UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

TXR No. 0052680

Date: July 8, 2004

MEMORANDUM

Subject: **Fluazifop-P-butyl**. Report of the Metabolism Assessment Review Committee.

PC Code: 122809.
DP Barcode: 298939.

From: Sherrie L. Kinard, Chemist
David Anderson, Toxicologist
Reregistration Branch 2
Health Effects Division (7509C)

and

William P. Eckel, Ph.D.
Environmental Risk Branch II
Environmental Fate and Effects Division (7507C)

Through: Alan Nielsen, Branch Senior Scientist
Reregistration Branch 2
Health Effects Division (7509C)

and

Christine Olinger, Chairperson
Metabolism Assessment Review Committee
Health Effects Division (7509C)

To: Yan Donovan, Executive Secretary
Metabolism Assessment Review Committee
Health Effects Division (7509C)

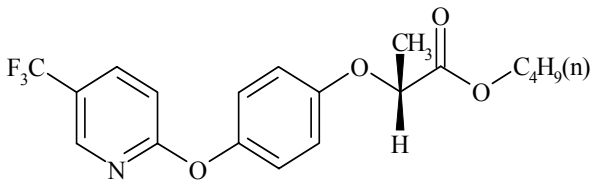
1. INTRODUCTION

Identification of Chemical

Fluazifop-P-butyl [(*R*)-2-(4-((5-(trifluoromethyl)-2-pyridinyl)oxy)phenoxy)propanoic acid, butyl ester] is a selective herbicide registered for use for postemergence control of perennial and annual grass weeds. Fluazifop-P-butyl is currently registered for food/feed use on apricot, asparagus, carrot, cherry, coffee, cotton, endive (escarole), garlic, macadamia nut, nectarine, onion, peach, pecan, pepper, plum, prune, rhubarb, soybeans, sweet potato, and yam.

Fluazifop-P-butyl is the resolved isomer (R enantiomer) of fluazifop-butyl [(*R,S*)-2-(4-((5-(trifluoromethyl)-2-pyridinyl)oxy)phenoxy)propanoic acid, butyl ester]. The fluazifop-butyl isomers are List B chemicals. Fluazifop-butyl (PC code 122805) has been canceled and only fluazifop-p-butyl is being supported for reregistration.

TABLE 1.1. Test Compound Nomenclature

Chemical structure	
Common name	Fluazifop-P-butyl
Company experimental name	$C_{19}H_{20}F_3NO_4$
IUPAC name	383.37
CAS name	butyl (2*R*)-2-(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}phenoxy)propanoate
CAS #	(*R*)- 2-(4-((5-(trifluoromethyl)-2-pyridinyl)oxy)phenoxy)propanoic acid, butyl ester
End-use formulation (EUP)	79241-46-6

Issues for the Committee

The briefing memorandum should include specific questions the review team is asking the MARC to consider. This is particularly important when a chemical is being considered multiple times so the MARC can focus on specific issues.

1. Does the committee agree that for the tolerance expression in plant and livestock commodities, and for purposes of risk assessment, the residue of concern are combined residues of fluazifop-P-butyl and free and conjugated forms of the resolved isomer of fluazifop?

2. Does the committee agree that for the tolerance expression in rotational crop commodities, and for purposes of risk assessment, the residue of concern in rotational crops can be the same as plant and livestock until new data can be submitted?

3. Does the committee agree that fluazifop-P-butyl and the environmental degradates fluazifop-acid and 5-trifluoromethyl-2-pyridone should be included in the risk assessment?

2. MARC MEETING INFORMATION

Decision

Table 2.1. Fluazifop-P-butyl Residues of Concern in Crops, Livestock, Rotational Crops, and Water		
Residues of Concern		
Matrix	For Tolerance Expression	For Risk Assessment
Plants	Parent and Fluazifop-acid (free and conjugated)	Parent, Fluazifop-acid (free and conjugated), 5-trifluoromethyl-2-pyridone, and 2-(4-hydroxyphenoxy) propionic acid (free and conjugated)
Livestock	Parent and Fluazifop-acid (free and conjugated)	Parent and Fluazifop-acid (free and conjugated)
Rotational Crops	No decision	No decision
Water	N/A	Parent and Fluazifop-acid

Meeting Date: March 3, 2004

MARC Rationale

Plants:. Both pyridyl label and phenyl label metabolism studies were conducted on plants. Fluazifop-acid (free and conjugated), 5-trifluoromethyl-2-pyridone, and 2-(4-hydroxyphenoxy) propionic acid are the major residues (>10% TRR). Based on their structures, MARC was unable to conclude that these major metabolites will be significantly less toxic than the parent and therefore, recommended that for risk assessment, the residues of concern are parent, fluazifop-acid (free and conjugated), 5-trifluoromethyl-2-pyridone, and 2-(4-hydroxyphenoxy) propionic acid (free and conjugated). There are no specific toxicity concerns for all other minor metabolites. The analytical method detects parent and fluazifop-acid (free and conjugated). MARC concluded that for tolerance expression, parent and fluazifop-acid (free and conjugated) are the residues of concern since they are adequate to determine misuse.

Livestock: Livestock metabolism study conducted on dairy cattle dosed with a mixture of [phenyl-U-^{14}C]fluazifop-butyl and [pyridyl-^{14}C]fluazifop-butyl at 2.49 ppm in the diet (0.55x MTDB) indicated that fluazifop (free and conjugated) was identified as the major component in all cow tissues, at 36.9% TRR (<0.001 ppm) in muscle, 31.8% TRR (<0.002 ppm) in fat, 61.0% TRR (0.024 ppm) in kidney, and 61.7% TRR (0.014 ppm) in liver. The majority of the

radioactivity in milk was lipophilic in nature and was converted to fluazifop upon base hydrolysis (67.7% TRR, 0.030 ppm); TLC analysis of the major extract prior to base hydrolysis indicated that the major residue in milk was a triglyceride ester(s) of fluazifop. The metabolite 2-(4-hydroxyphenoxy)-5-trifluoromethyl pyridine was the only other metabolite identified, at 11.8% TRR (0.005 ppm) in kidney and 10.3% TRR (0.002 ppm) in liver. MARC concluded that 2-(4-hydroxyphenoxy)-5-trifluoromethyl pyridine can be excluded based on the following: 1) the absolute residue value is relatively low (about 0.01 ppm); 2) it is not likely to be significantly more toxic than the parent; 3) kidney and liver are not high consumption items. In the poultry study (both phenyl and pyridyl-^{14}C label), fluazifop-acid was identified as the only major component in all matrices. Therefore, the residues of concern for risk assessment and tolerance expression in livestock are parent and fluazifop-acid (free and conjugated).

