.

TABLE C.2.3. Summary of Characterization and Identification of Radioactive Residues in Laying Hen Matrices Following Dosing with [Phenyl-U-^{14}C]Flumiclorac Pentyl at 9.9 ppm.

Compound	Egg Yolk, Day 5		Gizzard		Fat		Kidney		Liver		Muscle, breast		Skin	
	TRR = 0.015 ppm		TRR = 1.634 ppm		TRR = 0.006 ppm		TRR = 0.223 ppm		TRR = 0.056 ppm		TRR = 0.011 ppm		TRR = 0.026 ppm	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
Flumiclorac pentyl	--	--	29.1	0.476	--	--	--	--	--	--	9.1	0.001	1.1	<0.001
AFCA	--	--	11.8	0.194	--	--	9.8	0.022	2.0	0.001	--	--	1.6	<0.001
IMCA	4.0	<0.001	29.2	0.477	4.8	<0.001	11.7	0.026	13.9	0.008	18.2	0.002	10.2	0.003
4-OH-IMCA	--	--	--	--	1.5	<0.001	11.7	0.026	3.6	0.002	--	--	--	--
SAT-IMCA	--	--	--	--	--	--	4.9	0.011	7.1	0.004	--	--	--	--
Unknowns	--	--	1.3	0.022	--	--	4.5	0.010	1.8	0.001	--	--	1.5	<0.001
Aqueous extract	2.8	<0.001	--	--	--	--	--	--	--	--	18.2	0.002	--	--
Protease hydrolysate	14.1	0.002	--	--	--	--	--	--	--	--	--	--	--	--
Precipitated solids	--	--	7.6 [1]	0.124	--	--	--	--	33.9	0.019	--	--	--	--
Total identified	4.0	<0.001	70.1	1.147	6.3	<0.001	38.1	0.085	26.6	0.015	27.3	0.003	12.9	<0.004
Total characterized	16.9	<0.003	8.9	0.146	--	--	4.5	0.010	35.7	0.020	18.2	0.002	1.5	<0.001
Total extractable	82.4	<0.013	92.5	1.512	88.5	0.005	95.1	0.212	94.7	0.053	72.7	0.008	95.9	0.025
Unextractable (PES)[2]	NR	NR	NR	NR	3.0	<0.001	NR	NR	NR	NR	27.3	0.003	NR	NR
Accountability[3]	100		100		91.5		100		100		100		100	

[1] Solids precipitated during the preparation of the aqueous extract for analysis were subjected to acid hydrolysis; HPLC analysis identified flumiclorac pentyl and IMCA (each <0.01 ppm).

[2] Residues remaining after exhaustive extractions; not reported (NR) following protease hydrolysis of nonextractable residues of egg yolk, gizzards, kidney, liver, and skin.

[3] Accountability was 100% because extractable and nonextractable residues were normalized for egg yolk, gizzards, kidney, liver, and skin; actual recoveries reported by the petitioner were 92-118%.

C.3. Proposed Metabolic Profile

FIGURE C.3.1. Proposed Metabolic Profile of Flumiclorac Pentyl in Laying Hens.

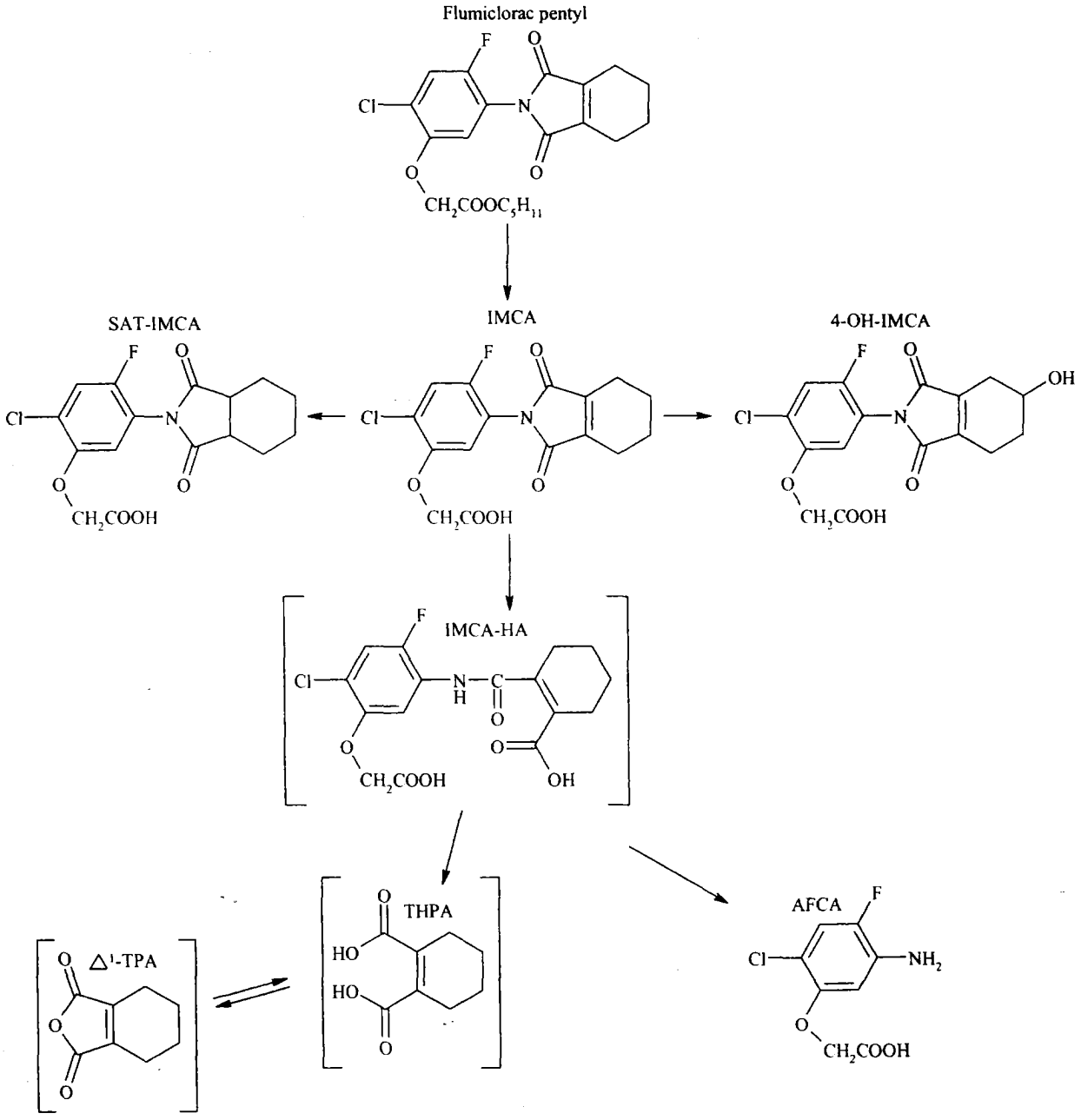
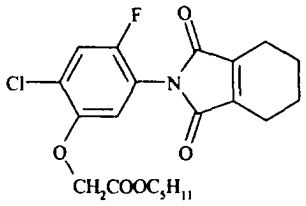
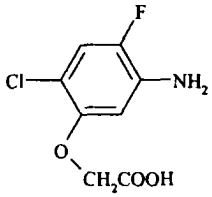
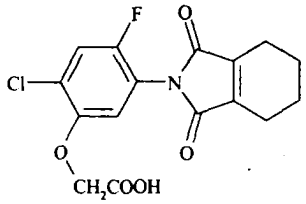
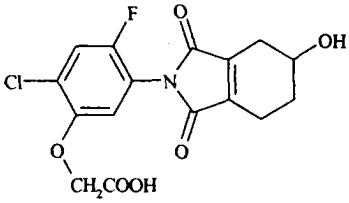
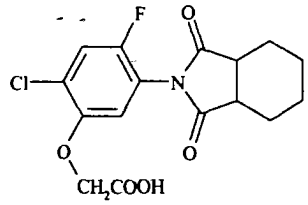


TABLE C.3.1. Identification of Compounds from Metabolism Study		
Common name/code Figure C.3.1 ID No.	Chemical name	Chemical structure
Flumiclorac pentyl; S-23031	acetic acid, {2-chloro-4-fluoro-5-(1,3,4,5,6,7-hexahydro-1,3-dioxo-2H-isoindol-2-yl)phenoxy}-,pentyl ester or 2-chloro-4-fluoro-5-(1,3,4,5,6,7-hexahydro-1,3-dioxo-2H-isoindol-2-yl)phenoxy]acetic acid, pentyl ester	
AFCA	5-amino-2-chloro-4-fluorophenoxyacetic acid	
IMCA	2-chloro-4-fluoro-5-(3,4,5,6-tetrahydrophthalimido)phenoxyacetic acid	
4-OH-IMCA	2-chloro-4-fluoro-5-(4-hydroxy-3,4,5,6-tetrahydrophthalimido)phenoxyacetate	
SAT-IMCA	2-chloro-4-fluoro-5-(1,2-cyclohexanedicarboximido)phenoxyacetate	

D. CONCLUSION

Total radioactive residues, determined by the analytical laboratory, were <0.001 ppm in egg whites (Day 4), 0.015 ppm in egg yolk (Day 5), 1.634 ppm in gizzards, 0.223 ppm in kidney, 0.056 ppm in liver, 0.009 ppm in breast muscle, 0.006 ppm in fat, and 0.026 ppm in skin from hens dosed orally with [phenyl-U-^{14}C]flumiclorac pentyl at ~10 ppm in the diet for 7 consecutive days. A large portion of the administered dose was excreted, accounting for 78% of the administered dose.

