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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: 06/28/2005

MEMORANDUM

SUBJECT: Flumiclorac Pentyl: HED Chapter of the Tolerance Reassessment Eligibility Decision Document (TRED). PC Code: 128724, DP Barcode: D302019.
Regulatory Action: Phase 1 Reregistration Action
Risk Assessment Type: single Chemical Aggregate

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1.0 Executive Summary

The Health Effects Division (HED) of EPA's Office of Pesticide Programs has evaluated the toxicity and exposure data bases for the pesticide active ingredient flumiclorac pentyl and has conducted a human health risk assessment in support of the Reregistration Eligibility Decision (RED) for this active ingredient.

Use Information

Flumiclorac pentyl [(2-chloro-4-fluoro-5-(1,3,4,5,6,7-hexahydro-1,3-dioxo-2H-isoindol-2-yl)phenoxy)acetic acid, pentyl ester] 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.

Toxicology

The available toxicity data on flumiclorac pentyl are adequate to assess the chemical's hazard potential. Technical flumiclorac pentyl has low acute toxicity via the oral, dermal and inhalation routes of exposure. It is a slight eye irritant and is a dermal sensitizer. Flumiclorac pentyl has low toxicity potential following long-term exposures. In the rat, the kidney is a potential target organ at high dose levels. Effects included urinary incontinence, increased water consumption, increased urine volume, increased urine volume and increased kidney weights in the females, and increased squamous epithelial cells in urinary sediment and increased kidney weights in the males. Nephropathy was evident in males rats in a two-generation reproduction study following administration of high dose levels. In dogs, toxicity consisted of decreases in body weight (males), prolongation of activated partial thromboplastin time (females), increase in globulin levels (females) and increase in the alpha-2 fraction of the serum protein electrophoresis (females).

Flumiclorac pentyl did not cause developmental toxicity in rat or rabbit fetuses and did not adversely affect reproductive parameters in rats in a two-generation study. There is no quantitative or qualitative evidence of increased susceptibility of rat or rabbit fetuses after *in utero* and/or postnatal exposure to flumiclorac pentyl in the developmental and reproduction studies. Dose-response relationships are well-characterized and clear NOAELs/LOAELs have been identified for the critical effects. Therefore, the special FQPA safety factor can be reduced to 1X, since the degree of concern is low and there are no residual uncertainties for pre- and/or postnatal toxicity.

No evidence of neurotoxicity was observed in any study. Based on the weight of evidence, a developmental neurotoxicity (DNT) study is not required for flumiclorac pentyl.

No evidence for carcinogenicity was seen in mice or rats. The chemical was negative for gene mutation in *Salmonella typhimurium* and did not induce micronucleus formation in the mouse or unscheduled DNA synthesis in rat hepatocytes. Results for chromosome aberrations in CHO cells were weakly positive without metabolic activation but negative in the presence of activation.

A chronic reference dose (cRfD) of 1.0 mg/kg/day was established for flumiclorac pentyl based on the NOAEL of 100 mg/kg/day in the chronic dog study and an uncertainty factor of 100 (10X for interspecies extrapolation and 10X for intraspecies variation). Decreased body weight gain in males, and increased clotting time (males and females), and increased globulin levels and alpha-2 fraction of the serum protein electrophoresis occurred in this study at the LOAEL of 1000 mg/kg/day. An acute reference dose (aRfD) was not established, since an endpoint attributable to a single exposure was not identified from the available database.

Residue Chemistry

The available residue chemistry data are adequate to assess human dietary exposure to flumiclorac pentyl from the consumption of treated food commodities. Permanent tolerances are established for residues of flumiclorac pentyl, including all the metabolites of flumiclorac pentyl. The tolerance levels are 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. Residues in ruminant and poultry commodities may be classified under 40 CFR §180.6(a)(3); i.e., no expectation of finite residues. Therefore, tolerances for livestock commodities are not required at the present time. However, the petitioner should 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. Also, information pertaining to sample storage intervals are needed to support the poultry metabolism studies.

Environmental Fate

The available environmental fate data for flumiclorac pentyl are adequate to assess the residues of concern in drinking water. The water exposure/risk pathway analysis included parent flumiclorac pentyl and the major degradate in the aerobic soil metabolism study (IMCA or flumiclorac-acid) in its assessment. IMCA is a metabolite in both plants and animals and is not considered a regulated metabolite in foods. Therefore, the water concentrations provided by EFED may be considered to be conservative estimates. Since estimated exposures and risks based on these drinking water levels are low, refinement of the drinking water concentrations to exclude the degradate is not warranted.

Residential Exposure

There is potential post-application, non-occupational (residential) exposure and in particular potential exposure to children through the use of flumiclorac pentyl on such sites listed on one of the product labels (EPA Reg. No. 59639-122) as golf courses, parks, recreation areas, schools, apartment buildings etc. Short-term risk assessments have been completed for residential postapplication scenarios.

Children were identified as the most sensitive of potentially exposed populations to residential post-application exposures to flumiclorac pentyl. There are four possible exposure scenarios for a toddler or child: hand to mouth, turf to mouth, soil to mouth and playing on treated turf. Since a dermal endpoint of concern was not selected, dermal risks were not assessed. The *SOPs For Residential Exposure Assessment (Reference B)* define several pathways that apply to post application exposure on treated turf and were utilized for these scenarios. MOEs raqnged from 58,230 to 1.75 E^7.

Occupational Exposure

A Section 3 registration is being requested for the end-use product containing flumiclorac pentyl as active ingredient. The proposed uses include the use of Resource™ herbicide (flumiclorac pentyl ester 10.1%, liquid) on cotton (0.054 lb ai/A) by ground or aerial equipment. Handler exposures are expected to be short-/intermediate-term in duration. Long-term exposures (> 6 months) are not expected. Since no chemical-specific data for assessing human exposures during pesticide handling activities were submitted to the Agency in support of the registration of flumiclorac pentyl, the Health Effects Division (HED) used surrogate data from the Pesticide Handlers Exposure Database (PHED) Version 1.1. Defaults established by the HED Science Advisory Council for Exposure were used for acres treated per day and body weight. All MOEs were above the level of concern at the baseline level (91,000 - 1,100,000) and at the engineering control level (for aerial application; 1,600,000). Dermal exposure was not assessed, since a dermal endpoint of concern has not been identified for flumiclorac pentyl.

Dietary Exposure Assessment

A chronic dietary risk assessment was conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™),Version 2.00, and the Lifeline Model Version 2.0, which use food consumption data from the USDA's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. The Tier 1 chronic analysis assumed 100% crop treated and tolerance-level residues for all foods. Drinking water was incorporated directly in the dietary assessment using the chronic estimated drinking water concentration (EDWC) for surface water generated by the FIRST model.

The resulting chronic dietary exposure estimates using the DEEM-FCID model were less than 1% of the cPAD for the U.S. population and all population subgroups. Flumiclorac pentyl chronic dietary exposure (food + water) was estimated at 0.000034 mg/kg/day for the U.S. population (<0.01% of the cPAD) and 0.000074 mg/kg/day (<0.01% of the cPAD) for the most highly exposed population subgroup (Children, 3 to 5 yrs. old). Estimated chronic exposures

using the Lifeline model were consistent with the DEEM-FCID results (<0.01% of the cPAD for the U.S. population and all population subgroups).

Aggregate Risk

Short- and long-term (chronic) aggregate risk assessments were conducted for flumiclorac pentyl. The short-term assessment considered both dietary (food + water) and residential exposures. The long-term assessment considered dietary exposure only, since the current uses of flumiclorac pentyl are not expected to result in long-term residential exposure. Intermediate-term residential exposures are not anticipated and therefore, an intermediate-term aggregate risk assessment was not conducted.

The results of the chronic dietary assessment indicate that the combined exposure to flumiclorac pentyl from food and water is well below HED's level of concern, with estimated exposures representing <0.01% of the cPAD for the U.S. population and all population subgroups, including infants and children. When the chronic dietary exposure is combined with short-term residential exposure, the resulting aggregate risks for children are also below HED's level of concern. The MOE of concern for short-term aggregate risk is 100. Since the estimated short-term aggregate risk MOE for children (toddlers) is 46,000 short-term aggregate is not considered to be of concern for flumiclorac pentyl.

Conclusions

Flumiclorac pentyl is a relatively low toxicity pesticide whose potential routes of exposure include food, drinking water and residential areas. Under the conditions of its current use, human health risks to workers handling the pesticide or to the general population are below HED's level of concern. Aggregate risk MOEs from the consumption of food/drinking water and from exposure to the pesticide in residential settings exceed 100 for all populations, including infants and children.

2.0 Ingredient Profile

Flumiclorac pentyl [(2-chloro-4-fluoro-5-(1,3,4,5,6,7-hexahydro-1,3-dioxo-2H-isoindol-2-yl)phenoxy)acetic acid, pentyl ester] 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.

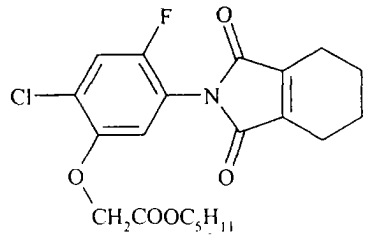
2.1 Summary of Supported Uses

Flumiclorac pentyl is registered for postemergence application to field corn and soybeans; registration for use on cotton as a defoliant is pending.

Table 2.1. 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

2.2 Structure and Nomenclature

TABLE 2.2. 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

2.3 Physical and Chemical Properties

Flumiclorac pentyl is a non-volatile solid with low water solubility.

TABLE 2.3. 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	

3.0 Metabolism Assessment

3.1 Comparative Metabolic Profile

Rat metabolism: In the rat, flumiclorac pentyl is rapidly absorbed and eliminated; after 48 hours, 92.7-97.8% of the administered radioactivity was recovered in the urine and feces. Tissue accumulation of radio-labeled residues was found to be very low, with detectable amounts noted only in the kidney and liver. The primary metabolic transformation involves deesterification to a phenoxyacetic acid derivative. Table 3.4 summarizes the structures of flumiclorac pentyl and its transformation products. In further reactions, the deesterified residues can be cleaved of the imide moiety or undergo a series of hydroxylation and/or sulfonation reactions.

Plant metabolism: In plants, flumiclorac pentyl is rapidly degraded to several polar metabolites with no substantial residues of the parent (approximately 3% of the total residue). The pathways of degradation include hydrolysis of the ester and imide linkages and hydroxylation and reduction of the tetrahydrophthalimide moiety. 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%); further metabolism and conjugation leads to the incorporation of 25-50% of the applied labeled into bound residues.