Rotational Crop: No decision was made on rotational crops due to no information being available on identification of metabolites. Radioactive residues (expressed as fluazifop-butyl equivalents) were <0.01 ppm in all crops grown to maturity in ^{14}C-Phenyl labeled fluazifop-butyl treated soil at (0.33 x Rate) and hence no rotational crop tolerances may be needed. However, wheat straw and sugar beet foliage had 0.10 ppm and 0.03 ppm total residues, respectively, following treatment with pyridyl labeled fluazifop-butyl with the same rate.

Drinking Water: Environmental fate studies indicated that parent is not mobile and not persistent. Aerobic soil metabolism studies showed that the half-life of the parent ester is on the order of a few hours. The major degradates (>10% of applied radiation in any fate study) are fluazifop-acid and 5-trifluoromethyl-2-pyridone. Fluazifop-acid is not very persistent in aerobic soil (half-lives 11 to 26 days) but is stable in flooded (anaerobic) soil, and in hydrolysis studies. Fluazifop-acid is considered to be mobile (Koc 8.3 to 51) and therefore can potentially reach to surface and ground water. MARC recommended to include fluazifop-acid in the drinking water assessment. MARC concluded that 5-trifluoromethyl-2-pyridone can be excluded based on the following: 1) the exposure level is very low relative to fluazifop-acid based on its later formation in the degradation process; 2) there is not obvious evidence of it being hihgly toxic in the rat based on the results of the parent toxiccology studies and its presence as a rat metabolite (albeit at a very low level); 3) no special concerns were identified in literature; and 4) it is sufficiently protective to regulate the parent and the fluazifop-acid. MARC concluded the residues of concern for drinking water assessment are parent and fluazifop-acid.

Members Attended: Alberto Protzel, Abdallah Khasawinah, Yan Donovan, Norman Birchfield, Leung Cheng, Rick Loranger, Pauline Wagner, John Doherty, Christine Olinger, PV Shah, Bill Wassell.

Members in Absentia: Leonard Keifer.

Non Members: William Eckel, Diana Locke, David Anderson, Sahafenyen Mohsen.

3. BRIEFING MATERIALS

RESIDUE CHEMISTRY

Tolerances are established under 40 CFR §180.411(a)(1) and (c)(1) for residues of fluazifop-butyl and free and conjugated fluazifop, expressed as fluazifop, in/on cotton commodities, soybean commodities, tabasco pepper, and animal commodities, and under §180.411(a)(2) and (c)(2) for residues of fluazifop-P-butyl and free and conjugated fluazifop (R isomer), expressed as fluazifop, in/on asparagus, carrots, coffee, endive, stone fruit, macadamia nuts, onion, pecans, rhubarb, spinach, and sweet potatoes.

The Phase 4 Reviews for fluazifop-butyl and fluazifop-P-butyl were completed 2/26/91. The Phase 4 Reviews identified many studies (43 studies) that were adequate for Phase 5 review; however, Phase 5 review of these studies has not yet been completed.

Use Information

Fluazifop-P-butyl [(*R*)-2-(4-((5-(trifluoromethyl)-2-pyridinyl)oxy)phenoxy)propanoic acid, butyl ester] is a selective herbicide registered for use for postemergence control of perennial and annual grass weeds. Fluazifop-P-butyl products are registered in the U.S. to Syngenta Crop Protection, Inc. under the trade names Fusilade®, Fusion®, and Typhoon®. Currently, the 0.086, 0.47, 1, 2, and 4 lb/gal emulsifiable concentrate (EC) formulations of fluazifop-P-butyl are registered for use on food/feed crops. The products are typically applied as postemergence foliar applications using ground or aerial equipment.

Table 3.1. Summary of Directions for Use of Fluazifop-P-butyl (only crops in metabolism studies maximum applications listed).						
Site Name	Applic. Timing, Type, and Equip.	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Soybean	**Foliar** Band treatment/Broadcast Aircraft/Ground	.375 lb A	NS	.75 lb/cc	90	Do not graze treated areas or harvest for forage or hay. Rotational/plant back crop restriction. Do not apply when wind velocity is 10 mph or greater.
Carrot (including tops)	**Postemergence** Band treatment/Broadcast/Chemigation/Low volume spray (concentrate)/Spot treatment Aircraft/Band sprayer/Ground/Sprayer/Sprinkler irrigation	.375 lb A 1.5 lb/1 gal	NS 2/1 yr	.75 lb/cc	45	Rotational/plant back crop restriction. Geographic allowable: AK AL AR AZ CA CO CT DE FL GA HI IA ID IL IN KS KY LA MA MD ME MI MN MO MS MT NC ND NE NH NJ NM NV NY OH OK OR PA RI SC SD TN TX UT VA VT WA WI WV WY
Celery	Not Currently Registered for Use on Celery.					
Grape	Not Currently Registered for Use on Grape.					
Sugar Beet	Not Currently Registered for Use on Sugar Beet.					

Physical/Chemical Properties

TABLE 3.2. Physicochemical Properties	
Parameter	**Value**
Melting point/range	Decomposes at 210 °C 164 °C at 0.02 mm Hg
pH	Not dispersible in water
Density	1.22 g/cc (PAI) and 1.20 g/cc (T) at 20 °C
Water solubility	1 mg/L
Solvent solubility	Soluble in most organic solvents >500 g/L in acetone, dichloromethane, ethyl acetate, hexane, methanol, toluene, and xylene
Vapor pressure	3×10^{-8} KPa at 20 °C
Dissociation constant, pK_a	-3.1 (by calculation)
Octanol/water partition coefficient, $Log(K_{OW})$	4.5 at 20 °C
UV/visible absorption spectrum	not available

Summary of Metabolism Data - Crops

Overall Summary. The nature of the residue in soybeans is understood. Additional metabolism data for a root/tuber crop and a leafy vegetable remain outstanding.

***Soybean* (MRIDs 41994701-41994703).** An adequate soybean metabolism study has been submitted. Total radioactive residues (TRR) were 11.1 ppm in soybeans collected 63 days following a single foliar application of [phenyl-^{14}C] fluazifop-butyl (racemic mixture) at 0.91 lb ai/A (1.8x the maximum seasonal rate). The foliage was not collected or analyzed; product labels currently bear a restriction against grazing or harvesting forage or hay. Soybeans were subjected to extraction and characterization/identification of residues. Unconjugated fluazifop (compound II) was found to account for 28% TRR, lipohilic conjugates of fluazifop were found to account for 23.4% TRR, and polar conjugates of 2-(4-hydroxyphenoxy)propionic acid (compound III) were found to account for 25.5% TRR. The lipophilic conjugates consisted of fluazifop conjugated with glyceride esters, some of which were identified as glycerol dioleate, glycerol dilinoleate, and a hybrid oleate-linoleate ester of glycerol. The maximum residue of any individual lipophilic conjugate of fluazifop was <7.2%. The unidentified portion of the residue, 19.4% TRR, consisted of unextracted radioactivity (3.5%), unidentified ether-soluble radioactivity containing at least 6 compounds (8.3%), and water-soluble radioactivity (7.8%). Therefore, the majority of the residue in soybeans was found to be fluazifop acid in free or conjugated forms.