The majority of the radioactivity (~73-92% TRR) in egg yolk, gizzards, fat, kidney, liver, breast muscle, and skin was extractable (using acidic ACN, ACN, and/or methylene chloride). Protease hydrolysis released additional radioactivity (2.7-14.1% TRR, 0.002-0.141 ppm) from the nonextractable solids of egg yolk, gizzard, kidney, liver, and skin. Nonextractable residues remaining after solvent extraction and/or enzyme hydrolysis accounted for <10% TRR or <0.01 ppm in all matrices. Egg white and thigh muscle samples were not extracted because of low radioactivity.

Approximately 4-13% of the TRR in egg yolk, fat, and skin, 27-38% TRR in kidney, liver, and breast muscle, and 70% TRR in gizzard were identified; all metabolites were identified at levels ≤0.01 ppm except in gizzards and kidney. The parent was identified as a major residue in gizzard accounting for 29.1% TRR (0.476 ppm) and was detected at low levels in muscle and skin. IMCA was also identified as a major residue in gizzard and was also identified in kidney, liver, muscle, and skin at significant levels, but was only detected in egg yolk and fat at low levels. The metabolite AFCA was identified in gizzards at significant levels, and in kidney and liver as a minor metabolite. The metabolite 4-OH-IMCA was a major component identified in kidney, and was also identified in fat and liver at low levels. SAT-IMCA was identified as a minor metabolite in kidney and liver. The metabolites AFCA and IMCA were also identified in the protease hydrolysates of nonextractable residues of gizzards, kidney, liver, and skin. Additional residues, each present at <10% TRR or <0.01 ppm were characterized as polar or other unknowns in gizzards, kidney, liver, muscle, and skin. Flumiclorac pentyl and IMCA were identified in the gizzard acid hydrolysate of solids precipitated during the concentration of the aqueous extract.

The petitioner proposed that flumiclorac pentyl is rapidly metabolized and excreted in hens. Based on the phenyl- and THP-labeled hen metabolism studies the proposed metabolic reactions in hens involve: (i) initial hydrolysis of the pentyl ester of flumiclorac pentyl to form IMCA; (ii) hydrolysis of the imide and subsequent formed amide; (iii) hydroxylation of the cyclohexane ring; and (iv) olefin reduction.

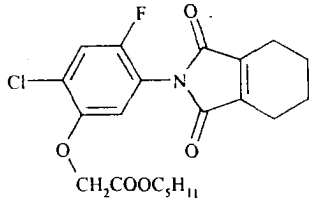
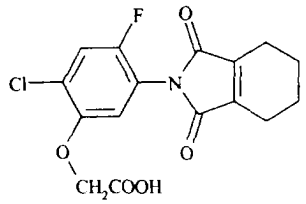
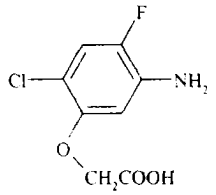
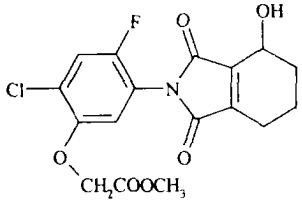
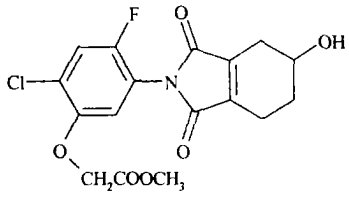
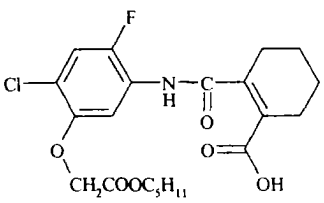
E. REFERENCES

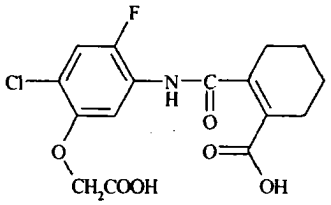
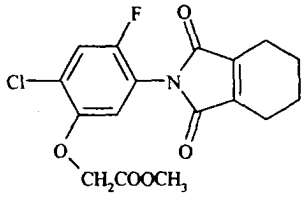
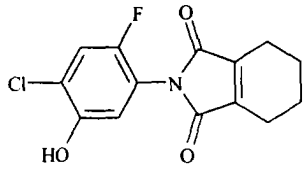
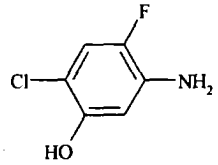
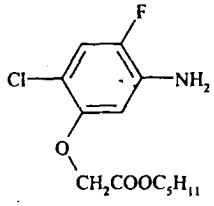
DP Barcode: D174474
Subject: PP#2G4078: New Chemical EUP: V-23031, Flumiclorac-Pentyl on Field Corn and Soybeans. Evaluation of Analytical Methods and of Residue Data.
From: J. Garbus
To: J. Miller and A. Kocialski
Dated: 7/28/92
MRIDs: 42187400-42187405, 42169849-42169859, and 42187407-42187408.

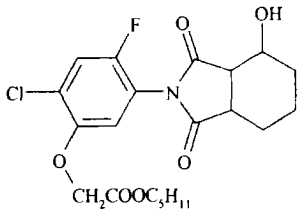
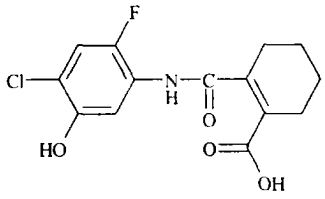
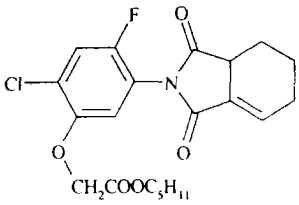
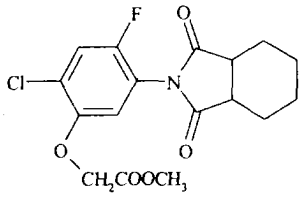
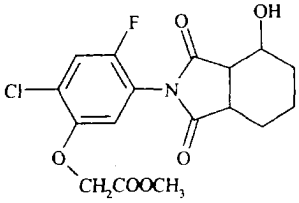
F. DOCUMENT TRACKING

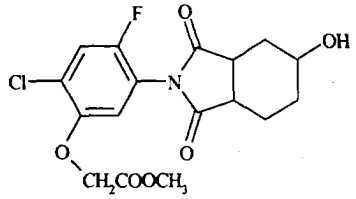
RDI: Catherine Eiden (24-JUN-2005)
Petition Number(s): PP#3F6767
DP Barcode(s): D308674
PC Code: 128724

Template Version September 2003

APPENDIX I. Chemical Names and Structures of Reference Standards Used in Hen Metabolism Study.		
Common name/code Figure C.3.1 ID No.	Chemical name	Chemical structure
Flumiclorac pentyl; S-23031	acetic acid, {2-chloro-4-fluoro-5-(1,3,4,5,6,7-hexahydro-1,3-dioxo-2H-isoindol-2-yl)phenoxy}-,pentyl ester or 2-chloro-4-fluoro-5-(1,3,4,5,6,7-hexahydro-1,3-dioxo-2H-isoindol-2-yl)phenoxy]acetic acid, pentyl ester	
IMCA	2-chloro-4-fluoro-5-(3,4,5,6-tetrahydrophthalimido)phenoxyacetic acid	
AFCA	5-amino-2-chloro-4-fluorophenoxyacetic acid	
3-OH-IMCA-ME	methyl 2-chloro-4-fluoro-5-(3-hydroxy-3,4,5,6-tetrahydrophthalimido)phenoxyacetate	
4-OH-IMCA-ME	methyl 2-chloro-4-fluoro-5-(4-hydroxy-3,4,5,6-tetrahydrophthalimido)phenoxyacetate	
031-HA	N-(4-chloro-2-fluoro-5-pentoxycarbonylmethoxyphenyl)-3,4,5,6-tetrahydrophthalamic acid	

APPENDIX I. Chemical Names and Structures of Reference Standards Used in Hen Metabolism Study.		
Common name/code Figure C.3.1 ID No.	Chemical name	Chemical structure
IMCA-HA	N-(5-carboxymethoxy-4-chloro-2-fluorophenyl)-3,4,5,6-tetrahydrophthalamic acid	
IMCA-ME	methyl 2-chloro-4-fluoro-5-(3,4,5,6-tetrahydrophthalimido)phenoxyacetate	
IMFP	N-(4-chloro-2-fluoro-5-hydroxyphenyl)-3,4,5,6-tetrahydrophthalimide	
AMFP	5-amino-2-4-fluorophenol	
AFE	pentyl 5-amino-2-chloro-4-fluorophenoxyacetate	