Livestock metabolism: In livestock, flumiclorac pentyl is rapidly metabolized and excreted. Based on the phenyl- and THP-labeled goat metabolism studies, the proposed metabolic reactions in goats involves: (i) initial hydrolysis of the pentyl ester of flumiclorac pentyl to form IMCA; (ii) further metabolism of IMCA by cleavage of the imide ring to form AFCA and

THPA, which are readily excreted; (iii) formation of SAT-IMCA in liver and kidney via a reduction process; and (iv) hydrolysis of SAT-IMCA to form HPA in goat kidney, urine and feces. 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 ring and subsequently formed amide; (iii) hydroxylation of the cyclohexane ring; and (iv) olefin reduction.

Water degradates: In water, parent flumiclorac pentyl was found to degrade rapidly to a variety of compounds. IMCA was the major degradate found in the aerobic soil metabolism studies, although it was also found not to be persistent.

Qualitatively, the metabolism of flumiclorac pentyl is similar across the various matrices studied. The major metabolites and degradates found in the plant, livestock and water studies were also found in the rat metabolism study.

3.2 Nature of the Residue in Foods

3.2.1. Description of Primary Crop Metabolism

The qualitative nature of flumiclorac pentyl residues in field corn, soybean, and cotton is understood based on the adequate field corn and soybean metabolism studies.

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. The risk assessment team determined that flumiclorac-pentyl, per se, is the residue of concern for plant commodities.

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. HED concluded that additional metabolic studies were not needed for corn, because the metabolism of flumiclorac pentyl in corn was similar to that in soybeans.

3.2.2 Description of Livestock Metabolism

The qualitative nature of flumiclorac pentyl residues in poultry and ruminants is understood based on the adequate goat and hen metabolism studies. The flumiclorac pentyl risk assessment team has determined that the residue of concern in livestock commodities is flumiclorac pentyl *per se*. The basis for this decision is as follows:

- Residues found in livestock matrices are similar to those found in plants. Accordingly, inclusion of livestock metabolites in the risk assessment is not warranted.
- The existing and proposed uses of flumiclorac pentyl are expected to result in low absolute residue levels in livestock commodities. Accordingly, the flumiclorac pentyl risk assessment team has classified flumiclorac pentyl residues under 40 CFR §180.6(a)(3).

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.

Based on the metabolism study results, low levels of residues found in feedstuffs, and low tissue transfer ratios observed, the flumiclorac pentyl risk assessment team has classified flumiclorac pentyl residues under 40 CFR §180.6(a)(3), "no reasonable expectation of finite residues for meat, milk, poultry, and eggs." This conclusion should be reevaluated should the dietary burden to livestock be increased as a result of any additional new uses of flumiclorac pentyl.

3.2.3 Description of Rotational Crop Metabolism, including identification of major metabolites and specific routes of biotransformation

Identification and characterization of residues resulting from the confined rotational crop study was not possible due to the low residue levels found following treatment of soil at the maximum seasonal rate allowed for crops (0.11 lb ai/A). 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 so that residue characterization and identification can be accomplished.

3.3 Environmental Degradation

Acceptable data suggest that parent flumiclorac pentyl is not persistent or mobile. Flumiclorac pentyl hydrolyzes and metabolizes within hours or days into a number of bulky anionic degradates which are mobile and may be herbicidally active. However, the degradates representing major portions of the molecule also do not appear to be especially persistent, with soil half-lives of two weeks.

Under abiotic hydrolysis at pH 5 and 7, the tetrahydrophthalimido group appears to break off to form tetrahydrophthalic acid (THPA). At pH 5, the phenyl substituted ring moiety appears to be more stable, with pentyl 5-amino-2-chloro-4-fluorophenoxyacetate (AFE) the final product. At pH 7, this moiety degrades further to 5-amino-2-chloro-4-fluorophenoxyacetic acid (AFCA). At pH 9, degradation does not appear to be as complete, with 2-chloro-4-fluoro-5-(3,4,5,6-tetrahydrophthalimido) phenoxyacetic acid (IMCA), and N-(5-carboxymethoxy-4-chloro-2-

fluorophenyl)-3,4,5,6-tetrahydrophthalamic acid (IMCA-HA) the final products. Aerobic metabolism of flumiclorac pentyl appears to degrade it first to IMCA, and then to AFCA and THPA. Within 85 days, both AFCA and THPA may be metabolized further and become bound residues.

In the presence of light further breakdown and/or mineralization of flumiclorac pentyl degradates appears to be accelerate, although the half-life of parent flumiclorac pentyl appears to be unaffected. While less than 0.5% of the applied radioactivity is released as $^{14}CO_2$ from flumiclorac systems maintained in the dark, the irradiated aqueous system with phenyl-labeled flumiclorac pentyl released 22.81% of the applied radioactivity as $^{14}CO_2$. This effect is less striking on soil: 7.32% of the applied radioactivity was mineralized to $^{14}CO_2$ when phenyl-labeled flumiclorac pentyl was applied to viable soil and irradiated for 21 days.

Field data appears to confirm that flumiclorac pentyl and its degradates do not leach. Although flumiclorac pentyl degrades to compounds that do not bind strongly to soil, these compounds themselves appear to be so short-lived that they degrade further before moving a significant distance through the soil. However, the fate of flumiclorac pentyl residues at the surface is less clear. In radiolabeled lysimeter studies, nearly 50% of the applied radioactivity appears to have dissipated to the atmosphere in the course of studies ranging from 112 to 120 days, with the fastest dissipation occurring in 14 days. This far exceeds the rate of mineralization reported in the laboratory, and raises the possibility that some of the parent material or degradates may be volatilizing. Herbicide drift due to volatilization is considered a significant risk to off-target plants.

In an unconfined field situation, some of the flumiclorac pentyl degradates could be entrained in runoff. Although the anaerobic aquatic metabolism study suggests that the majority of the material is associated with the soil rather than the water most of the time, there are periods when the majority of the material may associate with the water. In the field study in Kentucky, up to 28.65% of the applied radioactivity was found in the surface water at day 3. Many early flumiclorac pentyl degradates include large portions of the original molecule, and their off-site movement may represent a phytotoxicity hazard to non-target plants. However, flumiclorac pentyl degradates appear to be more susceptible to photolysis when they are in solution, and would be unlikely to persist for more than a few days in an aquatic environment.

3.4 Tabular Summary of Metabolites and Degradates

Table 3.4. Chemical Name and Structure of Flumiclorac Pentyl and Its Transformation Products.

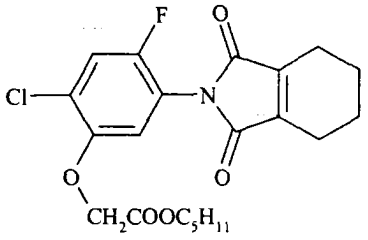
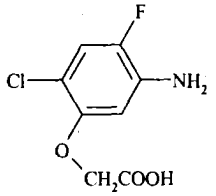
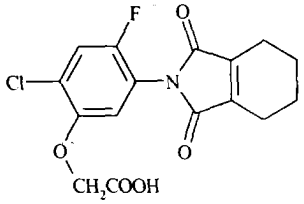
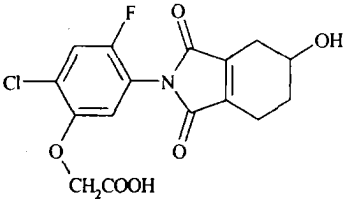
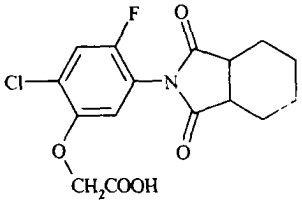
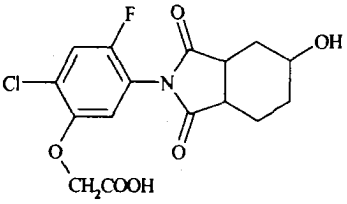
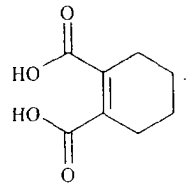
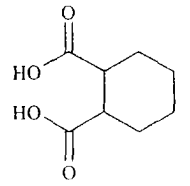
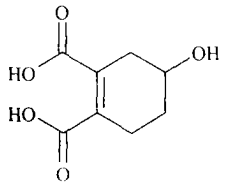
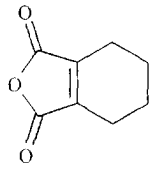
Company Name	Chemical Name	Structure
Flumiclorac pentyl; S-23031 or V-23031	Pentyl[2-chloro-4-fluoro-5-(1,3,4,5,6,7-hexahydro-1,3-dioxo-2H-isoindol-2-yl)phenoxy]acetate or Acetic acid, {2-chloro-4-fluoro-5-(1,3,4,5,6,7-hexahydro-1,3-dioxo-2H-isoindol-2-yl)phenoxy}-,pentyl ester or 2-chloro-4-fluoro-5-(1,3,4,5,6,7-hexahydro-1,3-dioxo-2H-isoindol-2-yl)phenoxy]acet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

Table 3.4. Chemical Name and Structure of Flumiclorac Pentyl and Its Transformation Products.		
Company Name	Chemical Name	Structure
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	

3.5 Toxicity Profile of Major Metabolites and Degradates

The HED Metabolism Committee discussed the metabolism of flumiclorac pentyl in plants, and reached the following conclusions (HED Metabolism Committee, R. Loranger, 27-JUL-1994):

1) The parent compound exhibits relatively low toxicity.
2) Based on the results of the rat metabolism study, the toxicology studies reflect exposure to the metabolites.
3) 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 corn and soybean uses.

The available metabolism data on soybeans and field corn may be used to support the proposed use on cotton. Although the shorter PHI for cotton may result in the expectation of somewhat higher flumiclorac pentyl residue levels in cotton RACs, HED notes that the maximum level found in undelinted cottonseed was only 0.11 ppm in the crop field trial studies. Because there is no evidence that any of the metabolites are more toxic than the parent, identification of residues of concern is based on expected abundance of metabolites/degradates in the various matrices considered.

3.6 Summary of Residues for Tolerance Expression and Risk Assessment

3.6.1 Tabular Summary

Table 3.6. Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	flumiclorac pentyl *per se*	flumiclorac pentyl *per se*
	Rotational Crop	flumiclorac pentyl *per se*	flumiclorac pentyl *per se*
Livestock	Ruminant	Not Applicable - no residues expected	Not Applicable - no tolerances required
	Poultry	Not Applicable - no residues expected	Not Applicable - no tolerances required
Drinking Water		flumiclorac pentyl and IMCA	Not Applicable

3.6.2 Rationale for Inclusion of Metabolites and Degradates

The flumiclorac pentyl risk assessment team has determined that the regulated residues in field corn, soybean, and cotton will include parent only for the purpose of tolerance enforcement and risk assessment. The basis for this decision is as follows:

- Low use rates and relatively long PHIs result in low residue levels being found in edible crop parts.