Note: This study was accepted (in 1991) even though the molecule was only labeled in one ring, and the identification of 2-(4-hydroxyphenoxy)propionic acid indicates that the molecule does split between the two rings.

Table 3.3. Summary of Characterization and Identification of Radioactive Residues in Soybean Matrices Following Application of Radiolabeled [Phenyl-^{14}c] Fluazifop-butyl (Racemic Mixture) at 0.91 lb ai/A (1.8x the Maximum Seasonal Rate).

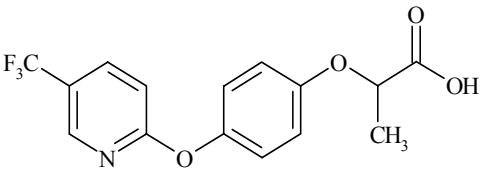
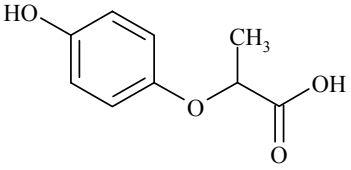
Compound	Fluazifop-butyl Phenyl Label* (TRR = 11.1 ppm)	
	% TRR	ppm
Fluazifop: unconjugated	28	3.1
Lipophilic Conjugates	23.4	2.6
2-(4-hydroxyphenoxy)propionic acid Conjugates	25.5	2.8
Total Unidentified	19.4	2.2
Total identified	76.9	8.5
Total characterized	76.9	8.5
Total extractable	94.6	10.5
Unextractable	3.5	0.4
Accountability[1]	98.2	

[1] Accountability = (Total extractable + Total unextractable)/(TRR from combustion analysis; see TABLE C.2.1) * 100.

FIGURE 3.1. Proposed Metabolic Profile of Fluazifop in Soybean.

No metabolic pathway was proposed for fluazifop-butyl in soybean.

TABLE 3.4. Identification of Compounds from Metabolism Study

Common name/code Figure 4.1 ID No.	Chemical name	Chemical structure
Fluazifop	2-(4-[5-(trifluoromethyl-2-pyridinyloxy]phenoxy)propionic acid	
Compound III	2-(4-hydroxyphenoxy)propionic acid	

Carrot (*MRID 00152494*). In the carrot study, test substances of [phenyl-U-^{14}C]fluazifop-butyl, [pyridyl-^{14}C]fluazifop-butyl, and [phenyl-U-^{14}C]fluazifop-P-butyl were each applied as a single foliar broadcast spray to immature carrot plants (64 days after planting) at 0.451-0.475 lb ai/A (fluazifop-butyl; ~0.6x the maximum seasonal rate) or 0.219 lb ai/A (fluazifop-P-butyl; 0.3x the maximum seasonal rate). Mature carrot roots were harvested 46 days following treatment; carrot tops were not collected for analysis. TRR were 0.18 and 0.33 ppm in carrot roots treated with [phenyl-^{14}C]fluazifop-butyl and [pyridyl-^{14}C]fluazifop-butyl, respectively. TRR were 0.15 ppm in carrot roots treated with [phenyl-^{14}C]fluazifop-P-butyl.

Fluazifop was the major residue identified in **fluazifop-butyl phenyl label roots**, accounting for 45.7% TRR (28.9% TRR free and 16.8% TRR conjugated). The metabolites 2-[4-(5-trifluoromethyl-2-pyridyloxy)phenoxy]propanol (11.3% TRR free and 1.8% TRR conjugated) and 2-(4-hydroxyphenoxy)propionic acid (4.8% TRR conjugated) were also identified.

Fluazifop was the major residue identified in **fluazifop-butyl pyridyl label roots**, accounting for 43.5% TRR (25.6% TRR free and 17.9% TRR conjugated). The metabolite 2-[4-(5-trifluoromethyl-2-pyridyloxy)phenoxy]propanol (7.7% TRR free and 2.8% TRR conjugated) was also identified in fluazifop-butyl pyridyl label roots. Based on ^{19}F-NMR analysis, the registrant estimated that ~4.4% and ~1% TRR were present in carrot roots as polar conjugates of an unknown (U4) and 5-trifluoromethyl-2-(1H)pyridone, respectively. Because U4 was observed in the ^{19}F-NMR spectrum, the registrant concluded that it contained a CF_3 moiety.

Fluazifop was the major residue identified in **fluazifop-P-butyl phenyl label roots**, accounting for 63.1% TRR (38.6% TRR free and 24.5% TRR conjugated). The metabolite 2-(4-hydroxyphenoxy)propionic acid (6.4% TRR conjugated) was also identified. ^{19}F-NMR analysis of the organosoluble phase following acid hydrolysis of aqueous-soluble residues indicated the presence of 5-trifluoromethyl-2-(1H)pyridone and U4, in a similar ratio to the ratio observed in the ^{19}F-NMR spectrum of fluazifop-butyl pyridyl label roots. Based on the fact that U4 was not observed in the TLC analysis of this fraction, the registrant concluded that U4 did not contain the phenyl ring and was formed by cleavage of fluazifop at the central linkage. The registrant concluded that 5-trifluoromethyl-2-(1H)pyridone and U4 were not formed stereospecifically from the R- or S-enantiomers of fluazifop.

Because the metabolite 2-[4-(5-trifluoromethyl-2-pyridyloxy)phenoxy]propanol was observed only at trace levels (<1% TRR) in carrot roots treated with fluazifop-P-butyl but accounted for ~10% TRR in carrot roots treated with fluazifop-butyl, the registrant concluded that 2-[4-(5-trifluoromethyl-2-pyridyloxy)phenoxy]propanol was formed stereospecifically from the S-enantiomer of fluazifop-butyl. The registrant also concluded that additional unknowns (U1 and U2/U3) characterized (each present at <7% TRR, ≤0.021 ppm) in the organosoluble fraction of fluazifop-butyl phenyl and pyridyl label root extracts contained an intact diphenyl ether moiety (because they were found in roots from both labels). In addition, because these unknowns were not found in fluazifop-P-butyl phenyl label roots, the registrant concluded that they were formed by the metabolism of the S-enantiomer of fluazifop-butyl and not the R-enantiomer.