APPENDIX I. Chemical Names and Structures of Reference Standards Used in Hen Metabolism Study.		
Common name/code Figure C.3.1 ID No.	Chemical name	Chemical structure
031-SAT-3-OH	pentyl 2-chloro-4-fluoro-5-(3-hydroxy-1,2-cyclohexanedicarboximido	
IMFP-HA	N-(4-chloro-2-fluoro-5-hydroxyphenyl)-3,4,5,6-tetrahydrophthalamic acid	
031-Δ^2-ISO	pentyl 2-chloro-4-fluoro-5-(1,4,5,6-tetrahydrophthalimido) phenoxyacetate	
SAT-IMCA-ME	methyl 2-chloro-4-fluoro-5-(cyclohexane-1,2-dicarboximido)phenoxyacetate	
SAT-3-OH-IMCA-ME	methyl 2-chloro-4-fluoro-5-(3-hydroxy-1,2-cyclohexanedicarboximido)phenoxyacetate	

APPENDIX I. Chemical Names and Structures of Reference Standards Used in Hen Metabolism Study.		
Common name/code Figure C.3.1 ID No.	Chemical name	Chemical structure
SAT-4-OH-IMCA-ME	methyl 2-chloro-4-fluoro-5-(4-hydroxy-1,2,-cyclohexanedicarboximido)phenoxyacetate	

Flumiclorac pentyl/PC Code 128724/Valent U.S.A. Corporation
OPPTS 860.1500
Crop Field Trial - Cotton

Primary Evaluator William H. Donovan
William H. Donovan, Ph.D.
Chemist
HED/RRB3
Date: 6/24/05

Approved by
for Catherine Eiden
Branch Chief
HED/RRB3
Date: 6/24/05

This DER was originally prepared under contract by Dynamac Corporation (20440 Century Boulevard, Suite 100; Germantown, MD 20874; submitted 01/26/2005). The DER has been reviewed by the Health Effects Division (HED) and revised to reflect current Office of Pesticide Programs (OPP) policies.

STUDY REPORTS:

46082808 Stearns, J. (2003) Magnitude of the Residues of Flumiclorac Pentyl Ester on Cotton, Undelinted Seed and Cotton Gin Byproducts. Project Number: 24838, V-02-24838. Unpublished study prepared by Sumitomo Chemical Co., Ltd. 184 p.

46102801 Green, C. (1998) Magnitude of the Residues of Flumiclorac Pentyl Ester on Cotton and Cotton Processing Fractions. Project Number: V-97-11707, V-11707-A, V-11707-B. Unpublished study prepared by Valent U.S.A. Corporation. 475 p.

EXECUTIVE SUMMARY:

Valent U.S.A. Corporation has submitted residue field trial data for flumiclorac pentyl on cotton. Thirteen trials were conducted in Regions 2 (NC; 1 trial), 4 (AR, LA, and MS; 3 trials), 8 (OK and TX; 6 trials), and 10 (AZ and CA; 3 trials) between the 1997 and 2002 growing seasons. Cotton was harvested from six trials using stripper equipment and from seven trials using picker equipment. The number and locations of conducted field trials are in accordance with OPPTS Guideline 860.1500.

At each field trial site, cotton plants were treated with a single postemergence foliar application of Resource Herbicide®, an emulsifiable concentrate (EC) formulation containing 0.86 lb ai/gal of flumiclorac pentyl, at a target rate of ~0.094 lb ai/A; the actual applied rate ranged 0.092 to 0.096 lb ai/A. Application was made using ground equipment in ~10-20 gal/A of water, with an adjuvant added to the spray solution. Samples of mature cotton were harvested 6 to 8 days posttreatment from each test location using either stripper or picker harvest equipment. Samples were then ginned to yield fuzzy seed (undelinted cottonseed) and gin trash (gin byproducts). These cotton commodities were analyzed for residues of flumiclorac pentyl using a GC/NPD method (RM-29-2a) with a validated LOQ of 0.02 ppm. This method is adequate for data collection based on acceptable method recoveries.

The maximum storage intervals of samples, from harvest to analysis, were 119 days (3.9 months) for cottonseed and 142 days (4.7 months) for gin byproducts. Supporting storage stability data were included in the residue field studies; refer to the 860.1380 DER for MRIDs 46082808 and 46102801. These data indicate that residues of flumiclorac pentyl are stable under frozen conditions in/on cotton undelinted seed for up to ~2 months and in/on gin byproducts for up to ~4 months.

The maximum residues of flumiclorac pentyl in/on treated samples harvested by stripper equipment were 0.11 ppm for undelinted cottonseed and 0.83 ppm for cotton gin byproducts. The maximum residues of flumiclorac pentyl in/on treated samples harvested by picker equipment were 0.06 ppm for undelinted cottonseed and 2.2 ppm for cotton gin byproduct.

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the cotton field trial residue data are classified as scientifically acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document DP Barcode D308674.

COMPLIANCE:

Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided. No deviations from regulatory requirements were reported which would impact the validity of the study.

A. BACKGROUND INFORMATION

Flumiclorac pentyl is an N-phenylphthalimide derivative herbicide used for the control of broadleaf weeds. Its mode of action is through the accumulation of porphyrins in susceptible plants; the photosensitizing action of accumulated porphyrins may cause membrane lipid peroxidation which leads to irreversible damage of membrane function and structure in the plant. Flumiclorac pentyl is registered for postemergence application to field corn and soybeans; registration for use on cotton as a defoliant is pending. The PC code and nomenclature of flumiclorac pentyl are listed below in Table 1. The physicochemical properties of flumiclorac pentyl are listed in Table 2.

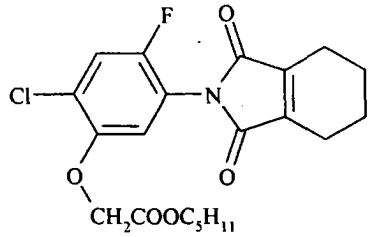
TABLE 1. Flumiclorac Pentyl Nomenclature	
Chemical Structure	
Common name	Flumiclorac pentyl
Company experimental name	S-23031 or V-23031
Molecular Formula	$C_{21}H_{23}ClFNO_5$
Molecular Weight	423.9
IUPAC name	Pentyl (2-chloro-5 (cyclohex-1-ene-1,2-dicarboximido)-4-fluorophenoxy) acetate
CAS name	Pentyl[2-chloro-4-fluoro-5-(1,3,4,5,6,7- hexahydro-1,3-dioxo-2H-isoindol-2-yl)phenoxy]acetate
CAS #	87546-18-7
PC Code	128724

TABLE 2. Physicochemical Properties of Flumiclorac Pentyl		
Parameter	Value	Reference
Melting point	88.9-90.1 °C	PP#2G4078; D174474, 7/28/92, J. Garbus
pH	6.03 at 25 °C	
Density, bulk density, or specific gravity	1.3316 g/mL at 20 °C	
Water solubility	0.189 mg/L at 25 °C	
Solvent solubility	g/100 mL at 25 °C: hexane 0.328 n-octanol 1.60 methanol 4.78 Solvesso 150 27.1 acetonitrile 58.9 acetone 59.0 tetrahydrofuran 69.7 N-methyl 2-pyrrolidinone 134.0 methylene chloride 288.0	
Vapor pressure	$<1 \times 10^{-7}$ mm Hg at 22.4 °C	
Dissociation constant, pK_a	No dissociation at pH ≤7; flumiclorac pentyl decomposes at pH ≥9.	
Octanol/water partition coefficient	Log P_{OW} = 4.99 at 19.7-21.0 °C	
UV/visible absorption spectrum	Not available	

B. EXPERIMENTAL DESIGN

B.1. Study Site Information

TABLE B.1.1. Trial Site Conditions.

Trial Identification: County, State; Year (Trial ID)	Soil characteristics				Meteorological data	
	Type	%OM	pH	CEC	Overall monthly rainfall range (inches) [1]	Overall temperature range (°C)
Washita, OK; 1997 (V11707-A)	Devel-Grandfield Complex	Not applicable			Not provided	
Uvalde, TX; 1997 (V-11707-B)	Uvalde	Not applicable			Not provided	
Hale, TX; 1997 (V-11707-C)	Randall	Not applicable			Not provided	
Swisher, TX; 1997 (V-11707-D)	Pullman	Not applicable			Not provided	
Lubbock, TX; 1997 (V-11707-E)	Olton Clay Loam	Not applicable			Not provided	
Hockley, TX; 1997 (V-11707-F)	Amarillo	Not applicable			Not provided	
Martin, NC; 2002 (V-24838-02-A)	Not provided	Not applicable			0-6.8	Not provided
Drew, AR; 2002 (V-24838-02-B)	Not provided	Not applicable			1.6-7.3 (I)	Not provided
St. Landry Parish, LA; 2002 (V-24838-02-C)	Not provided	Not applicable			2.4-12.5	Not provided
Washington, MS; 2002 (V-24838-02-D)	Not provided	Not applicable			2.0-5.1 (I)	Not provided
Fresno, CA; 2002 (V-24838-02-E)	Not provided	Not applicable			0-1.2 (I)	Not provided
Tulare, CA; 2002 (V-24838-02-F)	Not provided	Not applicable			0 (Oct only)	Not provided
Pinal, AZ; 2002 (V-24838-02-G)	Not provided	Not applicable			0-1.3 (I)	Not provided

[1] I = irrigation received.