- The tolerance enforcement methods for plants (RM 29-1 and RM 29-2) were developed to detect parent only. The overall low residue levels found in foods precludes the need for including metabolites in the tolerance expression and developing the additional analytical methodology that would be required for enforcement purposes.

Because there is no reasonable expectation of quantifiable residues of flumiclorac pentyl occurring in livestock commodities [40 CFR §180.6(a)(3)], no tolerances are appropriate for livestock commodities. In the case of drinking water, flumiclorac pentyl and IMCA were included in the drinking water modeling. IMCA was included because it was the major degradate found in the aerobic soil metabolism study. No other degradates were included because the addition of other molecules to the water assessment would be unlikely to change the input parameter derived from the aerobic soil metabolism studies (half-life in soil); consequently, the quantitative results would not be significantly affected by inclusion of additional degradates.

4.0 Hazard Characterization/Assessment

4.1 Hazard Characterization

Flumiclorac pentyl (S-23031) has low acute toxicity with no deaths occurring near the limit dose for oral, inhalation, and dermal studies (Table 4.1a). Clinical signs of toxicity suggestive of irritation were observed only in animals treated by inhalation. The chemical caused slight eye irritation, which cleared after 24 hours. It is a dermal sensitizer.

Flumiclorac has low toxicity potential. In the rat, the kidney is a potential target organ at high dose levels. Long-term administration of flumiclorac (≥ 443.8 mg/kg/day) to female rats resulted in urinary incontinence, increased water consumption, increased urine volume and increased kidney weights. Male rats treated with 744.9 mg/kg/day doses displayed increased squamous epithelial cells in urinary sediment, increased urine volume and increased kidney weights. Although no renal pathological lesions were noted in the chronic oral rat study, nephropathy was observed in a two-generation rat reproduction study in which male rats were administered ≥781 mg/kg/day dose levels. The NOAEL for the nephropathy was 16 mg/kg/day; due to dose spacing the potential renal toxicity at dose levels below 781 mg/kg/day were not assessed. Female rats exhibited increased kidney weights at dose levels of ≥925 mg/kg/day). Urinalysis was not performed so urinary incontinence, a clinical correlate of potential renal damage, was not confirmed in the two-generation reproduction study. The nephropathy was characterized as a "syndrome of renal tubular changes, beginning with a dilatation of the convoluted tubules followed by necrosis of the tubular epithelium and regeneration of epithelial cells."

Toxicity in the dogs was manifested as significant decreases in body weight (males) and alterations in activated partial thromboplastin time (females), a measurement of clotting time in the plasma. Prolongation of activated partial thromboplastin time was noted in female dogs administered 1000 mg/kg/day for 90 days or for 1 year. The females also exhibited a slight increase in globulin levels between weeks 26 through 52, and a slight increase in the alpha-2 fraction of the serum protein electrophoresis at week 52. Cumulative body weight gain in male dogs treated with 1000 mg/kg/day for 1 year was 30% of the control level during weeks 0-4 and 42-47% of the control level during the remainder of the study. There was no effect on food efficiency.

No evidence of neurotoxicity was observed in any study.

In developmental toxicity studies, maternal toxicity was evident in rabbits as increased mortality at 800 mg/kg/day, the highest dose tested. No maternal toxicity was observed in rats at doses up to 1500 mg/kg/day. No developmental toxicity was observed in either species. Fetal body weight was similar between the treated and control groups and no treatment-related external, visceral, or skeletal abnormalities were found.

Reproductive performance was not affected in a two-generation reproduction toxicity study in which flumiclorac pentyl was administered to male and female rats at nominal

dietary concentrations of 0, 200, 10,000, and 20,000 ppm (0, 16-17, 781-878, 1610-1821 mg/kg/day, respectively, for males and 0, 18-19, 925-936, 1821-1909 mg/kg/day, respectively, for females). As mentioned above, evidence of parental toxicity in the mid- and high-dose groups included increased kidney weight in F_1 males and F_0 and F_1 females and nephropathy in F_0 and F_1 males. Weight gain during premating was comparable between the treated and control groups of both generations.

Body weight of the high-dose F_2 pups was significantly less than that of the controls on lactation day 21. The effect on absolute body weight was due to decreased weight gain by the high-dose pups (85% of the control level) during lactation days 14-21. The effect on F_2 pup body weight is considered to be a systemic effect after the pups began eating the treated diet. The LOAEL is 20,000 ppm and the NOAEL is 10,000 ppm.

No evidence for carcinogenicity was seen in mice or rats. Administration of flumiclorac pentyl to mice for 19 months and to rats for 24 months did not result in an increase in overall tumor incidence or an increase in the incidence of any specific type of tumor. The chemical was negative for gene mutation in *Salmonella typhimurium* and did not induce micronucleus formation in the mouse or unscheduled DNA synthesis in rat hepatocytes. Results for chromosome aberrations in CHO cells were weakly positive without metabolic activation but negative in the presence of activation.

No systemic toxicity was observed at the limit dose (1000 mg/kg/day) in the dermal toxicity study in the rat.

Flumiclorac pentyl is rapidly absorbed, metabolized, and excreted by the rat following oral administration. The major metabolic route is deesterification to a phenoxyacetic acid derivative followed by cleavage of the imide moiety or hydroxylation and/or sulfonation reactions. Detectable residues were found only in liver and kidney. No major sex differences in metabolic profiles have been observed after an oral dose, but females had higher accumulation of residues in the kidney than males. After oral dosing, elimination of parent compound is almost exclusively in the feces and excretion of metabolites occurs via the urine.

The data base for flumiclorac pentyl is complete. No data gaps have been identified.

Table 4.1a	Acute Toxicity Profile - Flumiclorac pentyl			
Guideline No.	**Study Type**	**MRID(s)**	**Results**	**Toxicity Category**
870.11	Acute oral [rat] (S-23031)	42169812	LD_{50} = >5000 mg/kg	IV
870.11	Acute oral [rat] (V-23031 0.83 EC)	42169813	LD_{50} = 4.1 g/kg (m) LD_{50} = 3.2 g/kg (f) LD_{50} = 3.6 g/kg (both)	III
870.12	Acute dermal [rat] (S-23031)	42169814	LD_{50} = >2000 mg/kg	III
870.12	Acute dermal [rat] (V-23031 0.83 EC)	42169815	LD_{50} = >2000 mg/kg	III
870.13	Acute inhalation [rat] (S-23031)	42169816	LC_{50} = >5.94 mg/L	IV
870.13	Acute inhalation [rat] (V-23031 0.83 EC)	42169817	LC_{50} = 5.51 mg/L	IV
870.24	Acute eye irritation [rabbit] (S-23031)	42169818	slight	III
870.24	Acute eye irritation [rabbit] (V-23031 0.83 EC)	42169819	irritating	II
870.25	Acute dermal irritation [rabbit] (V-23031 0.83 EC)	42169820	moderate	II
870.26	Skin sensitization [guinea pig] (S-23031)	42169822	extreme (Maximization method)	Sensitizer
870.26	Skin sensitization [guinea pig] (V-23031 0.83 EC)	4.22e+15	none (Buehler's method) strong (Maximization method)	Nonsenitizing Sensitizer

Table 4.1b Subchronic, Chronic and Other Toxicity Profile		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100 90-Day oral toxicity (rat)	42169823 (1990) 42310801 (addendum) Acceptable/guideline M: 0, 6.6, 67, 664, 1359 mg/kg/d F: 0, 7.4, 73.8, 726, 1574 mg/kg/d	NOAEL = ≥1359/1574 mg/kg/day (M/F) LOAEL = not identified
870.3150 90-Day oral toxicity (dog)	42169827 (1991) 42310802 (addendum) Acceptable/guideline M&F: 0, 10, 100, 1000 mg/kg/d	NOAEL = 100 mg/kg/day LOAEL = 1000 mg/kg/day based on increased clotting time in females.
870.3200 21/28-Day dermal toxicity	42825815 (1991) Acceptable/guideline M&F: 0, 100, 300, 1000 mg/kg/day	NOAEL = 1000 mg/kg/day (limit dose)
870.3250 90-Day dermal toxicity	N/A	N/A
870.3465 90-Day inhalation toxicity	N/A	N/A
870.3700a Prenatal developmental (rat)	42169832 (1990) 42169831 (range-finding, 1990) Acceptable/guideline F: 0, 50, 500, 1500 mg/kg/d (GD 6-15)	**Maternal** NOAEL = ≥1500 mg/kg/day LOAEL = not identified **Developmental** NOAEL = ≥1500 mg/kg/day LOAEL = not identified
870.3700b Prenatal developmental (rabbit)	42169830 (1991) 42169829, 42169828 (range-finding, 1990) Acceptable/guideline F: 0, 100, 200, 400, 800 mg/kg/d (GD 6-19)	**Maternal** NOAEL = 400 mg/kg/day LOAEL = 800 mg/kg/day based on mortality **Developmental** NOAEL = ≥800 mg/kg/day LOAEL = not determined
870.3800 Reproduction and fertility effects (rat)	42169835 (1991) 42169834 (range-finding, 1990) Acceptable/guideline M: 0, 16, 781, 1610 mg/kg/d F: 0, 18, 925, 1869 mg/kg/d	**Parental/Systemic** NOAEL = 16/18 mg/kg/day (M/F) LOAEL = 781/925 mg/kg/day (M/F) based on increased kidney weight in males and females and nephropathy in males. **Reproductive** NOAEL = ≥1610/1869 mg/kg/day (M/F) LOAEL = not identified. **Offspring** NOAEL = 781/925 mg/kg/day (M/F) LOAEL = 1610/1869 mg/kg/day (M/F) based on decreased body weight/body weight in F_2 pups.