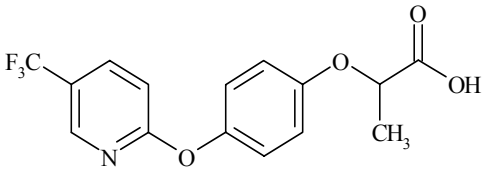
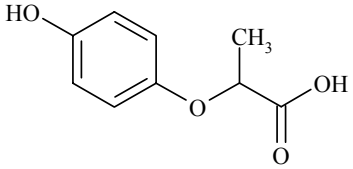
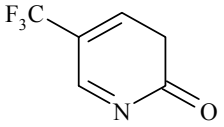
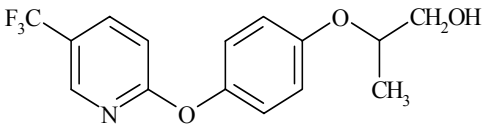
Table 3.5. Summary of Characterization and Identification of Radioactive Residues in Carrot Roots Following Application of Fluazifop-butyl at 0.451-0.475 lb ai/A or Radiolabeled Fluazifop-P-butyl at 0.219 lb ai/A.						
Compound	Fluazifop-butyl Phenyl Label		Fluazifop-butyl Pyridyl Label		Fluazifop-P-butyl Phenyl Label	
	TRR = 0.18 ppm		TRR = 0.33 ppm		TRR = 0.15 ppm	
	% TRR	ppm	%TRR	ppm	% TRR	ppm
Fluazifop: free	28.9	0.052	25.6	0.084	38.6	0.058
conjugated	16.8	0.030	17.9	0.059	24.5	0.037
2-[4-(5-Trifluoromethyl-2-pyridyloxy)phenoxy]propanol: free	11.3	0.020	7.7	0.025	Trace (<1)	--
conjugated	1.8	0.003	2.8	0.009	Trace (<1)	--
2-(4-Hydroxyphenoxy)propionic acid (conjugated)	4.8	0.009	--	--	6.4	0.010
5-Trifluoromethyl-2-(1H)pyridone (conjugated)	--	--	~1.0	0.003	--	--
Unknowns 1-3	8.3	0.015	8.9	0.029	--	--
Unknown 4 (conjugated)	--	--	~4.4	0.015	--	--
Aqueous soluble	2.9	0.006	4.2	0.014	4.0	0.006
Aqueous soluble after acid hydrolysis	6.2	0.011	7.5	0.025	8.4	0.013
Total identified	63.6	0.114	55.0	0.180	69.5	0.105
Total characterized	17.4	0.032	25.0	0.083	12.4	0.019
Total extractable	87.8	0.159	87.7	0.290	91.8	0.138
Unextractable (PES)[1]	12.2	0.022	12.3	0.041	8.2	0.012
Accountability[2]	100		100		100	

[1] Residues remaining after exhaustive extractions.

[2] Accountability = (Total extractable + Total unextractable)/(TRR from combustion analysis; see TABLE C.2.1) * 100.

FIGURE 3.2. Proposed Metabolic Profile of Fluazifop-butyl in Carrot

No metabolic pathway was proposed for fluazifop-butyl in carrots. However, the registrant stated that fluazifop (free and conjugated) was the major metabolite resulting from phenyl- and pyridyl-labeled fluazifop-butyl and phenyl-labeled fluazifop-P-butyl in/on carrot roots. The metabolite 2-[4-(5-trifluoromethyl-2-pyridyloxy)phenoxy]propanol and three unknowns containing an intact phenyl pyridyl ether moiety were only present in carrot roots treated with fluazifop-butyl; the registrant concluded that these residues were formed stereospecifically from the S-enantiomer of fluazifop-butyl. Metabolites 2-(4-hydroxyphenoxy)propionic acid and 5-trifluoromethyl-2-(1H)pyridone and an unknown cleavage product containing a CF_3 moiety did not appear to be formed stereospecifically.

TABLE 3.6. Identification of Compounds from Carrot Metabolism Study		
Common name/code Figure C.3.1 ID No.	Chemical name	Chemical structure
Fluazifop	2-(4-[5-(trifluoromethyl-2-pyridinyloxy]phenoxy)propionic acid	
Compound III	2-(4-hydroxyphenoxy)propionic acid	
Compound X	5-trifluoromethyl-2-(1H)pyridone	
Compound XXXIV	2-[4-(5-trifluoromethyl-2-pyridyloxy)phenoxy]propanol	

***Celery* (MRID 40693102).** In the celery study, [phenyl-U-^{14}C]fluazifop-P-butyl and [pyridyl-^{14}C]fluazifop-P-butyl were each applied as two foliar broadcast spray applications to celery plants 35 and 50 days after transplanting. For the phenyl label study, celery plants received 0.40 lb ai/A at the first application and 0.16 lb ai/A at the second application, for a total rate of 0.56 lb ai/A (0.75x the maximum seasonal rate for leafy vegetables). For the pyridyl label study, celery plants received 0.37 lb ai/A at the first application and 0.32 lb ai/A at the second application, for a total application rate of 0.70 lb ai/A (0.9x the maximum seasonal rate for leafy vegetables). Mature celery plants were harvested 30 days following treatment, and the stem and top leaves were separated for analysis. TRR were 0.31 and 0.05 ppm, respectively, in celery leaves and stem treated with [phenyl-^{14}C]fluazifop-P-butyl and were 0.64 and 0.08 ppm, respectively, in celery leaves and stem treated with [pyridyl-^{14}C]fluazifop-P-butyl.

In **phenyl label stem**, fluazifop was the major residue identified (11.0% TRR free, 31.4% TRR conjugated). Metabolites 2-(4-hydroxyphenoxy) propionic acid (18.2% TRR conjugated) and 2-[4-(3-hydroxy-5-trifluoromethyl-2-pyridyloxy)phenoxy]propionic acid (4.2% TRR conjugated) were also identified. In **phenyl label leaves**, fluazifop was the major residue identified (4.7% TRR free, 47.9% TRR conjugated); the parent fluazifop-P-butyl was also identified at minor levels (2.0% TRR). Metabolites 2-(4-

hydroxyphenoxy) propionic acid (7.9% TRR conjugated) and 2-[4-(3-hydroxy-5-trifluoromethyl-2-pyridyloxy)phenoxy]propionic acid (2.0% TRR conjugated) were also identified. In addition, 2-[4-(5-trifluoromethyl-2-pyridyloxy)phenoxy]propanol was identified at very low levels (<1% TRR conjugated).