The weather conditions were provided only for the application day for the stripper cotton trials (OK and TX). Actual precipitation data, but no temperature data were provided for the picker cotton trials. All field trial logs included general statements of the weather conditions. Weather conditions were cited as normal for the growing season, with the following exceptions. None of the weather deviations were expected to have an adverse impact on the study results.

For the OK trial (V-11707-A), June was cooler than normal, and August and October were wetter than normal. For the TX trial (V-11707-B), temperatures were generally hotter than normal and above normal rainfall occurred in April and June, but September and July were dryer than normal. For the TX trial (V-11707-C), weather conditions were slightly wetter than normal compared to the previous ten years, especially between May and September resulting in a later cotton. For the TX trial (V-11707-D), temperatures for May, June, and November were slightly below normal, and July and September temperatures were slightly above normal; rainfall from May through November was above normal. For the TX trials (V-11707-E and V-11707-F), weather conditions were generally cooler than normal and slightly wetter than normal. For the NC trial (V-24838-02-A), precipitation was slightly lower compared to 10-year averages.

For the AZ trial (V-24838-02-B), precipitation was above average for October. For the LA trial (V-24838-02-C), the planting season was generally dry, except precipitation was above average for July, August, and October. For the MS trial (V-24838-02-D), precipitation was slightly below normal for May and June, and above normal for October. For the CA and AZ trials (V-24838-02-E and V-24838-02-G), precipitation was below normal but supplemented with irrigation. For the CA trial (V-24838-02-F), weather conditions were slightly cooler than normal.

TABLE B.1.2. Study Use Pattern.

Location: County, State; Year (Trial ID)	EP[1]	Application					Tank Mix Adjuvants	Harvest Procedures
		Method; Timing	Vol. (GPA[2])	Rate (lb ai/A)	RTI[3] (days)	Total Rate (lb ai/A)		
Washita, OK; 1997 (V11707-A)	0.86 lb/gal EC	Broadcast foliar; cut-out, boll opening	10.4	0.095	N/A	0.095	Herbimax Oil	Stripper equipment
Uvalde, TX; 1997 (V-11707-B)	0.86 lb/gal EC	Broadcast foliar; 80-90% open	10.3	0.096	N/A	0.096	AgriDex	Stripper equipment
Hale, TX; 1997 (V-11707-C)	0.86 lb/gal EC	Broadcast foliar; 100% open	9.9	0.094	N/A	0.094	Riverside Prime Oil	Stripper equipment
Swisher, TX; 1997 (V-11707-D)	0.86 lb/gal EC	Broadcast foliar; 100% open	9.8	0.094	N/A	0.094	Riverside Prime Oil	Stripper equipment
Lubbock, TX; 1997 (V-11707-E)	0.86 lb/gal EC	Broadcast foliar; mature, >90% open	10.0	0.094	N/A	0.094	AgriDex	Stripper equipment
Hockley, TX; 1997 (V-11707-F)	0.86 lb/gal EC	Broadcast foliar; mature, >80% open	10.1	0.096	N/A	0.096	AgriDex	Stripper equipment
Martin, NC; 2002 (V-24838-02-A)	0.86 lb/gal EC	Broadcast foliar	14.0	0.093	N/A	0.093	Crop Oil (1 qt/A)	Picker equipment
Drew, AR; 2002 (V-24838-02-B)	0.86 lb/gal EC	Broadcast foliar; 85% open	9.9	0.094	N/A	0.094	Crop Oil (1 qt/A)	Picker equipment
St. Landry Parish, LA; 2002 (V-24838-02-C)	0.86 lb/gal EC	Broadcast foliar; mature	17.9	0.096	N/A	0.096	Crop Oil (1 qt/A)	Picker equipment
Washington, MS; 2002 (V-24838-02-D)	0.86 lb/gal EC	Broadcast foliar; 95% open bolls	15.4	0.096	N/A	0.096	Crop Oil (1 qt/A)	Picker equipment
Fresno, CA; 2002 (V-24838-02-E)	0.86 lb/gal EC	Broadcast foliar; 70% open bolls	20.2	0.095	N/A	0.095	Crop Oil (1 qt/A)	Picker equipment
Tulare, CA; 2002 (V-24838-02-F)	0.86 lb/gal EC	Broadcast foliar; ~80% open bolls	19.4	0.092	N/A	0.092	Crop Oil (1 qt/A)	Picker equipment
Pinal, AZ; 2002 (V-24838-02-G)	0.86 lb/gal EC	Broadcast foliar; mature, ~90% open bolls	15.3	0.096	N/A	0.096	Crop Oil (1 qt/A)	Picker equipment

[1] EP = End-use Product.
[2] GPA = Gallons per acre
[3] RTI = Retreatment Interval; not applicable (N/A) because only one application was made.

TABLE B.1.3. Trial Numbers and Geographical Locations.

NAFTA Growing Region	Cotton		
	Submitted	Requested	
		Canada	US [1]
1			
1A			
2	1 (picker)		1
3			
4	3 (picker)		3
5			
5A			
5B			
6			1
7			
7A			
8	6 (stripper) [2]		4
9			
10	3 (picker)		3
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
Total	**13**		**12**

[1] As per OPPTS 860.1500, Tables 1 and 5; at least 3 field trials of each type of harvesting (stripper and picker) are required (860.1000, Table 1).
[2] One trial (V-11707-B) is close to the border for Region 6 and may be applied to that location requirement.

B.2. Sample Handling and Preparation

A single untreated and duplicate treated cotton samples were mechanically harvested using either stripper (6 trials) or picker (7 trials) equipment from each trial site. Samples were frozen within five hours of collection and shipped frozen to the Food Protein R&D Center at Texas A&M University (Bryan, TX) for processing; one set of samples (AZ trial) was shipped overnight at ambient conditions and frozen upon receipt. Cotton samples were ginned, and ginned cottonseed (fuzzy or undelinted) and gin trash (gin byproducts) were collected and frozen. Frozen cotton

undelinted seed and gin byproduct samples were shipped to Valent Technical Center (Dublin, CA) for residue analysis. Samples were stored frozen (-20 °C) at the analytical laboratory until maceration and analysis.

Separate unginned cottonseed samples from one of the TX trials were shipped to the Food Protein R&D Center at Texas A&M University (Bryan, TX) for processing into meal, hulls, and refined oil. Refer to the 860.1520 DER for MRID 46102801 for the results of the processing study.

B.3. Analytical Methodology

Samples of cotton undelinted seed and gin byproducts were analyzed for residues of flumiclorac pentyl using a GC Method (RM-29-2a) entitled "Determination of Residues of Flumiclorac Pentyl Ester in Cotton Seed." This method is a modified version of Method RM-29-2 (current enforcement method for flumiclorac pentyl in/on soybeans), in which the cleanup step uses an alumina column instead of the silica column. The validated limit of quantitation (LOQ) was 0.02 ppm, and the reported limit of detection (LOD) was 0.01 ppm for undelinted cottonseed and gin byproducts.

Briefly, homogenized samples were sequentially extracted with 2% acetic acid in acetonitrile (ACN; 2x) and ACN:water (1:1, v:v), and then filtered. A 5% sodium chloride solution was added to the combined extracts, and residues were partitioned (2x) into methylene chloride. The combined methylene chloride phases were concentrated by rotary evaporation to remove the solvent, and residues were redissolved in ACN (saturated with hexane). Residues were then partitioned with hexane (saturated with ACN). The ACN phase was concentrated to remove the solvent, and residues were redissolved in hexane:ethyl acetate (4:1, v:v) for clean up through an alumina column; residues were eluted with hexane/ethyl acetate. The eluant was concentrated, and residues were redissolved in acetone for GC analysis using nitrogen-phosphorous detection (NPD) and external calibration standards. Samples of gin byproducts from one trial were analyzed by GC using mass selective detection.

Method verification (reproducibility) was conducted by the analytical laboratory prior to analysis of the treated cotton samples. Recoveries ranged 81-94% (mean = 88% ± 5; n = 9) in/on untreated cottonseed fortified with flumiclorac pentyl at 0.020 and 0.10 ppm.

C. RESULTS AND DISCUSSION

Concurrent method recovery data are presented in Table C.1. The data-collection method is adequate for data collection based on acceptable concurrent method recovery data. Apparent residues of flumiclorac pentyl were reported as below the method LOD (<0.01 ppm) in/on all samples of untreated cottonseed and gin byproducts, except for two untreated cotton gin byproduct samples which bore residues of 0.03 and 0.04 ppm (greater than the method LOQ). The petitioner did not provide an explanation for the residues in the control samples; however,

the quantifiable residues in the untreated gin byproduct samples are not of concern because residues in the respective treated samples were at least twice that of the untreated sample.