Table 4.1b Subchronic, Chronic and Other Toxicity Profile		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.4100b Chronic toxicity (dog)	42825817 (1992) Acceptable/guideline M&F: 0, 10, 100, 1000 mg/kg/d	NOAEL = 100 mg/kg/day LOAEL = 1000 mg/kg/day based on decreased body weight gain in male; increased clotting time, increased globulin levels, and increased alpha-2 fraction of the serum protein electrophoresis in females.
870.4200b Carcinogenicity (mouse)	42883905 (1992) Acceptable/guideline M: 0, 31.5, 307.9, 731.4 mg/kg/d F: 0, 37.8, 368.1, 850.2 mg/kg/d	NOAEL = 731.4 mg/kg/day (MF); 850.2 mg/kg/day (F) LOAEL = not identified **no evidence of carcinogenicity**
870.4300 Chronic/Carcino-genicity (rat)	42883906 (1992) Acceptable/guideline M: 0, 3.5, 35.4, 360.4, 744.9 mg/kg/d F: 0, 4.3, 43.6, 443.8, 919.4 mg/kg/d	NOAEL = ≥744.9/919.4 mg/kg/day (M/F) LOAEL = not identified **no evidence of carcinogenicity**
Gene Mutation 870.5100 (*Salmonella typhimurium*)	42169836 (1989) Unacceptable/guideline (upgradable)	negative up to 5000 µg/plate with and without metabolic activation (information needs to be provided that the tester strains were properly maintained and that they were checked for genetic markers)
Cytogenetics 870.5375 (CHO)	42169838 (1989) Unacceptable/guideline (upgradable)	negative for chromosome aberration up to 400 µg/mL with metabolic activation; weak, positive response without activation (documentation needed indicating that the cell cultures were properly maintained and periodically checked for both mycoplasma contamination and karyotype stability)
Micronucleus 870.5395 (mouse)	42169837 (1990) Acceptable/guideline	negative at doses up to 5000 mg/kg
Unscheduled DNA Synthesis 870.5550 (rat hepatocytes)	42169839 (1989) Acceptable/guideline	negative at concentration up to 300µg/mL in cultured rat hepatocytes
870.6200a Acute neurotoxicity screening battery		not required
870.6200b Subchronic neurotoxicity screening battery		not required

Table 4.1b Subchronic, Chronic and Other Toxicity Profile		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.6300 Developmental neurotoxicity		not required
870.7485 Metabolism and pharmacokinetics (rat)	42169840 (1991) Unacceptable/guideline (upgradable)	rapid absorption and excretion; major metabolic route is deesterification to a phenoxyacetic acid derivative followed by cleavage of the imide moiety or hydroxylation and/or sulfonation reactions (data needed on characterization of the metabolites containing the phthalimide moiety, a specification sheet for the analysis of the labeled test article, methods used to isolate and identify 4-OH-IMCA isomers and 5-OH-IMCA-SA, biliary excretion)
Special studies		none required

4.2 FQPA Hazard Considerations

4.2.1 Adequacy of the Toxicity Data Base

Data are adequate for evaluation of effects resulting from *in utero* and post-natal exposure. Acceptable developmental toxicity studies have been conducted in rodents and non-rodents, and a reproductive toxicity study in rodents is available.

4.2.2 Evidence of Neurotoxicity

Neurotoxicity studies have not been conducted with flumiclorac pentyl. However, no evidence of neurotoxicity was observed in any study. No clinical signs indicative of toxicity were noted in subchronic and chronic studies in dogs, rats, or mice.

4.2.3 Developmental Toxicity Studies

Developmental toxicity studies have been conducted with flumiclorac pentyl in the rat and rabbit. Rats were administered 0, 50, 500, or 1500 mg/kg/day by oral gavage on GDs 6-15. Rabbits were treated orally with 0, 100, 200, 400, or 800 mg/kg/day on GDs 6-19. The high dose was greater than the limit dose for rats and slightly less than the limit dose for rabbits. Maternal toxicity, demonstrated by increased mortality, was evident only in rabbits at the highest dose.

No developmental toxicity was observed in either species. Fetal body weight was similar between the treated and control groups and no treatment-related external, visceral, or skeletal abnormalities were found.

4.2.4 Reproductive Toxicity Study

In a two-generation reproduction toxicity study flumiclorac pentyl was administered to male and female rats at nominal dietary concentrations of 0, 200, 10,000, and 20,000 ppm (0, 16-17, 781-878, 1610-1821 mg/kg/day, respectively, for males and 0, 18-19, 925-936, 1821-1909 mg/kg/day, respectively, for females during premating). The premating intervals were approximately 74 days for the F_0 animals and approximately 81 days for the F_1 animals. One litter was produced in each generation. Reproductive performance was not affected in either generation. Evidence of parental toxicity in the mid- and high-dose groups included increased kidney weight in F_1 males and F_0 and F_1 females and nephropathy in F_0 and F_1 males. Weight gain during premating was comparable between the treated and control groups of both generations.

Body weight of the high-dose F_2 pups was significantly less than that of the controls on lactation day 21. The effect on absolute body weight was due to decreased weight gain by the high-dose pups (85% of the control level) during lactation days 14-21. The effect on F_2 pup body weight is considered to be a systemic effect after the pups began eating the treated diet.

4.2.5 Additional Information from Literature Sources

No additional information on the toxicity of flumiclorac pentyl was identified in the open literature.

4.2.6 Pre-and/or Postnatal Toxicity

4.2.6.1 Determination of Susceptibility

No quantitative or qualitative evidence supports increased susceptibility of rat or rabbit fetuses from *in utero* exposure to flumiclorac pentyl in the developmental toxicity studies. Post-natal growth is reduced only after direct exposure to the test material. Decreased offspring growth occurred at a dose that also resulted in systemic parental effects during premating (i.e., subchronic) exposure.

4.2.6.2 Degree of Concern Analysis and Residual Uncertainties for Pre and/or Post-natal Susceptibility

There is no degree of concern and there are no residual uncertainties. No quantitative or qualitative sensitivity was observed in the rat and rabbit developmental studies or in the 2-generation reproduction study in the rat. Based on the lack of evidence of pre- and/or postnatal susceptibility following exposure to flumiclorac pentyl, and considering the lack of residual uncertainties for pre- and/or postnatal toxicity, no special FQPA

safety factor is needed (i.e., 1X). There is no concern for developmental neurotoxicity resulting from exposure to flumiclorac pentyl.

4.3 Recommendation for a Developmental Neurotoxicity Study

4.3.1 Evidence that supports requiring a Developmental Neurotoxicity study

The available data do not support the recommendation for a developmental neurotoxicity study.

4.3.2 Evidence that supports not requiring a Developmental Neurotoxicity study

The available data on the toxicity of flumiclorac pentyl do not support the recommendation for a developmental neurotoxicity study.

4.4 Hazard Identification and Toxicity Endpoint Selection

4.4.1 Acute Reference Dose (aRfD) - Females age 13-49

An endpoint attributable to a single exposure was not identified from the available database.

4.4.2 Acute Reference Dose (aRfD) - General Population

An endpoint attributable to a single exposure was not identified from the available database.

4.4.3 Chronic Reference Dose (cRfD)

Study Selected: Chronic Dog OPPTS: 870.4100b

MRID No.: 42825817

Executive Summary: In a 1-year oral toxicity study (MRID 42825817), S-23031 (94.6% a.i.; Batch No. PYG-89081-M) was administered in gelatin capsules to 5 male and 5 female Beagle dogs per group at doses of 0, 10, 100, and 1000 mg/kg/day.

All animals survived until scheduled sacrifice. No treatment-related clinical signs of toxicity, changes in urinalysis parameters, or ophthalmoscopic lesions were observed. Body weight of the high-dose males was slightly less than that of the controls throughout the study due to consistently lower body weight gain. Cumulative body weight gain by the high-dose males was 30% of the control level during weeks 0-4 and 42-47% of the control level during the remainder of the study.

Food consumption by the high-dose males was only slightly less than that of the controls (data not included) resulting in no effects on food efficiency. Body weight, food consumption, and food efficiency were not affected by treatment in females.

A significant ($p \leq 0.05$) prolongation of activated partial thromboplastin time (APTT) was observed in high-dose males and females beginning at week 13. The most pronounced effect was at weeks 13 and 26 when APTT for high-dose males and females was 156-157% and 190-199% of controls, respectively. Alkaline phosphatase activity was significantly increased ($p \leq 0.05$) in high-dose males at weeks 26, 39, and 52 (167, 183, and 249% of control, respectively) and in high-dose females at week 26 (276% of control). High-dose females also exhibited increased globulin levels, and increased alpha-2 fraction of the serum protein electrophoresis.

Gross necropsy was unremarkable and organ weights were not affected by treatment. No treatment-related microscopic lesions were observed.

Therefore, the chronic toxicity LOAEL for S-23031 in dogs is 1000 mg/kg/day based on decreased body weight gain (males) increased clotting time (males and females), and increased globulin levels, and increased alpha-2 fraction of the serum protein electrophoresis (females). The NOAEL is 100 mg/kg/day for males and females.

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirement for a chronic toxicity study [OPPTS 870.3150 (82-1b)] in dogs.

Dose and Endpoint for establishing cRfD: Chronic NOAEL of 100 mg/kg/day based on decreased weight gain in males and increased clotting time and alkaline phosphatase activity in males and females at 1000 mg/kg/day.

Uncertainty Factor (UF): 100; includes 10x for interspecies extrapolation and 10x for intraspecies extrapolation.

Comments about Study/Endpoint/UF: The duration of dosing and the endpoint are appropriate for this scenario. The chosen endpoint is the highest NOAEL available and is still much less than the lowest LOAEL from other chronic oral toxicity studies and the two-generation reproductive toxicity study. The increased clotting time may be indicative of a bleeding or clotting disorder. Increased globulin and alpha-2 protein levels may be indicative of inflammation or tissue damage.

Chronic RfD = $\frac{100 \text{ mg/kg/day}}{100}$ = **1.0 mg/kg/day**

4.4.4 Incidental Oral Exposure (Short and Intermediate Term)

Study Selected: 42825817 OPPTS:

MRID No.: See Section 4.4.3

Executive Summary: See Section 4.4.3 - Chronic Reference Dose (cRfD).

Dose and Endpoint: See Section 4.4.3

Uncertainty Factor (UF): 100; includes 10x for interspecies extrapolation and 10x for intraspecies extrapolation.

Comments about Study/Endpoint/UF: The dog study is considered most appropriate for this scenario. The dog study was selected over the two-generation reproduction study because it provided reasonable dose spacing to select a reasonable NOAEL. The reproduction study was conducted with wide dose spacing. The chosen endpoint from the dog study is the highest NOAEL available and is still much less than the lowest LOAEL from other chronic oral toxicity studies and the two-generation reproductive study. This endpoint is protective of mortality observed in the developmental rabbit toxicity study. In the main study (MRID 42169830), 4 of 17 rabbits treated with 800 mg/kg/day were found dead, one each on GD 13 and 17 and 2 on GD 26. The NOAEL was 400 mg/kg/day. In the range-finding study (MRID 42169829), 1 out of 6 rabbits treated with 500 mg/kg/day died on day 29. No mortality was observed at 300 mg/kg/day.

4.4.5 Dermal Absorption

A dermal absorption study is not available. No hazard quantitation is needed for dermal exposure of any duration.