In **pyridyl label stem**, fluazifop was the major residue identified (10.0% TRR free, 29.6% TRR conjugated). Metabolites 5-trifluoromethyl-2-pyridone (2.0% TRR free, 0.8% TRR conjugated) and 2-[4-(3-hydroxy-5-trifluoromethyl-2-pyridyloxy)phenoxy]propionic acid (1.1% TRR conjugated) were also identified. In **pyridyl label leaves**, fluazifop was the major residue identified (2.7% TRR free, 60.0% TRR conjugated). Metabolites 5-trifluoromethyl-2-pyridone (9.6% TRR free) and N-[1-carboxy-2-(5-trifluoromethyl-2-pyridylthio)ethyl]malonamic acid (5.1% TRR free) were also identified. In addition, 2-[4-(3-hydroxy-5-trifluoromethyl-2-pyridyloxy)phenoxy]propionic acid was identified at very low levels (<1% TRR conjugated). The registrant stated that a portion of the unidentified aqueous-soluble residues, 6.8% TRR, was due to 5-trifluoromethyl-2-pyridone; however, no explanation was provided for this statement. If this 6.8% TRR is in addition to the 9.6% TRR identified in the original extracts, 5-trifluoromethyl-2-pyridone would account for 16.4% TRR (0.104 ppm) in celery leaves.

Table 3.7. Summary of Characterization and Identification of Radioactive Residues in Celery Stem and Leaves Following Application of [Pyridyl-^{14}C]Fluazifop-P-butyl at 0.696 lb ai/A. [1]				
Compound	Celery Stem		Celery Leaves	
	TRR = 0.08 ppm		TRR = 0.64 ppm	
	% TRR	ppm	% TRR	ppm
Fluazifop: free	10.0	0.008	2.7	0.017
conjugated	29.6	0.024	60.0	0.384
5-trifluoromethyl-2-pyridone: free	2.0	0.002	9.6	0.061
conjugated	0.8	0.001	--	--
2-[4-(3-hydroxy-5-trifluoromethyl-2-pyridyloxy)phenoxy]propionic acid (conjugated)	1.1	0.001	0.3	0.002
N-[1-carboxy-2-(5-trifluoromethyl-2-pyridylthio)ethyl]malonamic acid	--	--	5.1	0.033
Unknowns [2]	3.4	0.003	5.8	0.037
Organosoluble polar material	3.5	0.003	3.5	0.022
Aqueous soluble after acid hydrolysis	34.6	0.028	20.3 [3]	0.130
Total identified	43.5	0.035	77.7	0.497
Total characterized	41.5	0.033	29.6	0.189
Total extractable	91.6	0.073	94.4	0.604
Unextractable (PES) [4]	8.4	0.007	5.6	0.036
Accountability [5]	100		100	

[1] These summary data are reported as presented by the registrant; the registrant used the average %TRR value from two TLC analyses. Ppm values were calculated by the study reviewer from the %TRR values provided by the registrant; ppm totals may vary due to rounding.

[2] At least 5 compounds in stem; at least 4 compounds in leaves.

[3] In their summary table, the registrant stated that 6.8% of this TRR (0.044 ppm) is due to 5-trifluoromethyl-2-pyridone. No explanation was provided.

[4] Residues remaining after exhaustive extractions.

[5] Accountability = (Total extractable + Total unextractable)/(TRR from combustion analysis; see TABLE C.2.1) * 100.

FIGURE 3.3. Proposed Metabolic Profile of Fluazifop-P-butyl in Celery.

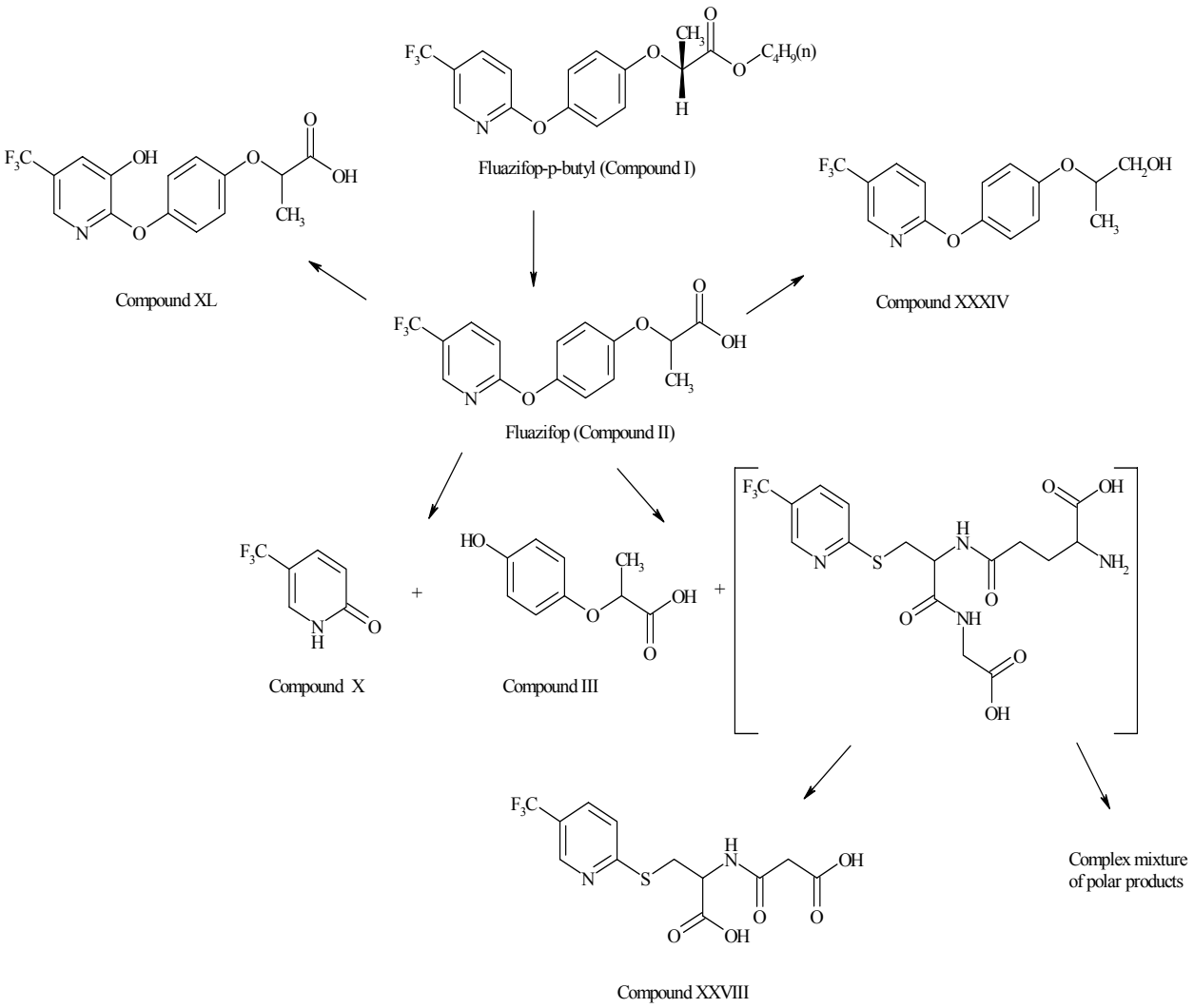
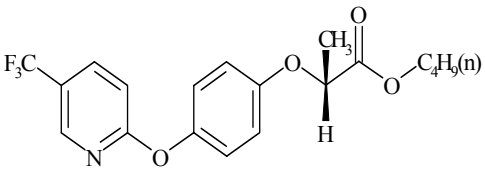
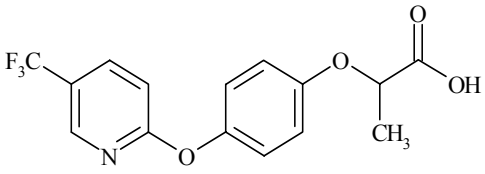
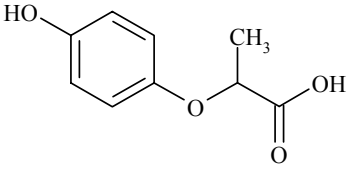
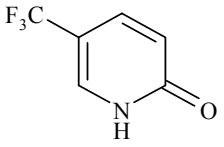
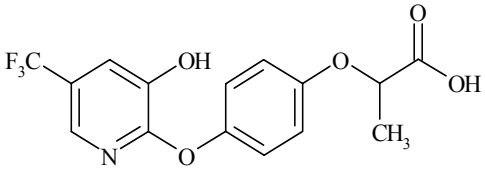
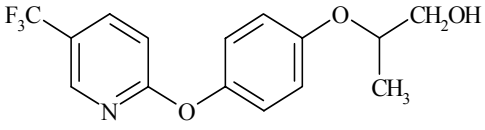
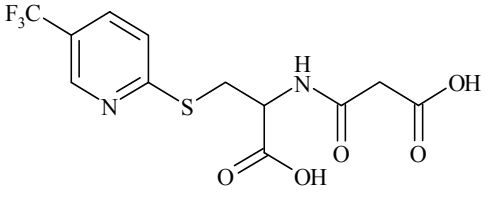