Sample storage conditions and intervals are summarized in Table C.2. The maximum storage interval of samples, from harvest to analysis, was 119 days (3.9 months) for cottonseed and 142 days (4.7 months) for gin byproducts. In support of the crop field trial studies, the petitioner submitted storage stability data (refer to the 860.1380 DER for MRIDs 46082808 and 46102801) which suggest that residues of flumiclorac pentyl are stable under frozen conditions in/on cotton undelinted seed for up to ~2 months and in/on gin byproducts for up to ~4 months. The available storage stability data support the storage conditions and intervals of samples from the submitted cotton field trials.

Residue data from the cotton field trials are reported in Table C.3. A summary of residue data for cotton undelinted seed and gin byproducts following treatment with the 0.86 lb/gal EC formulation is presented in Table C.4. Residues of flumiclorac pentyl were 0.02-0.11 ppm in/on undelinted cottonseed harvested using stripper equipment 7-8 days following a single broadcast foliar application of the 0.86 lb/gal EC formulation at 0.094-0.096 lb ai/A; flumiclorac pentyl residues were 0.17-0.83 ppm in/on the respective cotton gin byproduct samples.

Residues of flumiclorac pentyl were <0.02-0.06 ppm in/on undelinted cottonseed harvested using picker equipment 6-7 days following a single broadcast foliar application of the 0.86 lb/gal EC formulation at 0.092-0.096 lb ai/A; flumiclorac pentyl residues were 0.03-2.2 ppm in/on the respective cotton gin byproduct samples.

Residue levels were lower in cottonseed samples harvested using picker equipment versus stripper equipment, but maximum residues in gin byproducts were higher from cotton harvested with picker equipment. It is noted that residues were highly variable between trials for picker cotton gin byproducts. The petitioner stated that higher residues were observed in two stripper cotton field trials (V-11707-C and V-11707-D) than in the other stripper cotton trials, possibly due to the use of ethephon, which was applied 2-3 weeks prior to the flumiclorac pentyl application.

Thirteen cotton field trials were conducted in Regions 2 (NC; 1 trial), 4 (AR, LA, and MS; 3 trials), 8 (OK and TX; 6 trials), and 10 (AZ and CA; 3 trials) during the 1997 and 2002 growing seasons. Cotton was harvested from six trials using stripper equipment and from seven trials using picker equipment. The number and locations of field trials are in accordance with OPPTS Guideline 860.1500.

TABLE C.1. Summary of Concurrent Recoveries of Flumiclorac Pentyl from Cotton Matrices.

Matrix	Spike level (ppm)	Sample size (n)	Recoveries (%)	Mean ± std dev
MRID 46082808				
Cotton, undelinted seed	0.02	2	68.6, 88.9	81.0 ± 7.2
	0.10	2	74.7, 82.6	
	0.20	1	80.3	
	2.0	2	85.8, 86.0	
Cotton, gin byproducts	0.02	1	76.8	83.3 ± 9.8
	0.10	3	67.5, 76.8, 93.4	
	0.20	3	85.0, 91.7, 94.0	
	0.50	1	94.0	
	1.0	1	74.2	
	2.0	3	73.1, 79.1, 93.6	
MRID 46102801				
Cotton, undelinted seed	0.020	4	98, 99, 102, 114	100 ± 8.2
	0.100	5	90, 91, 95, 98, 111	
Cotton, gin byproducts	0.020	4	81, 90, 94, 95	89 ± 6.9
	0.100	5	78, 82, 90, 93, 97	

TABLE C.2. Summary of Storage Conditions.

Matrix (RAC or Extract)	Storage Temp. (°C)	Actual Storage Duration [1]	Interval of Demonstrated Storage Stability [2]
Cotton, undelinted seed (MRID 46082808)	-20	103-119 days (3.4-3.9 months)	Stable under frozen conditions in/on cotton undelinted seed for 61 days (2.0 months) and cotton gin byproducts for up to 124 days (4.1 months)
Cotton, gin byproducts (MRID 46082808)		108-142 days (3.6-4.7 months)	
Cotton, undelinted seed (MRID 46102801)		28-55 days (0.9-1.8 months)	
Cotton, gin byproducts (MRID 46102801)		29-57 days (1.0-1.9 months)	

[1] Samples were analyzed within 0-29 days of extraction, except for 4 picker cotton trials where cottonseed samples were analyzed 42-44 days after extraction.

[2] Refer to the 860.1380 DER for MRIDs 46082808 and 46102801 for the storage stability results submitted in conjunction with the field trials.

TABLE C.3. Residue Data from Cotton Field Trials with Flumiclorac Pentyl.

Trial ID (City, State; Year)	Region	Crop; Variety	Total Rate (lb ai/A)	PHI (days)	Commodity or Matrix	Flumiclorac Pentyl Residues (ppm) [1]
Washita, OK; 1997 (V11707-A)	8	Stripper cotton; Paymaster HS-200	0.095	8	undelinted seed	0.02, 0.03
					gin byproducts	0.17, 0.21
Uvalde, TX; 1997 (V-11707-B)	8	Stripper cotton; Sure Grow 12S	0.096	7	undelinted seed	0.02, 0.02
					gin byproducts	0.18, 0.20
Hale, TX; 1997 (V-11707-C)	8	Stripper cotton; Paymaster 145	0.094	7	undelinted seed	0.06, 0.07
					gin byproducts	0.54, 0.58
Swisher, TX; 1997 (V-11707-D)	8	Stripper cotton; Paymaster HS-280	0.094	7	undelinted seed	0.08, 0.11
					gin byproducts	0.71, 0.82
Lubbock, TX; 1997 (V-11707-E)	8	Stripper cotton; PM 2200 RR	0.094	7	undelinted seed	0.02, 0.02
					gin byproducts	0.65, 0.83
Hockley, TX; 1997 (V-11707-F)	8	Stripper cotton; All-Tex Atlas	0.096	7	undelinted seed	0.03, 0.03
					gin byproducts	0.24, 0.31
Martin, NC; 2002 (V-24838-02-A)	2	Picker cotton; Fiber Max 989	0.093	7	undelinted seed	ND, ND
					gin byproducts	0.03, 0.03
Drew, AR; 2002 (V-24838-02-B)	4	Picker cotton; FM 958	0.094	6	undelinted seed	ND, (0.01)
					gin byproducts	0.59, 1.0
St. Landry Parish, LA; 2002 (V-24838-02-C)	4	Picker cotton; DP 458 B/RR	0.096	7	undelinted seed	ND, 0.03
					gin byproducts	0.17, 0.19
Washington, MS; 2002 (V-24838-02-D)	4	Picker cotton; Stoneville 4892 BR	0.096	7	undelinted seed	ND, ND
					gin byproducts	0.06, 0.06
Fresno, CA; 2002 (V-24838-02-E)	10	Picker cotton; Roundup Ready Acala	0.095	7	undelinted seed	ND, (0.01)
					gin byproducts	2.0, 2.2
Tulare, CA; 2002 (V-24838-02-F)	10	Picker cotton; GTO Maxxa	0.092	6	undelinted seed	(0.01), 0.06
					gin byproducts	1.0, 1.3
Pinal, AZ; 2002 (V-24838-02-G)	10	Picker cotton; Delta Pine 388	0.096	7	undelinted seed	0.04, 0.06
					gin byproducts	0.72, 1.0

[1] The method LOQ was 0.02 ppm and the method LOD was 0.01 ppm. Residues reported by the petitioner below the LOQ are cited in parentheses, and residues reported by the petitioner as <0.01 ppm are cited as nondetectable (ND).

TABLE C.4. Summary of Residue Data from Cotton Field Trials with Flumiclorac Pentyl.									
Cotton Matrix [Harvest Equipment]	Total Applic. Rate (lb ai/A)	PHI (days)	Residue Levels (ppm) [1]						
			n	Min.	Max.	HAFT[2]	Median (STMdR[3])	Mean (STMR[4])	Std. Dev.
Undelinted cottonseed [stripper]	0.094-0.096	7-8	12	0.02	0.11	0.10	0.03	0.04	0.03
Cotton, gin byproducts [stripper]	0.094-0.096	7-8	12	0.17	0.83	0.77	0.43	0.45	0.26
Undelinted cottonseed [picker]	0.092-0.096	6-7	14	<0.02	0.06	0.05	0.01	0.02	0.02
Cotton, gin byproducts [picker]	0.092-0.096	6-7	14	0.03	2.2	2.1	0.66	0.74	0.72

[1] For calculation of the minimum, maximum, and HAFT residues, the LOQ (0.02 ppm) was used for residues reported below the LOQ in Table C.3.; for calculation of the median, mean, and standard deviation, half the LOQ (0.01 ppm, equivalent to the LOD) was used for residues reported below the LOQ.
[2] HAFT = Highest Average Field Trial.
[3] STMdR = Supervised Trial Median Residue.
[4] STMR = Supervised Trial Mean Residue.

D. CONCLUSION

The submitted field trial data reflect a single postemergence foliar application of a 0.86 lb/gal EC formulation made to cotton at ~0.094 lb ai/A. Cottonseed was harvested using stripper or picker equipment at a 6- to 8-day PHI, and ginned for undelinted seed and gin byproduct samples. Acceptable methods were used for quantitation of residues in/on cotton undelinted seed and gin byproducts.

E. REFERENCES

None.