4.4.6 Dermal Exposure (Short- and Intermediate-Term)

No hazard quantitation is required for any duration. No systemic effects were observed in the 21-day dermal rat study at dose levels up to 1000 mg/kg/day. There are no developmental or reproductive toxicity concerns. There are no long-term dermal exposures to flumiclorac pentyl in humans.

4.4.7 Inhalation Exposure (Short- and Intermediate-Term)

Study Selected: Chronic Dog OPPTS: 870.4100b

MRID No.: See Section 4.4.3

Executive Summary: See Section 4.4.3

Dose and Endpoint: See Section 4.4.3

Uncertainty Factor (UF): 100; includes 10x for interspecies extrapolation and 10x for intraspecies extrapolation.

Comments about Study/Endpoint/UF: Appropriate inhalation toxicity studies were not available for any exposure scenario. The chosen endpoint is the highest NOAEL available and is still much less than the lowest LOAEL from other chronic oral toxicity studies and the two-generation reproductive toxicity study. This endpoint is also protective of mortality observed in the developmental rabbit toxicity study. In the main study (MRID 42169830), 4 of 17 rabbits treated with 800 mg/kg/day were found dead, one each on GD 13 and 17 and 2 on GD 26. The NOAEL was 400 mg/kg/day. In the range-finding study (MRID 42169829), 1 out of 6 rabbits treated with 500 mg/kg/day died on day 29. No mortality was observed at 300 mg/kg/day. There are no long-term inhalation exposures to flumiclorac pentyl in humans.

4.4.8 Margins of Exposure

The following margins of exposure (MOEs) represent HED's level of concern for occupational and residential (non-dietary) exposure risk assessments:

Route of Exposure	Duration of Exposure		
	Short-Term (1-30 Days)	Intermediate-Term (1 - 6 Months)	Long-Term (> 6 Months)
Occupational Exposure			
Dermal	N/A	N/A	N/A
Inhalation	100	100	100
Residential (non-dietary) Exposure			
Oral	100	100	N/A
Dermal	N/A	N/A	N/A
Inhalation	100	100	100

For occupational exposure (all durations), inhalation exposure risk assessments, an MOE of 100 is required. The MOE is based on 10x for intraspecies variation, and 10x for interspecies extrapolation. For residential exposures, an MOE of 100 is required, and is based on 10x for intraspecies variation, 10x for interspecies extrapolation and a 1x special FQPA factor.

4.4.9 Recommendation for Aggregate Exposure Risk Assessments

As per FQPA, 1996, when there are potential residential exposures to the pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures. The toxicity endpoints selected for the oral and inhalation routes of exposure may be aggregated because the same study was selected for both routes. No short-, intermediate- or long-term dermal endpoints have been identified for flumiclorac pentyl.

4.4.10 Classification of Carcinogenic Potential

No evidence for carcinogenicity was seen in mice or rats. Administration of flumclorac-pentyl to mice for 19 months and to rats for 24 months did not result in an increase in overall tumor incidence or increase the incidence of any specific type of tumor at doses approaching the limit dose. The chemical was negative for gene mutation in *Salmonella typhimurium* and did not induce micronucleus formation in the mouse or unscheduled DNA synthesis in rat hepatocytes. Results for chromosome aberrations in CHO cells showed a weak, positive response without metabolic activation but were negative in the presence of activation.

Table 4.4. Summary of Toxicological Doses and Endpoints for Flumiclorac pentyl for Use in Human Risk Assessments

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (females 13-49)	NA		NA
Acute Dietary (general population)	NA		NA
Chronic Dietary (all populations)	NOAEL = 100 mg/kg/day UF = 100 **Chronic RfD** = 1.0 mg/kg/day	FQPA SF = 1 cPAD = 1.0 mg/kg/d / 1 = 1.00 mg/kg/day	Chronic - dog LOAEL = 1000 mg/kg/day based on decreased body weight gain (males), increased clotting time (males and females), and increased globulin levels and increased alpha-2 fraction of the serum protein electrophoresis (females)
Incidental Oral Short-Term (1 - 30 days)	NOAEL = 100 mg/kg/day UF = 100 **Chronic RfD** = 1.0 mg/kg/day	FQPA SF = 1 cPAD = 1.0 mg/kg/d / 1 = 1.00 mg/kg/day MOE = 100 (residential)	Chronic - dog LOAEL = 1000 mg/kg/day based on decreased body weight gain (males), increased clotting time (males and females), and increased globulin levels and increased alpha-2 fraction of the serum protein electrophoresis (females)

Table 4.4. Summary of Toxicological Doses and Endpoints for Flumiclorac pentyl for Use in Human Risk Assessments

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Incidental Oral Intermediate-Term (1 - 6 months)	NOAEL = 100 mg/kg/day UF = 100 **Chronic RfD** = 1.0 mg/kg/day	FQPA SF = 1 cPAD = 1.0 mg/kg/d / 1 = 1.00 mg/kg/day MOE = 100 (residential)	Chronic - dog LOAEL = 1000 mg/kg/day based on decreased body weight gain (males), increased clotting time (males and females), and increased globulin levels and increased alpha-2 fraction of the serum protein electrophoresis (females)
Dermal Short-Term (1 - 30 days)	NA	NA	NA
Dermal Intermediate-Term (1 - 6 months)	NA	NA	NA
Dermal Long-Term (> 6 months)	NA	NA	NA
Inhalation Short-Term (1 - 30 days)	NOAEL = 100 mg/kg/day UF = 100 **Chronic RfD** = 1.0 mg/kg/day	FQPA SF = 1 cPAD = 1.0 mg/kg/d / 1 = 1.00 mg/kg/day MOE = 100 (occupational & residential)	Chronic - dog LOAEL = 1000 mg/kg/day based on decreased body weight gain (males), increased clotting time (males and females), and increased globulin levels and increased alpha-2 fraction of the serum protein electrophoresis (females)
Inhalation Intermediate-Term (1 - 6 months)	NOAEL = 100 mg/kg/day UF = 100 **Chronic RfD** = 1.0 mg/kg/day	FQPA SF = 1 cPAD = 1.0 mg/kg/d / 1 = 1.00 mg/kg/day MOE = 100 (occupational & residential)	Chronic - dog LOAEL = 1000 mg/kg/day based on decreased body weight gain (males), increased clotting time (males and females), and increased globulin levels and increased alpha-2 fraction of the serum protein electrophoresis (females)
Inhalation Long-Term (> 6 months)	NA	NA	NA
Cancer (oral, dermal, inhalation)	**Classification:** no evidence of carcinogenicity		

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable

* Refer to Section 4.5

4.5 Special FQPA Safety Factor

Based on the hazard and exposure data, HED recommends that the special FQPA SF be reduced to 1X. The recommendation is based on the following:

- There is no evidence of increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure to flumiclorac pentyl.
- There is no concern for neurotoxicity.
- The dietary food exposure assessment utilizes tolerance level residues and 100% crop treated (CT) information for all commodities. By using these screening-level assumptions, chronic exposures/risks will not be underestimated.
- The dietary drinking water assessment utilizes values generated by models and associated modeling parameters which are designed to provide conservative, health protective, high-end estimates of water concentrations.

4.6 Endocrine disruption

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following recommendations of its Endocrine Disruptor and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

In the available toxicity studies on flumiclorac pentyl, there was no estrogen, androgen, and/or thyroid mediated toxicity. When additional appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, flumiclorac pentyl may be subjected to further screening and/or testing to better characterize effects related to endocrine disruption.

5.0 Public Health Data

Only a few minor incidents have been reported by the registrant; other sources of incident data and the scientific literature have not reported any adverse effects in humans.

5.1 Incident Reports

5.2 Other

6.0 Exposure Characterization/Assessment

6.1 Dietary Exposure/Risk Pathway

6.1.1 Residue Profile

Reference: 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 Barcode: D302003, William Donovan, 24-JUN-2005.

The nature of the residue in plants and animals is adequately understood based on the available corn, soybean, goat and hen metabolism studies. In plants, flumiclorac pentyl is extensively metabolized by hydrolysis of the ester and imide linkages and hydroxylation and reduction of the tetrahydrophthalimide moiety. The metabolism of flumiclorac pentyl in animals involves similar reactions to those observed in plants.

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,* and that the term fodder be replaced by stover in the tolerance listing. There are currently no tolerances for flumiclorac pentyl residues in livestock commodities or for inadvertent residues in rotational crops.

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. Therefore, tolerances for livestock commodities are not required at the present time.

Adequate enforcement methods are available for the determination of flumiclorac pentyl *per se* in/on plant commodities. 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 limit of quantitation (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 Memo dated 10/19/94, J. Garbus). 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). At this time, HED has determined that livestock enforcement methods are not required for the purposes of reregistration and PP#3F6767 since there is no expectation of finite secondary residues.

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 stover samples, flumiclorac pentyl residues were consistently below the LOQ of 0.01 ppm. HED concludes that the reassessed tolerances of 0.01 ppm each for the above RACs are appropriate. The available data suggest that a 90-day PHI for grain and stover would be appropriate; this interval is covered by the existing label restriction against applying flumiclorac pentyl to corn any later than the 10-leaf stage.

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 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.

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 should submit a revised Section F to increase the proposed tolerance levels on: (i) undelinted cottonseed from 0.1 to 0.2 ppm; and (ii) cotton gin byproducts from 2.0 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 tolerance level of 0.02 ppm is appropriate to cover the residues found in soybean hulls.

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.

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.

6.1.2 Chronic Dietary Exposure and Risk

Reference: *Flumiclorac pentyl Chronic Dietary Exposure Assessment for the Reregistration Eligibility Decision and New Use on Cotton*; DP Barcode: D302002; Susan Stanton, 06/30/05.

A chronic dietary risk assessment was conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™),Version 2.00, and the Lifeline Model Version 2.0, which use food consumption data from the USDA's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. In this assessment the chronic dietary exposure and risk estimates resulting from food and drinking water intake were determined for the general U.S. population and various population subgroups. An endpoint of concern attributable to a single dose was not identified for flumiclorac pentyl; therefore, an acute RfD was not established and an acute dietary risk assessment was not conducted.

The Tier 1chronic analyses assumed tolerance level residues, 100% crop treated and DEEM default processing factors for all food commodities. Drinking water was incorporated directly in the dietary assessment using the Tier 1point estimate for surface water generated by the FIRST model (See sec. 6.2, below).

The resulting chronic dietary exposure estimates using the DEEM-FCID model were less than 1% of the cPAD for the U.S. population and all population subgroups. Flumiclorac pentyl chronic dietary exposure (food + water) was estimated at 0.000034 mg/kg/day for the U.S. population (<0.01% of the cPAD) and 0.000074 mg/kg/day (<0.01% of the cPAD) for the most highly exposed population subgroup (Children, 3 to 5 yrs. old). Estimated chronic exposures using the Lifeline model were consistent with the DEEM-FCID results (<0.01% of the cPAD for the U.S. population and all population subgroups).