TABLE 3.8. Identification of Compounds from Metabolism Study		
Common name/code Figure 3.3 ID No.	Chemical name	Chemical structure
Fluazifop-P-butyl	butyl (R)-2-(4-((5-(trifluoromethyl)-2-pyridinyl)oxy)phenoxy)propanoate	
Fluazifop	2-(4-[5-(trifluoromethyl-2-pyridinyloxy]phenoxy)propionic acid	
Compound III	2-(4-hydroxyphenoxy)propionic acid	
Compound X	5-trifluoromethyl-2-pyridone	
Compound XL	2-[4-(3-hydroxy-5-trifluoromethyl-2-pyridyloxy)phenoxy]propionic acid	
Compound XXXIV	2-[4-(5-trifluoromethyl-2-pyridyloxy)phenoxy]propanol	
Compound XXVIII	N-[1-carboxy-2-(5-trifluoromethyl-2-pyridylthio)ethyl]malonamic acid	

Additional Data.

Grape: In the grape study, a mixture of [phenyl-U-^{14}C]fluazifop-P-butyl and [pyridyl-^{14}C]fluazifop-P-butyl was applied as three basal spray applications to a single grape vine. The first application was made at the early bunch formation stage at 0.60 lb ai/A; the second application was made 42 days later at 0.15 lb ai/A; and the third application was made 29 days after the second application at 0.68 lb ai/A. The total application rate was 1.42 lb ai/A (1.3x the maximum seasonal rate to orchard crops). Immature grapes were harvested 21 and 30 days following the first application and 3 and 18 days following the second application, and mature grapes were harvested 14 and 30 days following the third application. TRR were <0.01 ppm in immature and mature grapes harvested from all sampling intervals. The maximum TRR (0.009 ppm) were observed in mature grapes harvested 30 days following the last of the three basal applications. No characterization/identification of residues was conducted.

A separate subsample of mature grapes harvested 14 days following the third basal application, with a TRR of 0.007 ppm, was processed into juice and pulp to determine the distribution of radioactivity. Radioactivity in juice and pulp were 0.006 and 0.013 ppm, respectively. The registrant concluded that residues do not concentrate in juice but may concentrate (2x) in pulp.

Sugar beet: In the sugar beet study, [phenyl-U-^{14}C]fluazifop-butyl and [pyridyl-^{14}C]fluazifop-butyl were each applied as a single direct application to the foliage of sugar beet plants at the six-leaf stage and to the surrounding soil at ~2.6 lb ai/A (3.5x the maximum seasonal rate for root and tuber vegetables). Mature sugar beet roots were harvested ~90 days following treatment; sugar beet tops were not collected for analysis. TRR were 0.049 and 0.096 ppm in phenyl and pyridyl label sugar beet roots, respectively. Sugar beet roots were initially surface washed with water and ACN, which removed ~3% TRR from the phenyl label roots and ~25% TRR from the pyridyl label roots; however, radioactivity in the surface washes was not characterized/identified. Fluazifop (18.4% TRR free, 2.9% TRR conjugated and 3.4% TRR bound) and the metabolite 2-(4-hydroxyphenoxy) propionic acid (7.3% TRR conjugated) were tentatively identified in **phenyl label roots**. Fluazifop (9.2% TRR free, ~4% TRR conjugated, and 0.7% TRR bound) and the metabolite 5-trifluoromethyl-2-pyridone (6.3% TRR free, 18.2% TRR conjugated, and 2.7% TRR bound) were tentatively identified in **pyridyl label roots**. Acid and base hydrolyses confirmed that conjugated 5-trifluoromethyl-2-pyridone is a metabolite of fluazifop-butyl in sugar beet root and not a degradate of fluazifop resulting from hydrolysis. Additional analyses confirmed the incorporation of radioactivity into sucrose, accounting for ~4% TRR.