F. DOCUMENT TRACKING

RDI: Catherine Eiden (24-JUN-2005)
Petition Number: PP#3F6767
DP Barcode: D308674
PC Code: 128724

Flumiclorac pentyl/PC Code 128724/Valent U.S.A. Corporation
OPPTS 860.1520
Processed Food and Feed - Cotton

Primary Evaluator William H. Donovan
William H. Donovan, Ph.D.
Chemist
HED/RRB3
Date: 6/24/05

Approved by
for Catherine Eiden
Branch Chief
HED/RRB3
Date: 6/24/05

This DER was originally prepared under contract by Dynamac Corporation (20440 Century Boulevard, Suite 100; Germantown, MD 20874; submitted 01/26/2005). The DER has been reviewed by the Health Effects Division (HED) and revised to reflect current Office of Pesticide Programs (OPP) policies.

STUDY REPORT:

46102801 Green, C. (1998) Magnitude of the Residues of Flumiclorac Pentyl Ester on Cotton and Cotton Processing Fractions. Project Number: V-97-11707. Unpublished study performed and submitted by Valent U.S.A. Corporation (Dublin, CA). 475 p.

EXECUTIVE SUMMARY:

Valent U.S.A. Corporation has submitted a cottonseed processing study with flumiclorac pentyl. In a trial conducted in TX, mature cotton was harvested 7 days following a single postemergence foliar application of Resource Herbicide®, an emulsifiable concentrate (EC) formulation containing 0.86 lb ai/gal of flumiclorac pentyl, at 0.096 lb ai/A. Cottonseed was ginned and processed into meal, hulls, and refined oil using small-scale processing procedures.

Samples of undelinted cottonseed and its processed commodities were analyzed for residues of flumiclorac pentyl using GC/NPD method RM-29-2a, with a validated LOQ of 0.02 ppm for all cotton matrices. This method is adequate for data collection based on acceptable concurrent method recovery data.

The maximum storage intervals of processing study samples from harvest to analysis were 104 days (3.4 months) for cottonseed, and 11 days (<1 month) for processed meal, hulls, and refined oil. The petitioner submitted storage stability data (refer to the 860.1380 DER for MRIDs 46082808 and 46102801) in conjunction with the cotton field trial data; these data indicate that residues of flumiclorac pentyl are stable under frozen conditions in/on undelinted cottonseed for up to ~2 months and cotton gin byproducts for up to ~4 months. The available storage stability data support the storage conditions and intervals of RAC samples from the submitted cotton processing study, and storage stability data are not required for the processed commodities because they were analyzed within 30 days of collection.

Residues of flumiclorac pentyl were 0.02-0.03 ppm in/on undelinted cottonseed (RAC) treated with the 0.86 lb/gal EC formulation at 0.096 lb ai/A. Residues of flumiclorac pentyl did not appear to concentrate (0.3x processing factors) in the processed commodities of cottonseed; residues were at or below the LOD (0.01 ppm) in all samples of meal, hulls, and refined oil processed from treated cottonseed. The observed processing factor of 0.3x from the current study does not exceed the theoretical concentration factors of 3.8x for hulls, 2.2x for meal, and 6.3x for refined oil (Table 3 of OPPTS 860.1520).

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the cottonseed processing study residue data are classified as acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document DP Barcode D308674.

COMPLIANCE:

Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided. No deviations from regulatory requirements were reported which would impact the validity of the study.

A. BACKGROUND INFORMATION

Flumiclorac pentyl is an N-phenylphthalimide derivative herbicide used for the control of broadleaf weeds. Its mode of action is through the accumulation of porphyrins in susceptible plants; the photosensitizing action of accumulated porphyrins may cause membrane lipid peroxidation which leads to irreversible damage of membrane function and structure in the plant. Flumiclorac pentyl is registered for postemergence application to field corn and soybeans; registration for use on cotton as a defoliant is pending. The PC code and nomenclature of flumiclorac pentyl are listed below in Table 1. The physicochemical properties of flumiclorac pentyl are listed in Table 2.

TABLE 1. Flumiclorac Pentyl Nomenclature

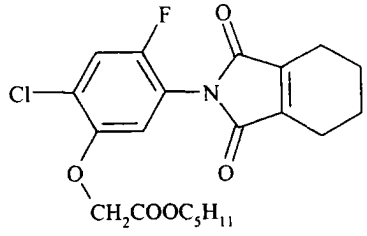
Chemical Structure	
Common name	Flumiclorac pentyl
Company experimental name	S-23031 or V-23031

TABLE 1. Flumiclorac Pentyl Nomenclature	
Molecular Formula	$C_{21}H_{23}ClFNO_5$
Molecular Weight	423.9
IUPAC name	Pentyl (2-chloro-5 (cyclohex-1-ene-1,2-dicarboximido)-4-fluorophenoxy) acetate
CAS name	Pentyl[2-chloro-4-fluoro-5-(1,3,4,5,6,7- hexahydro-1,3-dioxo-2H-isoindol-2-yl)phenoxy]acetate
CAS #	87546-18-7
PC Code	128724

TABLE 2. Physicochemical Properties of Flumiclorac Pentyl		
Parameter	Value	Reference
Melting point	88.9-90.1 °C	PP#2G4078; D174474, 7/28/92, J. Garbus
pH	6.03 at 25 °C	
Density, bulk density, or specific gravity	1.3316 g/mL at 20 °C	
Water solubility	0.189 mg/L at 25 °C	
Solvent solubility	g/100 mL at 25 °C: hexane 0.328 n-octanol 1.60 methanol 4.78 Solvesso 150 27.1 acetonitrile 58.9 acetone 59.0 tetrahydrofuran 69.7 N-methyl 2-pyrrolidinone 134.0 methylene chloride 288.0	
Vapor pressure	$<1 \times 10^{-7}$ mm Hg at 22.4 °C	
Dissociation constant, pK_a	No dissociation at pH ≤7; flumiclorac pentyl decomposes at pH ≥9.	
Octanol/water partition coefficient	Log P_{OW} = 4.99 at 19.7-21.0 °C	
UV/visible absorption spectrum	Not available	

B. EXPERIMENTAL DESIGN

B.1. Application and Crop Information

TABLE B.1.2. Study Use Pattern.								
Location (County, State; Year)	EP[1]	Application					Tank Mix Adjuvants	Harvest Procedures
		Method; Timing	Vol (GPA[2])	Rate (lb ai/A)	RTI[3] (days)	Total Rate (lb ai/A)		
Hockley, TX; 1997 (V-11707-F)	0.86 lb/gal EC	Broadcast foliar; mature, >80% open	10.1	0.096	N/A	0.096	AgriDex	Stripper equipment

[1] EP = End-use Product
[2] GPA = Gallons per acre
[3] RTI = Retreatment Interval; not applicable (N/A) because only one application was made

B.2. Sample Handling and Processing Procedures

A single untreated and treated bulk sample (~54 lbs) of mature cotton was harvested using stripper equipment and frozen within 0.5 hours of collection. Frozen samples were shipped to the Food Protein R&D Center at Texas A&M University (Bryan, TX) for processing. Samples of ginned cottonseed were processed within 95 days of harvest into meal, hulls, and refined oil using small scale processing procedures. The petitioner submitted adequate descriptions of the processing procedures and material balance information.

Briefly, cottonseed was first dried to the appropriate moisture (8%), and the burrs, sticks, and other plant parts (gin trash) removed with a stick extractor prior to ginning. The cleaned cottonseed was then saw-ginned to remove the majority of the lint, then cracked and screened to separate kernels from hulls. The kernel material, with some hull material, was heated, flaked, and expanded to form collets, and the collets were extracted with hexane. Warm air was passed through the extracted collets for desolventization, and a sample of cotton meal was collected from the desolventized collets. The hexane extract was evaporated to remove the hexane, yielding crude oil. The crude oil was then mixed with sodium hydroxide and heated to produce refined oil and soapstock.

Ginned cottonseed (undelinted; RAC) and processed samples were shipped to Valent Technical Center (Dublin, CA) for residue analysis. At Valent, the samples were stored under frozen conditions (-20 °C) until maceration (except oil) and analysis.

B.3. Analytical Methodology

Samples of ginned cottonseed (undelinted), meal, hulls, and refined oil were analyzed for residues of flumiclorac pentyl using GC Method RM-29-2a, the same method used for the analysis of RAC samples from the respective field trials (refer to the 860.1500 DER for MRID 46102801). This method is a modified version of Method RM-29-2 (current enforcement method for soybean commodities), in which the cleanup step uses an alumina column instead of a silica column. The validated limit of quantitation (LOQ) was 0.02 ppm, and the reported limit of detection (LOD) was 0.01 ppm for cottonseed, meal, hulls, and refined oil.

Briefly, homogenized samples, except oil, were sequentially extracted with 2% acetic acid in acetonitrile (ACN; 2x) and ACN:water (1:1, v:v), and then filtered. A 5% sodium chloride solution was added to the combined extracts, and residues were partitioned (2x) into methylene chloride. The combined methylene chloride phases were concentrated by rotary evaporation to remove the solvent, and residues were redissolved in ACN (saturated with hexane). Residues were then partitioned with hexane (saturated with ACN). The ACN phase was concentrated to remove the solvent, and residues were redissolved in hexane:ethyl acetate (4:1, v:v) for clean up through an alumina column; residues were eluted with hexane/ethyl acetate. The eluant was concentrated, and residues were redissolved in acetone for GC analysis using nitrogen-phosphorous detection (NPD) and external calibration standards.