Table 6.1 Results of Chronic Dietary Exposure Analysis Using both DEEM FCID and Lifeline Software[a]

Population Subgroup	cPAD (mg/kg/day)	DEEM-FCID™		Lifeline	
		Exposure (mg/kg/day)	% cPAD	Exposure (mg/kg/day)	% cPAD
General U.S. Population	1	0.00003	<0.01	0.000031	<0.01
All Infants (< 1 year old)	1	0.00006	<0.01	0.000048	<0.01

Table 6.1 Results of Chronic Dietary Exposure Analysis Using both DEEM FCID and Lifeline Software[a]					
Population Subgroup	cPAD (mg/kg/day)	DEEM-FCID™		Lifeline	
		Exposure (mg/kg/day)	% cPAD	Exposure (mg/kg/day)	% cPAD
Children 1-2 years old	1	0.00007	<0.01	0.000066	<0.01
Children 3-5 years old	**1**	**0.00007**	**<0.01**	**0.000073**	**<0.01**
Children 6-12 years old	1	0.00006	<0.01	0.000052	<0.01
Youth 13-19 years old	1	0.00004	<0.01	0.000038	<0.01
Adults 20-49 years old	1	0.00003	<0.01	0.000027	<0.01
Adults 50+ years old	1	0.00002	<0.01	0.000024	<0.01
Females 13-49 years old	1	0.00003	<0.01	0.000032	<0.01

[a] The values for the population with the highest risk are bolded.

6.2 Water Exposure/Risk Pathway

Reference: *Tier 1 Drinking Water Assessment for Flumiclorac pentyl on Corn and Soybeans (TRED) and Cotton (New Use)*; DP Barcodes: D311964 and D302004; W. P. Eckel, PhD; 03/17/05

The drinking water values used in the dietary risk assessment were provided by the Environmental Fate and Effects Division (EFED) and incorporated directly in the DEEM-FCID and Lifeline chronic analyses. The estimated drinking water concentrations (EDWCs) from surface and ground water sources were calculated using the Tier I FIRST and SCI-GROW models. The chronic EDWCs calculated using these models are summarized below in Table 6.2.

Flumiclorac pentyl is not persistent or mobile. Flumiclorac pentyl hydrolyzes and metabolizes within hours or days into a number of bulky anionic degradates which are mobile and may be herbicidally active. The major degradate in the aerobic soil metabolism studies is flumiclorac acid or IMCA. This compound is structurally similar to the parent compound and is, therefore, expected to have a similar toxicity. Based on these considerations, the team has determined that the residue of concern in drinking water consists of flumiclorac pentyl and its acid metabolite, IMCA. The estimated drinking water concentrations provided by EFED and used in the dietary assessment include both parent flumiclorac pentyl and IMCA.

Table 6.2. Summary of Estimated Chronic Surface and Ground Water Concentrations for Chemical.		
	Flumiclorac pentyl	
	Surface Water Conc., ppb [a]	Ground Water Conc., ppb [b]
Chronic	0.24	0.002

[a] From the Tier 1 FIRST model. Input parameters are based on 2 applications, 14 days apart, at 0.054 lb ai/A to corn, soybeans and cotton, assuming an aerobic soil half-life of 98.7 days, a hydrolysis half-life at pH 7 of 19 days and a K_{oc} of 98.7.

[b] From the SCI-GROW model assuming a maximum seasonal use rate of 0.054 lb ai/A, a K_{oc} of 98.7, and a half-life of 7.7 days.

The highest EDWC generated by the models (i.e., the surface water value of 0.24 ppb, based on applications to corn, soybeans and cotton) was used in the DEEM-FCID and Lifeline chronic analyses. The Lifeline model allows users to enter different water concentrations (or a distribution of concentrations) for each combination of season (4), census region (4), water source type (public or private system, private well, other), and setting (rural or urban). For this Tier I dietary analysis, the FIRST surface water estimate of 0.24 ppb was applied to each combination.

6.3 Residential (Non-Occupational) Exposure/Risk Pathway

Reference: Residential Exposure Assessment for the Tolerance Reassessment Eligibility Decision Document for Flumiclorac-pentyl. (R. Travaglini, DPBarcode: D317916, JUNE 30, 2005.)

One of the flumiclorac-pentyl product labels (EPA Reg. No. 59639-122) specifies for the control of weeds in non-agricultural settings which include golf course, parks, recreation areas as well as schools. Use of flumiclorac-pentyl in these types of settings could conceivably result in non-occupational or residential exposures. However, since a dermal endpoint was not selected and since outdoor post-application inhalation exposures are not of concern, the only route of exposure to be assessed is for incidental oral exposure to infants and children. Intermediate-term exposures are not anticipated. Therefore, HED assessed short-term incidental oral exposures for toddlers, the most sensitive population possibly exposed to flumiclorac-pentyl.

HED conducted screening level calculations based on the Science Advisory Council for Exposure Standard Operating policy No. 12: Recommended Revisions to the Standard Operating Procedures (SOPs) for Residential Exposure Assessments for the exposure scenarios described below which are the most likely to result in highest possible exposure by toddlers to the herbicide. For the purposes of the TRED process these are:

toddlers: incidental ingestion (hand-to-mouth)

incidental ingestion (object-to-mouth)

incidental ingestion (soil ingestion).

All MOEs, including the total toddler ingestion MOE, are well above 100 and therefore exposures to toddlers from flumiclorac-pentyl are not of concern.

Table 6.3. Short-Term Residential Exposure Estimates & MOEs for Flumiclorac-pentyl Treated Turf

resident	activity	DAT	Body wgt	ADD (mg/kg/day)	NOAEL	MOE
toddler	hand to mouth	0	15	0.0017	100	58230
toddler	object to mouth (turf)	0	15	0.00043	100	233000
toddler	soil ingestion	0	15	0	100	1.75 E^7

6.3.1 Home Uses

There are no registered home uses for flumiclorac-pentyl.

6.3.2 Recreational Uses

One product label contains application instruction for use on golf courses, parks and recreational areas. See Section 6.3 above.

6.3.3 Other (Spray Drift, etc.)

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method employed for [chemical]. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. On a chemical by chemical basis, the Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new data base submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift with specific products with significant risks associated with drift. However, since dermal exposures are not a matter of concern under normal use conditions at maximum application rates, any exposures caused by spray drift would be insignificant.

7.0 Aggregate Risk Assessments and Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure.

For most pesticide active ingredients, water monitoring data are considered inadequate to determine surface and ground water drinking water exposure estimates, so model estimates have been used to estimate residues in drinking water (EDWCs). In order to determine if aggregate risks are of concern, HED has historically calculated drinking water levels of comparison, or DWLOCs. The DWLOC is the maximum amount of a pesticide in drinking water that would be acceptable in light of combined exposure from food and residential pathways. The calculated DWLOCs were then compared to the EDWCs provided by EFED to determine if a potential concern existed for dietary exposure to residues in drinking water.

In order to fully implement the requirements of FQPA, HED and EFED have been working toward refining the screening-level DWLOC approach to conducting aggregate risk assessments that combine exposures across all pathways. As part of this process, EFED and HED have agreed that EDWCs can be used directly in dietary exposure assessments to calculate aggregate dietary (food + water) risk. This is done by using the relevant model value as a residue for drinking water (all sources) in the dietary exposure assessment. The principal advantage of this approach is that the actual individual body weight and water consumption data from the CSFII are used, rather than assumed weights and consumption for broad age groups. This refinement has been used in estimating the dietary exposure component in the flumiclorac pentyl aggregate risk assessments.

7.1 Acute Aggregate Risk

A toxicological endpoint of concern attributable to a single dose has not been identified for flumiclorac pentyl. Therefore, an acute aggregate risk assessment has not been conducted.

7.2 Short-Term Aggregate Risk

Short-term aggregate exposure takes into account residential exposure plus average exposure levels from residues of flumiclorac pentyl in food and water (considered to be a background exposure level). The registered residential uses of flumiclorac pentyl constitute short-term exposure scenarios, and endpoints have been selected for short-term incidental exposures. The acceptable MOE for short-term exposure is 100

Table 7.2 Short-Term Aggregate Risk						
Population	**Short-Term Scenario**					
	NOAEL mg/kg/day	**Level of Concern**	**Max. Exposure[2] mg/kg/day**	**Average Food + Water Exposure mg/kg/day**	**Residential Exposure[3] mg/kg/day**	**Aggregate MOE (food and residential)[4]**
Children, 3-5 yrs. old[5]	100	≤100	1	0	0.0017	46000

[1]Level of Concern (MOE) based on 10x for interspecies variation and 10x for intraspecies variation.
[2] Maximum Exposure (mg/kg/day) = NOAEL/ Level of Concern (MOE) = 100 mg/kg/day/100 = 1.0 mg/kg/day
[3] Residential Exposure = Oral exposure (toddler postapplication scenarios). There is no dermal endpoint of concern for flumiclorac pentyl.
[4] Aggregate MOE = [NOAEL ÷ (Avg Food and Water Exposure + Residential Exposure)]
[5]Population subgroup with highest dietary (food + water) exposure and only subgroup with anticipated post-application residential exposure. Dietary exposure from Table 6.1; Residential exposure = sum of ave. daily doses from all 3 toddler exposure scenarios in Table 6.3.2a

7.3 Intermediate-Term Aggregate Risk

All residential exposures are expected to be short-term in duration. Therefore, an intermediate-term aggregate risk assessment is not required.

7.4 Long-Term Aggregate Risk

The chronic aggregate risk assessment considered exposures from food and water only because there are no residential uses expected to contribute to chronic exposures for this chemical. Since water exposure was incorporated directly into the dietary exposure analysis, the dietary risk estimates reported in section 6.1 represent the total chronic aggregate risk for flumiclorac pentyl. The chronic aggregate risk estimates for the U.S. population and all subgroups are <0.01%.

7.5 Cancer Risk

A cancer aggregate risk assessment is not required, since there was no evidence of carcinogenicity in the toxicology studies submitted for flumiclorac pentyl.