Summary of Metabolism Data - Livestock

Overall Summary. The qualitative nature of the residue in livestock is not understood. New metabolism studies for ruminants and poultry must be submitted.

ICI Americas, Inc., now known as Syngenta Crop Protection, Inc., submitted metabolism

studies with dairy cattle and laying hens. These studies have been reviewed by HED and determined to be inadequate to satisfy data requirements because the dosing levels were too low to allow elucidation of the nature of the residue in livestock.

Meat and Milk **(MRID 00093842).** In the dairy cattle study, one cow was dosed with a mixture of [phenyl-U-^{14}C]fluazifop-butyl and [pyridyl-^{14}C]fluazifop-butyl at 2.49 ppm in the diet (0.55x the maximum theoretical dietary burden to dairy cattle; see Table 5). The cow was dosed twice per day for 7 consecutive days. TRR were 0.012-0.048 ppm in milk, 0.002-0.005 ppm in fat, 0.039 ppm in kidney, 0.024 ppm in liver, and 0.001 ppm in muscle. The majority (81.2%) of the administered dose was excreted, mostly in the urine (at least 78.1%). Fluazifop (free and conjugated) was identified as the major component in all cow tissues, at 36.9% TRR (<0.001 ppm) in muscle, 31.8% TRR (<0.002 ppm) in fat, 61.0% TRR (0.024 ppm) in kidney, and 61.7% TRR (0.014 ppm) in liver. The majority of the radioactivity in milk was lipophilic in nature and was converted to fluazifop upon base hydrolysis (67.7% TRR, 0.030 ppm); TLC analysis of the major extract prior to base hydrolysis indicated that the major residue in milk was a triglyceride ester(s) of fluazifop. The metabolite 2-(4-hydroxyphenoxy)-5-trifluoromethyl pyridine was the only other metabolite identified, at 11.8% TRR (0.005 ppm) in kidney and 10.3% TRR (0.002 ppm) in liver.

TABLE 3.9. Test Animal Dosing Regime

Regime	Level of administered dose (mg/day)	Food consumption (kg/day)	Vehicle	Timing/Duration
Oral	2.49	assuming 15	Gelatine capsules containing crushed dairy feed, via a feeding tube	Twice daily, approximately 1.5 hours after a.m. milking and immediately prior to p.m. milking, for 7 consecutive days

FIGURE 3.4. Pharmacokinetics of Fluazifop-butyl in Excreta and Milk of Lactating Mammal.

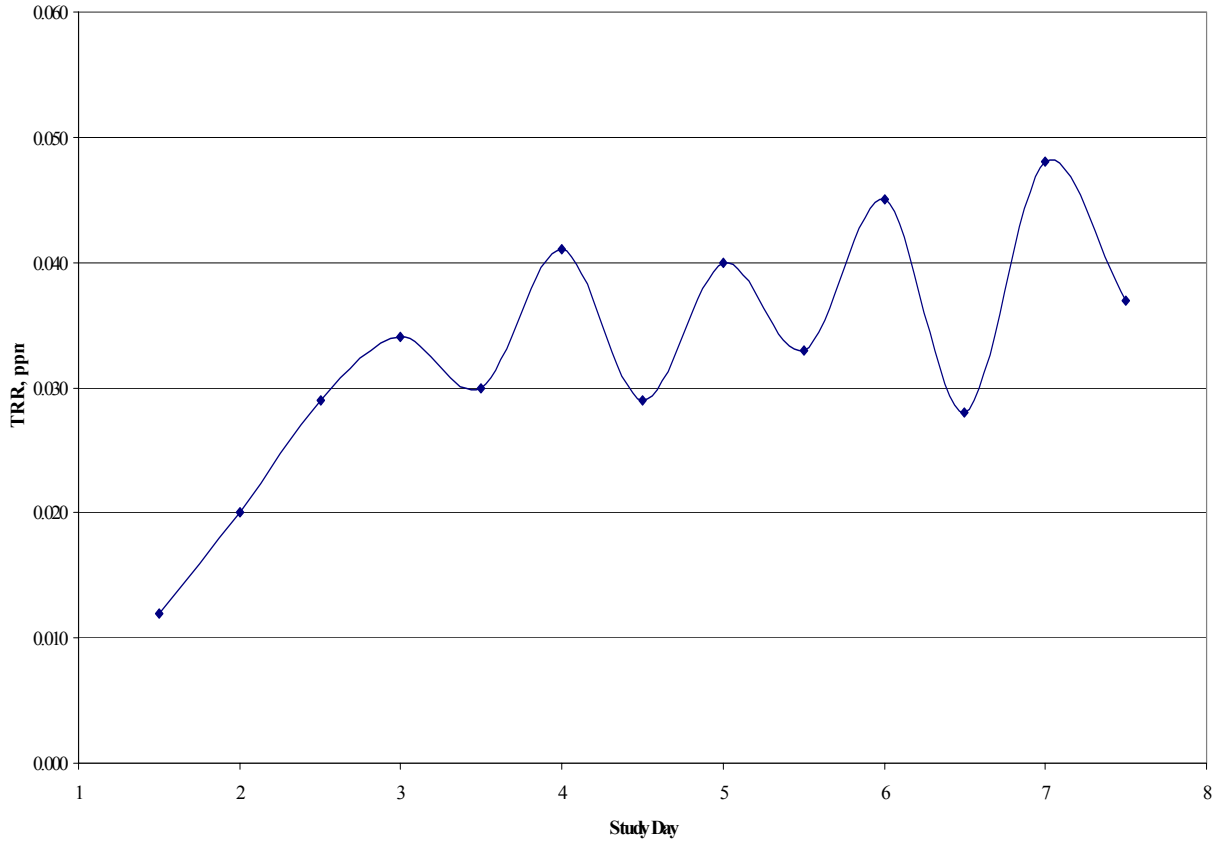
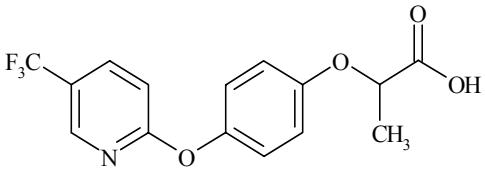
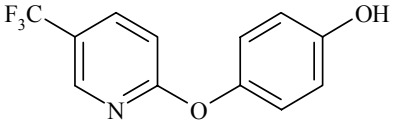
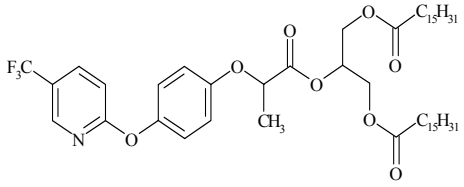
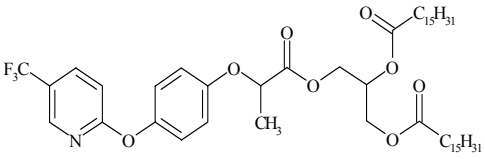