For refined oil samples, the same procedure was used, except that the initial solvent extraction and methylene chloride partitioning step was not conducted; extraction started with the ACN/hexane partitioning step.

C. RESULTS AND DISCUSSION

Concurrent method recovery data are presented in Table C.1. The data-collection method is adequate for data collection based on acceptable concurrent method recovery data. Apparent residues of flumiclorac pentyl were reported as below the method LOD (0.01 ppm) in/on all samples of untreated cotton undelinted seed, meal, hulls, and refined oil.

Sample storage intervals and conditions are summarized in Table C.2. Cottonseed and its processed commodities were stored frozen following processing until analysis. The maximum storage intervals of processing study samples from harvest to analysis were 104 days (3.4 months) for cottonseed, and 11 days (<1 month) for processed meal, hulls, and refined oil. The petitioner submitted storage stability data (refer to the 860.1380 DER for MRIDs 46082808 and 46102801) in conjunction with the cotton field trial data; these data indicate that residues of flumiclorac pentyl are stable under frozen conditions in/on cotton undelinted seed for up to ~2 months and cotton gin byproducts for up to ~4 months. The available storage stability data support the storage conditions and intervals of RAC samples from the submitted cotton processing study, and storage stability data are not required for the processed commodities because they were analyzed within 30 days of collection.

Residue data from the cottonseed processing study are reported in Table C.3. Residues of flumiclorac pentyl were 0.02-0.03 ppm in/on cotton undelinted seed (RAC) treated with the 0.86 lb/gal EC formulation at 0.096 lb ai/A. Residues of flumiclorac pentyl did not appear to concentrate (0.3x processing factor) in the processed commodities of cottonseed; residues were at or below the LOD (0.01 ppm) in all samples of meal, hulls, and refined oil processed from treated cottonseed.

The reported processing factors do not exceed the theoretical concentration factors. According to Table 3 of OPPTS 860.1520, the theoretical concentration factors are 3.8x for hulls, 2.2x for meal, and 6.3x for refined oil.

TABLE C.1. Summary of Concurrent Recoveries of Flumiclorac Pentyl from Cotton Matrices.

Matrix	Spike level (ppm)	Sample size (n)	Recoveries (%)	Mean ± std dev
Cotton, undelinted seed	0.020	1	88	85
	0.100	1	81	
Meal	0.020	1	88	87
	0.100	1	86	
Hulls	0.020	1	87	89
	0.100	1	91	
Refined oil	0.020	1	85	93 ± 5.9

TABLE C.1. Summary of Concurrent Recoveries of Flumiclorac Pentyl from Cotton Matrices.				
Matrix	Spike level (ppm)	Sample size (n)	Recoveries (%)	Mean ± std dev
	0.100	2	93, 95	
	0.500	1	99	

TABLE C.2. Summary of Storage Conditions			
Matrix	Storage Temp. (°C)	Actual Storage Duration[1]	Interval of Demonstrated Storage Stability
Cotton, undelinted seed	-20	104 days (3.4 months)	Stable under frozen conditions in/on cotton undelinted seed for 61 days (2.0 months) and cotton gin byproducts for up to 124 days (4.1 months) [2]
Meal, hulls, and refined oil		8-11 days (<1 month)	None required

[1] Cotton was ginned within 80 days of harvest and processed within 91-95 days of harvest. Samples were analyzed within 0-1 days of extraction.

[2] Refer to the 860.1380 DER for MRIDs 46082808 and 46102801 for the storage stability results submitted in conjunction with the cotton field trials.

TABLE C.3. Residue Data from Cottonseed Processing Study with Flumiclorac Pentyl.					
RAC	Processed Commodity	Total Rate (lb ai/A)	PHI (days)	Flumiclorac Pentyl Residues (ppm) [1]	Processing Factor
Cottonseed	undelinted (ginned) seed (RAC)	0.096	7	0.02, 0.03	--
	meal (solvent extracted)			<0.01, <0.01	<0.3x
	hulls			<0.01, <0.01	<0.3x
	refined oil			<0.01, 0.01	≤0.3x

[1] Results are for duplicate analyses of a single sample.

D. CONCLUSION

The cottonseed processing data indicate that residues of flumiclorac pentyl do not appear to concentrate (0.3x processing factor) in the processed commodities of cottonseed; residues were at or below the LOD (0.01 ppm) in all samples of meal, hulls, and refined oil processed from treated cotton undelinted seed bearing quantifiable residues (0.02-0.03 ppm). Acceptable methods were used for the quantitation of residues in/on cottonseed and its processed commodities.

E. REFERENCES

None.

F. DOCUMENT TRACKING

RDI: Catherine Eiden (24-JUN-2005)
Petition Number: PP#3F6767
DP Barcode: D308674
PC Code: 128724

Template Version September 2003

Flumiclorac pentyl/PC Code 128724/Valent U.S.A. Corporation
OPPTS 860.1380
Storage Stability - Cotton

Primary Evaluator William H. Donovan
William H. Donovan, Ph.D.
Chemist
HED/RRB3
Date: 6/24/05

Approved by
Catherine Eiden
Branch Chief
HED/RRB3
Date: 6/24/05

This DER was originally prepared under contract by Dynamac Corporation (20440 Century Boulevard, Suite 100; Germantown, MD 20874; submitted 01/26/2005). The DER has been reviewed by the Health Effects Division (HED) and revised to reflect current Office of Pesticide Programs (OPP) policies.

STUDY REPORTS:

46082808 Stearns, J. (2003) Magnitude of the Residues of Flumiclorac Pentyl Ester on Cotton, Undelinted Seed and Cotton Gin Byproducts. Project Number: 24838, V-02-24838. Unpublished study prepared by Sumitomo Chemical Co., Ltd. 184 p.

46102801 Green, C. (1998) Magnitude of the Residues of Flumiclorac Pentyl Ester on Cotton and Cotton Processing Fractions. Project Number V-97-11707. Unpublished study prepared by Valent U.S.A. Corporation. 475 p.

EXECUTIVE SUMMARY:

Valent U.S.A. Corporation has included the results of storage stability studies with flumiclorac pentyl as part of the cotton field trial submissions. In one study, untreated samples of undelinted cottonseed and gin byproducts were fortified with flumiclorac pentyl at 0.10 ppm and then stored frozen (- 20 °C) for 33 and 61 days. In another study, cotton gin byproduct samples with weathered residues from cotton field trials were stored frozen and re-extracted 99 and 124 days after the initial residue extraction. Fresh fortification samples were analyzed with the re-extracted samples. Samples were analyzed for residues of flumiclorac pentyl using a GC/NPD method (RM-29-2a) with a validated LOQ of 0.02 ppm. This method is adequate for data collection based on acceptable method recoveries.

The submitted storage stability data indicate that fortified residues of flumiclorac pentyl are reasonably stable under frozen storage conditions in/on undelinted cottonseed (storage stability recovery range of 80-102%) and cotton gin byproducts (storage stability recovery range of 87-120%) for up to 61 days (~2 months). The reviewed data also indicate that weathered residues of flumiclorac pentyl are reasonably stable under frozen storage conditions in/on cotton gin byproducts for up to 124 days (~4 months).

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the storage stability data are classified as scientifically acceptable. It is noted that raw data were not provided for the storage stability study using fortified samples, but the results of the storage stability study conducted with weathered residues in/on cotton gin byproducts, demonstrated stability for storage durations exceeding that of the fortified samples. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document DP Barcode D308674.

COMPLIANCE:

Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided. No deviations from regulatory requirements were reported which would have an impact on the validity of the study.

A. BACKGROUND INFORMATION

Flumiclorac pentyl is an N-phenylphthalimide derivative herbicide used for the control of broadleaf weeds. Its mode of action is through the accumulation of porphyrins in susceptible plants; the photosensitizing action of accumulated porphyrins may cause membrane lipid peroxidation which leads to irreversible damage of membrane function and structure in the plant. Flumiclorac pentyl is registered for postemergence application to field corn and soybeans; registration for use on cotton as a defoliant is pending. The PC code and nomenclature of flumiclorac pentyl are listed below in Table 1. The physicochemical properties of flumiclorac pentyl are listed in Table 2.