8.0 Cumulative Risk Characterization/Assessment

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to flumiclorac pentyl and any other substances and flumiclorac pentyl does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that flumiclorac pentyl has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

9.0 Occupational Exposure/Risk Pathway

Reference: Occupational and Residential Exposure/Risk Assessment for the New Uses of Flumiclorac Pentyl on Cotton. DP Barcode: D317916; Shi-Chi Wang; 6/30/05

9.1 Short/Intermediate/Long-Term Handler Risk

Exposure Scenarios

There are five handler scenarios that are expected to result in the highest exposure for the proposed uses:

- Mixing/Loading Liquid for Ground Applications (Scenario 1)
- Mixing/Loading Liquid for Aerial Applications (Scenario 2)
- Applying Sprays with Groundboom Equipment (Scenario 3)
- Applying Sprays Using Fix-Wing Aircraft (Scenario 4)
- Flagging during Aerial Application (Scenario 5)

Equations/Calculations

The following equations were used to calculate handler exposure and risk:

Inhalation Dose (mg/kg/day) = $\frac{\text{Rate (lb ai/acre) x UE (mg/lb ai) x Acres Treated (A/day)}}{\text{BW (kg)}}$

Where:

Rate (Application Rate)	=	Maximum application rate on product label (lb ai/acre)
UE (Unit Exposure)	=	Exposure value derived from August 1998 PHED Surrogate Exposure Table (mg/lb ai handled)
Acres Treated	=	Maximum number of acres treated per day (acres/day)
BW	=	Body weight (kg)

Inhalation MOE = $\frac{\text{Inhalation NOAEL (100 mg/kg/day)}}{}$

Inhalation Daily Dose (mg/kg/day)

Application Rate

The maximum application rates listed on the proposed labels provided by the Registration Division were used for all exposure assessments. The maximum rate is 0.054 lb ai/A.

Area Treated

Based on HED's Exposure Science Advisory Council Policy Number 9.1, 200 acres per day treated was assumed for application on cotton using groundboom equipment and 1,200 acres per day treated was assumed for application on cotton using fix-wing aircraft.

Body Weight

The average body weight for general population (70 kg) was used for this assessments.

Exposure Frequency

No data on the number of exposure days per year was provided For this risk assessment, it was assumed that handlers would be exposed for less than 6 months per year (i.e. short-/intermediate-term in duration).

Unit Exposures

The unit exposures used in this assessments are based on the PHED Version 1.1 as presented in the August 1998 PHED Surrogate Exposure Guide. PHED was designed by a task force of representatives from the U.S. EPA, Health Canada, the California Department of Pesticide Regulation, and member companies of the American Crop Protection Association. PHED is a software system consisting of two parts–a database of measured exposure values for workers involved in the handling of pesticides under actual field conditions and a set of computer algorithms used to subset and statistically summarize the selected data. Currently, the database contains values for over 1,700 monitored individuals (i.e., replicates).

Users select criteria to subset the PHED database to reflect the exposure scenario being evaluated. The subsetting algorithms in PHED are based on the central assumption that the magnitude of handler exposures to pesticides is primarily a function of activity (e.g., mixing/loading, applying), formulation type (e.g., wettable powders, granulars), application method (e.g., aerial, groundboom), and clothing scenarios (e.g., gloves, double layer clothing).

There are three basic risk mitigation approaches considered appropriate for controlling occupational exposures. These include administrative controls, the use of personal protective equipment or PPE, and the use of engineering controls. Occupational handler exposure assessments were completed by HED using baseline, PPE, and engineering controls. [Note: Administrative controls available generally involve altering application rates for handler exposure scenarios. These are typically not

utilized for completing handler exposure assessments.] The baseline clothing level scenario for occupational exposure scenarios is generally an individual wearing long pants, a long-sleeved shirt, no chemical resistant gloves, and no respirator. The first level of mitigation generally applied is PPE. As reflected in the calculations included herein, PPE may involve the use of an additional layer of clothing, chemical-resistant gloves, and a respirator. The next level of mitigation considered in the risk assessment process is the use of appropriate engineering controls which, by design, attempt to eliminate the possibility of human exposure. Examples of commonly used engineering controls include enclosed tractor cabs and cockpits, closed mixing/loading/transfer systems, and water-soluble packets.

Handlers' Exposure and Risk

All MOEs are above the levels of concern at the baseline level (91,000~1,100,000) and at the engineering control level (for aerial applications; 1,600,000). Assumptions and calculations of the risks for handlers are presented in Table 4.

The handler exposure estimates in this assessment are based on a central tendency estimate of unit exposure and an upper-percentile assumption for the application rate, and are assumed to be representative of high-end exposures. The uncertainties associated with this assessment stem from the use of surrogate exposure data (e.g., differences in use scenario and data confidence), and assumptions regarding that amount of chemical handled. The estimated exposures are believed to be reasonable high-end estimates based on observations from field studies and professional judgement.

Table 4. Non-Cancer Risk for Handlers.

Exposure Scenario (Scenario #)	Mitigation Level[a]	Inhalation Unit Exposure[b] (Ug/lb ai)	Application Rate (lb ai/A)	Amount Treated[c] (A/day)	Daily Inhalation Dose[d] (mg/kg/day)	Inhalation MOE[e]
Mixer/Loader						
Mixing/loading Liquid for Ground application (1)	Baseline	1.2	0.054	200	0.00019	530,000
Mixing/loading Liquid for Aerial application (2)	Baseline	1.2	0.054	1200	0.0011	91,000
Applicator						
Apply sprays with Groundboom (3)	Baseline	0.74	0.054	200	0.00011	910,000
Apply sprays with Fix-Wing aircraft (4)	Eng. Cont.	0.068	0.054	1200	0.000062	1,600,000
Flagger						
Flagging during Aerial application (5)	Baseline	0.35	0.054	350	0.000095	1,100,000

a Baseline consists of long-sleeve shirt, long pants, shoes, and socks and no respirator. Eng. Cont. consists of enclosed cockpit.

b Baseline Inhalation Unit Exposure represents no respiratory protection open mixing/loading, and open cab tractors, as appropriate. Eng. Cont. Inhalation Unit Exposure represents enclosed cockpit.

c Daily acres treated values are from EPA estimates of acreage that could be treated in a single day for each exposure scenario of concern.

d Daily inhalation dose (mg/kg/d) = (unit exposure (µg/lb ai) * (1mg/1000 µg) conversion * appl. rate (lb ai/acre) * daily acres treated body weight (70kg).

e Inhalation MOE = Inhalation NOAEL (100 mg/kg/d) / Inhalation daily dose (F). UF = 100.

9.2 Short/Intermediate/Long-Term Postapplication Risk

The post-application exposure assessments were not performed because no dermal endpoints were selected.

The technical material has a Category III for acute dermal toxicity, and a Category II for acute eye irritation & acute dermal irritation. Per the Worker Protection Standard (WPS), a **24-hr** restricted entry interval (REI) is required.

10.0 Data Needs and Label Requirements

10.1 Toxicology - none.

10.2 Product and Residue Chemistry

- 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 0.2 ppm; and (ii) cotton gin byproducts from 2.0 ppm to 3.0 ppm.

- Additional data are required concerning the UV/Visible absorption spectrum for the Valent USA Corporation 98.6% flumiclorac pentyl T (EPA Reg. No. 59639-81) [Guideline # 830.7050].

10.3 Occupational and Residential Exposure

- As indicated in the UCM, the registrant should submit revised product labeling (EPA Reg. No. 59632-92) which has been amended to reflect the proposed maximum application rate of 0.115 lbs. ai/a for non-agricultural use sites.

10.4 Environmental

- A phototoxicity study protocol is being requested for light-dependent peroxidizing herbicides which includes flumiclorac pentyl (Memorandum from Norman B. Birchfield, Thomas M. Steeger, Brian Montague to Elizabeth Leovey; dated March 7, 2001; entitled: Request for Phototoxicity Study Protocol for Light-Dependent Peroxidizing Herbicides)

References:

Occupational and Residential Exposure/Risk Assessment for the New Uses of Flumiclorac Pentyl on Cotton. DP Barcode: D317916; Shi-Chi Wang; 6/30/05.

Tier 1 Drinking Water Assessment for Flumiclorac pentyl on Corn and Soybeans (TRED) and Cotton (New Use); DP Barcodes: D311964 ane D302004; W. P. Eckel, PhD; 03/17/05.

Flumiclorac pentyl Chronic Dietary Exposure Assessment for the Reregistration Eligibility Decision and New Use on Cotton; DP Barcode: D302002; Susan Stanton, 06/30/05.

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 Barcode: D302003, William Donovan, 24-JUN-2005.

Appendices

1.0 TOXICOLOGY DATA REQUIREMENTS

The requirements (40 CFR 158.340) for food use for flumiclorac pentyl are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Test		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes	yes
870.3150	Oral Subchronic (nonrodent)	yes	yes
870.3200	21-Day Dermal	no	-
870.3250	90-Day Dermal	no	-
870.3465	90-Day Inhalation	no	-
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (rodent)	yes	yes[1]
870.4100b	Chronic Toxicity (nonrodent)	yes	yes
870.4200a	Oncogenicity (rat)	yes	yes[1]
870.4200b	Oncogenicity (mouse)	yes	yes
870.4300	Chronic/Oncogenicity	yes	yes
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5375	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5395	Mutagenicity—Micronucleus Formation	yes	yes
870.5550	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a	Acute Delayed Neurotox. (hen)	no	-
870.6100b	90-Day Neurotoxicity (hen)	no	-
870.6200a	Acute Neurotox. Screening Battery (rat)	no	-
870.6200b	90 Day Neuro. Screening Battery (rat)	no	-
870.6300	Develop. Neuro	no	-
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	no	-

[1]Satisfied by the combined chronic/oncogenecity study in rats.

2.0 NON-CRITICAL TOXICOLOGY STUDIES

Subchronic

In a 90-day oral toxicity study (MRID 42169827), S-23031 (94.7% a.i.; Batch No. PYG-88092-M) was administered in gelatin capsules to 4 male and 4 female Beagle dogs per group at doses of 0, 10, 100, and 1000 mg/kg/day.

All animals survived until scheduled sacrifice. No treatment-related clinical signs of toxicity or ophthalmoscopic lesions were observed. Body weight, food consumption, and food efficiency were not affected by treatment of either sex. Results of fecal examination, liver function test (BSP retention), renal function test (PAH retention), electrocardiogram, urinalysis, and clinical chemistry were similar between the treated and control groups. Gross necropsy was unremarkable and organ weights were not affected by treatment.

A significant ($p \leq 0.05$ or 0.01) prolongation of activated partial thromboplastin time (APTT) was observed in mid-dose females at weeks 4 and 8 (104-108% of control) and in high-dose females at weeks 4, 8, and 12 (119-124% of control). The magnitude of the effect in the mid-dose females is not considered adverse. No other changes in hematology parameters were found in treated males or females compared with the control animals.

Therefore, the subchronic toxicity LOAEL for S-23031 in dogs is 1000 mg/kg/day based on increased clotting time in females. The NOAEL is 100 mg/kg/day for females.

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirement for a subchronic toxicity study [OPPTS 870.3150 (82-1b)] in dogs.

In a 90-day oral toxicity study (MRID 42169826), S-23031 (94.4 or 94.7% a.i.; Batch No. PYG-88092 or PYG-88092-M, respectively) was administered in the diet to 12 male and 12 female Crj: CD (SD) rats per group at concentrations of 0, 100, 1000, 10,000, or 20,000 ppm. Time-weighted average doses were 0, 6.6, 67, 664, and 1359 mg/kg/day, respectively, for males and 0, 7.4, 73.8, 726, and 1574 mg/kg/day, respectively, for females. Additional groups of 6 rats/sex/dose were used for interim sacrifice after 4 weeks of treatment.

All animals survived until scheduled sacrifice. Occasional urine incontinence and stains of the fur were observed on the 20,000-ppm animals (incidence rate not given in the original DER). No other treatment-related clinical signs of toxicity were observed. Body weight was not affected by treatment of either sex. Food consumption was occasionally increased ($p \leq 0.01$) in the 20,000-ppm males and females most likely due to the high concentration of a non-nutritive substance in the diet. Water consumption by the 10,000- and 20,000-ppm groups was significantly increased ($p \leq 0.05$ or 0.01) during the first two and five weeks of the study for males and females, respectively.

No treatment-related ophthalmoscopic lesions or changes in hematology or clinical chemistry parameters were found in males or females after 4 and 13 weeks. At study termination, an increase in cholinesterase activity (compartment not defined) for females administered $\geq$1000 ppm was not considered adverse. Liver weight relative to body weight was increased in 20,000-ppm males at

interim sacrifice. At terminal sacrifice absolute and relative liver weights were increased in the 20,000-ppm males and females by 23-25% and 8-11%, respectively. In the 10,000- and 20,000-ppm groups, kidney weight relative to body weight was increased by 11% and 15%, respectively, for males and by 8% and 6%, respectively, for females at study termination. No treatment-related microscopic lesions were found in any organ of any animal, including the liver and kidney.

Therefore, the subchronic toxicity LOAEL for S-23031 in rats is not identified and the NOAEL is ≥20,000 ppm (1359 and 1574 mg/kg/day for males and females, respectively).

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirement for a subchronic toxicity study [OPPTS 870.3100 (82-1a)] in rats. Although a LOAEL was not identified, the doses exceeded the limit dose of 1000 mg/kg/day.

Chronic/Carcinogenicity

In a chronic toxicity/carcinogenicity study (MRID 42883906), S-23031 technical (Batch/lot # PYG-88092-M, 94.7% a.i.) was administered in the diet to groups of 50 male and 50 female Crj:CD(SD) rats at concentrations of 0, 100, 1000, 10,000, or 20,000 ppm (0, 3.5, 35.4, 360.4, or 744.9 mg/kg bw/day, respectively, for males and 0, 4.3, 43.6, 443.8, or 919.4 mg/kg bw/day, respectively for female) for 2 years. An additional 14 rats/sex/group were administered similar diets for 1 year for interim evaluation except that only 12 males were administered the 20,000-ppm diet.

No treatment-related effects were observed on the eyes during ophthalmoscopic examination or on hematologic parameters. The incidence of urinary staining was increased in male rats at 20,000 ppm and in female rats at 10,000 and 20,000 ppm. The incidence was significantly increased in main study males from week 7-30 and non-significantly increased from weeks 31-44. The incidence of urinary staining also was significantly increased in 20,000-ppm main study females throughout the study except for a few sporadic time points primarily during the last 6 months of the study and in 10,000-ppm main study females at sporadic time points during the first year of the study. The incidence of urinary staining was significantly increased in satellite females from weeks 26-35 and non-significantly increased from weeks 37-52; no effect on urinary staining was observed in satellite males. Mortality was not affected in male rats, but mortality was significantly increased in females at 100, 10,000, and 20,000 ppm, but not at 1000 ppm, compared with that of controls. The increased mortality is not considered treatment-related because it did not show a clear dose-related trend and no treatment-related causes of death were observed at any dose.

No treatment-related effects on body weight or weight gain were observed in male or female rats receiving any dose of the test material. No toxicologically significant effect on food consumption was observed in male or female rats receiving any dose of the test material; absolute and/or relative food consumption was slightly increased in both sexes at 20,000 ppm. Female rats in the 10,000 and 20,000-ppm groups consumed significantly ($p<0.05$ except as noted) more water than controls when measured at week 25 (+106% and +44% (N.S.), respectively) and week 52 (+43% and +32%, respectively). Relative water consumption (mL/kg bw) was significantly increased in 10,000- and 20,000-ppm group females at week 25 (+110% and +54%, respectively) and week 52 (+44% and +39%, respectively). Females in the 10,000- and 20,000-ppm groups had corresponding increases in urine volume (+105% to +171% , $p<0.05$) at weeks 25 and 51. Male rats in the 20,000-ppm

group had a significant increase (+67%) in urine volume and an increased incidence of squamous epithelial cells in urine (9/11 vs 2/12 for controls) at 103 week. Incontinence was observed at a low incidence throughout the study in 20,000-ppm group females.

No treatment-related and biologically significant changes in clinical chemistry parameters were observed in male or female rats because the statistically significant changes (γ-glutamyl transpeptidase activity in 20,000-ppm group males and α_1-globulin in 20,000-ppm group females) were not associated with any adverse microscopic findings. The statistically significant increases in absolute (liver, kidney, and spleen) and relative organ weights (liver and kidney) in males and the absolute (kidney) and relative (liver and kidney) organ weights in females were not associated with any microscopic findings in these organs. A significantly increased incidence of dark red spots on the liver of male rats (16/34 vs 6/33 rats surviving to termination) was observed at necropsy but no associated microscopic lesions were observed. The clinical chemistry changes, organ weights, and gross findings are not considered toxicologically significant. The incidence of hyperplastic nodules in the liver was increased in 20,000-ppm group males (5/50), but the incidence did not achieve statistical significance compared with that of controls (1/50) and the incidence also was within range of historical controls.

The lowest-observed-adverse-effect level (LOAEL) for S-23031 (flumiclorac pentyl) in female rats is 443.8 mg/kg/day based on urinary incontinence, increased water consumption, increased urine volume and increased kidney weights. The no-observed-adverse-effect level (NOAEL) in females is 43.6 mg/kg/day. The LOAEL in males is 744.9 mg/kg/day based on increased squamous epithelial cells in urinary sediment and increased kidney weights. The NOAEL in males is 360.4 mg/kg/day.

There were no treatment-related increases in the incidences of neoplasms in either male or female rats receiving any dose of the test material. The highest dietary concentration delivered a dose that was only 25% below the limit dose for males and it approximated the limit dose for females. Therefore, these animals were adequately dosed.

This chronic toxicity/carcinogenicity study in the rat is **Acceptable/Guideline** and it does satisfy the guideline requirement for a chronic toxicity/carcinogenicity study (OPPTS 870.4300; OECD 453) in the rat.

Oncogenicity

In a carcinogenicity study (MRID 42883905), S-23031 technical (Batch/lot # PYG-88092-M, 94.7% a.i.) was administered in the diet to groups of 51 male and 51 female Crj:CD-1 (ICR) mice at concentrations of 0, 300, 3000, or 7000 ppm (0, 31.5, 307.9, or 731.4 mg/kg bw/day, respectively, for males and 0, 37.8, 368.1, or 850.2 mg/kg bw/day, respectively for female) for 79 weeks. An additional 15 mice per sex/group were administered the same diets for 52 weeks for interim evaluation.

No treatment-related effects were observed on any parameter in female mice receiving any dose of the test material for 52 or 79 weeks, and no treatment-related effects were observed on mortality, clinical signs, body weight or weight gain, food consumption, or gross lesions in male mice

receiving any dose of the test material for 52 or 79 weeks. Erythrocyte count, hemoglobin level, and hematocrit were significantly decreased by 11-13% at week 52 and by 17-18% at week 79 in mid-dose male mice and by 6-8% at week 52 and by 10-11% at week 79 in high-dose male mice. However, a clear dose-related trend was not observed. Absolute and relative liver weights were significantly increased in high-dose males at interim sacrifice, but not at study termination. Absolute and relative liver weights were 29% and 24% greater in the high-dose group than in the controls. Microscopic examination showed that the incidence of hepatocyte hypertrophy was significantly increased in mid- and high-dose males in the interim sacrifice (9/10 and 10/10, respectively, vs 0/10 for controls) and main study groups (34/51 and 37/51, respectively, vs 4/51 for controls). The increased liver weight and hepatocyte hypertrophy are adaptive responses and are not toxicologically significant.

The no-observed-adverse-effect level (NOAEL) for male mice is ≥ 731.4 mg/kg bw/day and ≥ 850.2 mg/kg/day for female mice. A LOAEL was not identified.

There was no treatment-related increase in the incidences of neoplasms at any anatomical site in male or female mice receiving any dose of the test material. The animals were adequately dosed based on decreases in erythrocyte parameters in males. The male mice may not have been able to tolerate a higher dose because it would cause further depression in erythrocyte count, hemoglobin level, and hematocrit. The high dose to the females was 85% of the limit dose and is considered adequate for this study.

This carcinogenicity study in the mouse is **Acceptable/Guideline** and it does satisfy the guideline requirement for a carcinogenicity study (OPPTS 870.4200b; OECD 453) in the mouse.

21-Day Dermal

In a 21-day dermal study in Sprague-Dawley rats, males and females received repeated dermal dosing of test compound at 0, 100, 300, or 1000 (limit dose) mg/kg/day for 6 hours/day, 7 days/week for 21 days. No treatment-related effects were noted in mortality, body weight gain, food consumption, clinical pathology, or absolute and relative organ weights. Although gross pathological examination of the livers revealed an increased incidence of pale areas, no relevant histopathological changes were found. No treatment-related dermal toxicity was noted at the highest dose tested (1000 mg/kg/day).

Based on these findings, a NOAEL of 1000 mg/kg/day (limit dose) for systemic and dermal toxicity was established for male and female rats.

This dermal study in the rat is **Acceptable/Guideline** and it does satisfy the guideline requirement for a dermal toxicity study in rats.

3.0 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 stover 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 A.3.0.

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 to 0.2 ppm; and (ii) cotton gin byproducts from 2.0 to 3.0 ppm.

TABLE A.3.0. 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

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R110544

Chemical:	**Flumiclorac**
PC Code:	**128724**
HED File Code	**14000 Risk Reviews**
Memo Date:	**06/28/2005**
File ID:	**DPD302019**
Accession Number:	**412-05-0098**

HED Records Reference Center
07/11/2005