TABLE 1. Flumiclorac Pentyl Nomenclature

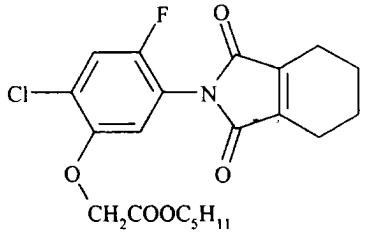
Chemical Structure	
Common name	Flumiclorac pentyl
Company experimental name	S-23031 or V-23031
Molecular Formula	$C_{21}H_{23}ClFNO_5$
Molecular Weight	423.9
IUPAC name	Pentyl (2-chloro-5 (cyclohex-1-ene-1,2-dicarboximido)-4-fluorophenoxy) acetate
CAS name	Pentyl[2-chloro-4-fluoro-5-(1,3,4,5,6,7- hexahydro-1,3-dioxo-2H-isoindol-2-yl)phenoxy]acetate

TABLE 1. Flumiclorac Pentyl Nomenclature	
CAS #	87546-18-7
PC Code	128724

TABLE 2. Physicochemical Properties of Flumiclorac Pentyl		
Parameter	Value	Reference
Melting point	88.9-90.1 °C	PP#2G4078; D174474, 7/28/92, J. Garbus
pH	6.03 at 25 °C	
Density, bulk density, or specific gravity	1.3316 g/mL at 20 °C	
Water solubility	0.189 mg/L at 25 °C	
Solvent solubility	g/100 mL at 25 °C: hexane 0.328 n-octanol 1.60 methanol 4.78 Solvesso 150 27.1 acetonitrile 58.9 acetone 59.0 tetrahydrofuran 69.7 N-methyl 2-pyrrolidinone 134.0 methylene chloride 288.0	
Vapor pressure	$<1 \times 10^{-7}$ mm Hg at 22.4 °C	
Dissociation constant, pK_a	No dissociation at pH ≤7; flumiclorac pentyl decomposes at pH ≥9.	
Octanol/water partition coefficient	Log P_{OW} = 4.99 at 19.7-21.0 °C	
UV/visible absorption spectrum	Not available	

B. EXPERIMENTAL DESIGN

B.1. Sample Handling and Preparation

In one study, samples of untreated cotton undelinted seed and gin byproducts were fortified with flumiclorac pentyl in acetone at 0.10 ppm. Fortified and unfortified samples were then stored in the freezer at approximately -20 °C. Stored fortified and fresh fortified samples of cottonseed and gin byproducts were analyzed following 33 and 61 days of storage. We note that raw data were not provided for the storage stability study using fortified samples.

In another study, treated cotton gin byproduct samples with weathered residues from cotton field trials were stored frozen and re-extracted 99 and 124 days after the initial extraction. Fresh fortification samples were analyzed with the re-extracted samples.

B.2. Analytical Methodology

Samples were analyzed for residues of flumiclorac pentyl using a GC Method (RM-29-2a). This method was also used for analysis of samples from the associated cotton field trials and is a modified version of Method RM-29-2 (current enforcement method for flumiclorac pentyl in/on

soybeans), in which the cleanup step uses an alumina column instead of a silica column. The validated limit of quantitation (LOQ) was 0.02 ppm, and the reported limit of detection (LOD) was 0.01 ppm for undelinted cottonseed and gin byproducts.

Briefly, homogenized samples were sequentially extracted with 2% acetic acid in acetonitrile (ACN; 2x) and ACN:water (1:1, v:v), and then filtered. A 5% sodium chloride solution was added to the combined extracts, and residues were partitioned (2x) into methylene chloride. The combined methylene chloride phases were concentrated by rotary evaporation to remove the solvent, and residues were redissolved in ACN (saturated with hexane). Residues were then partitioned with hexane (saturated with ACN). The ACN phase was concentrated to remove the solvent, and residues were redissolved in hexane:ethyl acetate (4:1, v:v) for clean up through an alumina column; residues were eluted with hexane/ethyl acetate. The eluant was concentrated and residues were redissolved in acetone for GC analysis using nitrogen-phosphorous detection (NPD) and external calibration standards.

A. RESULTS AND DISCUSSION

Concurrent method recovery data are presented in Table C.1. Based on these data, the GC/NPD method (RM-29-2a) is adequate for the determination of residues of flumiclorac pentyl in/on undelinted cottonseed and gin byproducts.

The results of the storage stability studies are presented in Tables C.2.1 (fortified samples) and C.2.2 (weathered samples). The submitted storage stability data indicate that residues of flumiclorac pentyl are relatively stable under frozen conditions in/on fortified cotton undelinted seed and gin byproducts for up to 61 days (~2 months), and in/on gin byproducts with weathered residues for up to 124 days (~4 months).

TABLE C.1. Summary of Method Recoveries of Flumiclorac Pentyl from Cotton Matrices.

Matrix (MRID)	Spike level (ppm)	Storage Interval (days)	Sample size (n)	Recovery (%)	Mean
Cotton, undelinted seed (46102801)	0.10 [1]	0	not specified	93	93
		33	not specified	83	83
		61	not specified	98	98
Cotton, gin byproducts (46102801)	0.10 [1]	0	not specified	94	94
		33	not specified	70	70
		61	not specified	100	100
Cotton, gin byproducts (46082808)	0.2, 2.0	0	2	93.6, 94.0	93.8
	2.0	99	2	73.1, 79.1	76.1
	0.02, 0.1	0	2	76.8, 76.8	76.8
	0.1, 0.2	124	2	85.0, 93.4	89.2

[1] Assumed to be fortified at the same level as the stored samples and reported concurrent recoveries were average values; raw data were not provided.

C.2.1. Stability of Fortified Flumiclorac Pentyl Residues in Cotton Matrices Following Storage at -20 °C (MRID 46102801).

Commodity	Spike level (ppm)	Storage interval (days)	Recovered residues (ppm)	% Recovery [1]
Cotton, undelinted seed	0.10	0	0.090, 0.095	97, 102
		33	0.074, 0.085	89, 102
		61	0.078, 0.081	80, 83
Cotton, gin byproducts	0.10	0	0.090, 0.097	96, 103
		33	0.066, 0.084	94, 120
		61	0.087, 0.096	87, 96

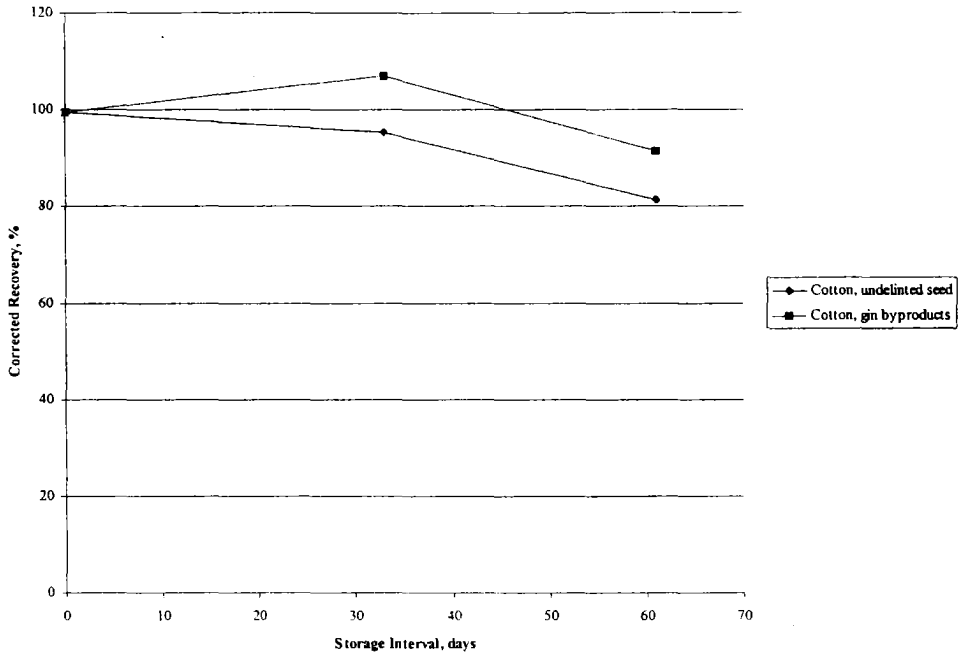
[1] Corrected for average procedural recovery.

C.2.2. Stability of Weathered Flumiclorac Pentyl Residues in Cotton Gin Byproducts Following Storage at -20 °C (MRID 46082808).

Commodity	Uncorrected Residues (ppm) at Initial Extraction (0 day)	Uncorrected Residues (ppm) following Storage		% Change [1]
		99 days	124 days	
Cotton, gin byproducts: Samples V-24838-H29 and -H30	2.029, 2.200	1.436, 2.075	--	-17.0
Cotton, gin byproducts: Samples V-24838-H17 and -H18)	0.169, 0.194	--	0.195, 0.192	+6.6

[1] Percent change was calculated by the study reviewer as average stored residues minus average initial residues, divided by average initial residues (x100); the petitioner used corrected residue values to calculate % change in stored samples.

FIGURE C.1. Graph of Storage Stability of Flumiclorac Pentyl Residues in Fortified



Cottonseed and Gin Byproducts.

D. CONCLUSION

The submitted storage stability data indicate that residues of flumiclorac pentyl are relatively stable under frozen conditions in/on cotton undelinted seed for up to 61 days (~2 months) and gin by products for up to 124 days (~4 months).

E. REFERENCES

None.

F. DOCUMENT TRACKING

RDI: Catherine Eiden (24-JUN-2005)
Petition Number: PP#3F6767
DP Barcode: D308674
PC Code: 128724

Template Version September 2003

13544

R110599

Chemical:	**Flumiclorac**
PC Code:	**128724**
HED File Code	**11500 Petition Files Chemistry**
Memo Date:	***06/24/2005***
File ID:	**DPD308674**
Accession Number:	**412-05-0098**

HED Records Reference Center
07/11/2005