Table 3.10.	**Summary of Characterization and Identification of Radioactive Residues in Livestock Matrices Following Application of Radiolabeled Fluazifop-butyl at 2.5 ppm in the Diet [1].**									
Compound	Muscle		Fat, omental		Kidney		Liver		Milk (Day 6 pm)	
	TRR = 0.001 ppm		TRR = 0.005 ppm		TRR = 0.039 ppm		TRR = 0.024 ppm		TRR = 0.045 ppm	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
Fluazifop: free	36.9	0.0004	31.8	0.0016	61.0	0.024	60.4	0.014	--	--
conjugated	--	--	--	--	--	--	1.3	<0.001	67.7 [2]	0.030
2-(4-hydroxyphenoxy)-5-trifluoromethyl pyridine: free	--	--	--	--	11.8	0.005	9.9	0.002	--	--
conjugated	--	--	--	--	--	--	0.4	<0.001	--	--

Compound	Muscle		Fat, omental		Kidney		Liver		Milk (Day 6 pm)	
	TRR = 0.001 ppm		TRR = 0.005 ppm		TRR = 0.039 ppm		TRR = 0.024 ppm		TRR = 0.045 ppm	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
Nonpolar compounds	--	--	--	--	4.3	0.002	--	--	--	--
Polar compounds	--	--	--	--	8.6	0.003	4.2	0.001	--	--
Nonpolar/polar compounds	--	--	--	--	--	--	0.8	<0.001	--	--
Lipophilic; hexane phases	--	--	34.0	0.0017	--	--	--	--	--	--
Nonpolar; ether and/or hexane	23.1	0.0003	4.7	0.0002	2.2	0.001	5.1	0.001	--	--
Polar; aqueous phase	12.2	0.0001	10.7	0.0005	5.5	0.002	--	--	4.7	0.002
Florisil eluates	–	--	–	--	–	–	–	–	10.2	0.005
Aqueous after hydrolysis	--	--	--	--	--	--	7.0	0.002	0.4	<0.001
NaOH; ether	--	--	--	--	--	--	--	--	0.2	<0.001
Total identified	36.9	0.0004	31.8	0.0016	72.8	0.028	72.0	0.017	67.7	0.030
Total characterized	35.3	0.0004	49.4	0.0025	20.6	0.008	17.1	0.004	15.5	0.007
Total extractable	89.5	0.0009	97.7	0.0049	94.3	0.037	89.9	0.022	98.9	0.045
Unextractable (PES) [3]	10.5	0.0001	2.3	0.0001	5.7	0.002	10.1	0.002	1.1	<0.001
Accountability [4]	100		100		100		100		100	

[1] Summary data are presented as reported by the registrant; values representing the remainder after identification are not included.
[2] Determined as fluazifop upon base hydrolysis; probably present in milk as a triglyceride ester of fluazifop.
[3] Residues remaining after exhaustive extractions.
[4] Accountability = (Total extractable + Total unextractable)/(TRR from combustion analysis; see TABLE C.2.1) * 100.

FIGURE 3.5. Proposed Metabolic Profile of Fluazifop-butyl in Meat and Milk

TABLE 3.11. Identification of Compounds from Metabolism Study		
Common name/code	Chemical name	Chemical structure
Fluazifop	2-(4-[5-(trifluoromethyl-2-pyridinyloxy]phenoxy)propionic acid	
Compound IV	2-(4-hydroxyphenoxy)-5-trifluoromethyl pyridine	
Compound XVI	1,2 and 1,3 dipalmityl triglyceride esters of fluazifop	 

Poultry and Eggs **(MRID 00093844).** In the poultry study, test substances of [phenyl-U-^{14}C]fluazifop-butyl and [pyridyl-^{14}C]fluazifop-butyl were each administered to a single laying hen at an average of 2.6 ppm (phenyl label) or 2.2 ppm (pyridyl label) in the diet (2.6x and 2.2x, respectively, the maximum theoretical dietary burden to poultry; see Table 5). The hens were dosed once a day for 14 consecutive days. TRR were <0.001-0.021 ppm in egg yolk, 0.002-0.008 ppm in egg albumen, 0.040-0.045 ppm in fat (peritoneal and subcutaneous), 0.027 ppm in liver, and 0.004-0.005 ppm in muscle (breast and leg) from the hen dosed with [phenyl-^{14}C]fluazifop-butyl, and were <0.001-0.021 ppm in egg yolk, 0.001-0.003 ppm in egg albumen, 0.029-0.039 ppm in fat (peritoneal and subcutaneous), 0.077 ppm in liver, and 0.008-0.011 ppm in muscle (breast and leg) from the hen dosed with [pyridyl-^{14}C]fluazifop-butyl. Radioactivity was highest in fat and liver, and lowest in muscle and egg albumen. The majority of the administered dose (97-98%) was found to have been excreted.

For the **phenyl label** hen, fluazifop was identified as the major component in all matrices, at 51.3% TRR (<0.003 ppm) in muscle, 69.7% TRR (0.019 ppm) in liver, and 85.1% TRR (<0.003 ppm) in egg albumen. The majority of the radioactivity in egg yolk and fat was lipophilic in nature. In egg yolk, the majority of the radioactivity in the lipophilic fraction was found to co-chromatograph with the isomeric dipalmityl triglyceride esters of fluazifop. In egg yolk and fat, a large portion of the lipophilic fraction was converted to fluazifop following base hydrolysis, accounting for ~47.3% TRR (0.009 ppm) in egg yolk and 70.8% TRR (0.030 ppm) in fat. Free fluazifop was also identified in egg yolk at ~12.4% TRR (0.002 ppm).

For the **pyridyl label** hen, fluazifop was identified as the major component in all matrices, at 68.0% TRR (0.007 ppm) in muscle and 65.9% TRR (0.051 ppm) in liver. The majority of the radioactivity in egg and fat was lipophilic in nature; a large portion was found to co-chromatograph with the isomeric dipalmityl triglyceride esters of fluazifop. In addition, the majority of this radioactivity was converted to fluazifop following base hydrolysis, accounting for 40.5% TRR (0.007 ppm) in whole egg and 65.3% TRR (0.022 ppm) in fat. Free fluazifop was also identified in whole egg at 15.3% TRR (0.003 ppm).

FIGURE 3.6. Pharmacokinetics of Fluazifop-butyl in Excreta and Eggs of Laying Poultry.

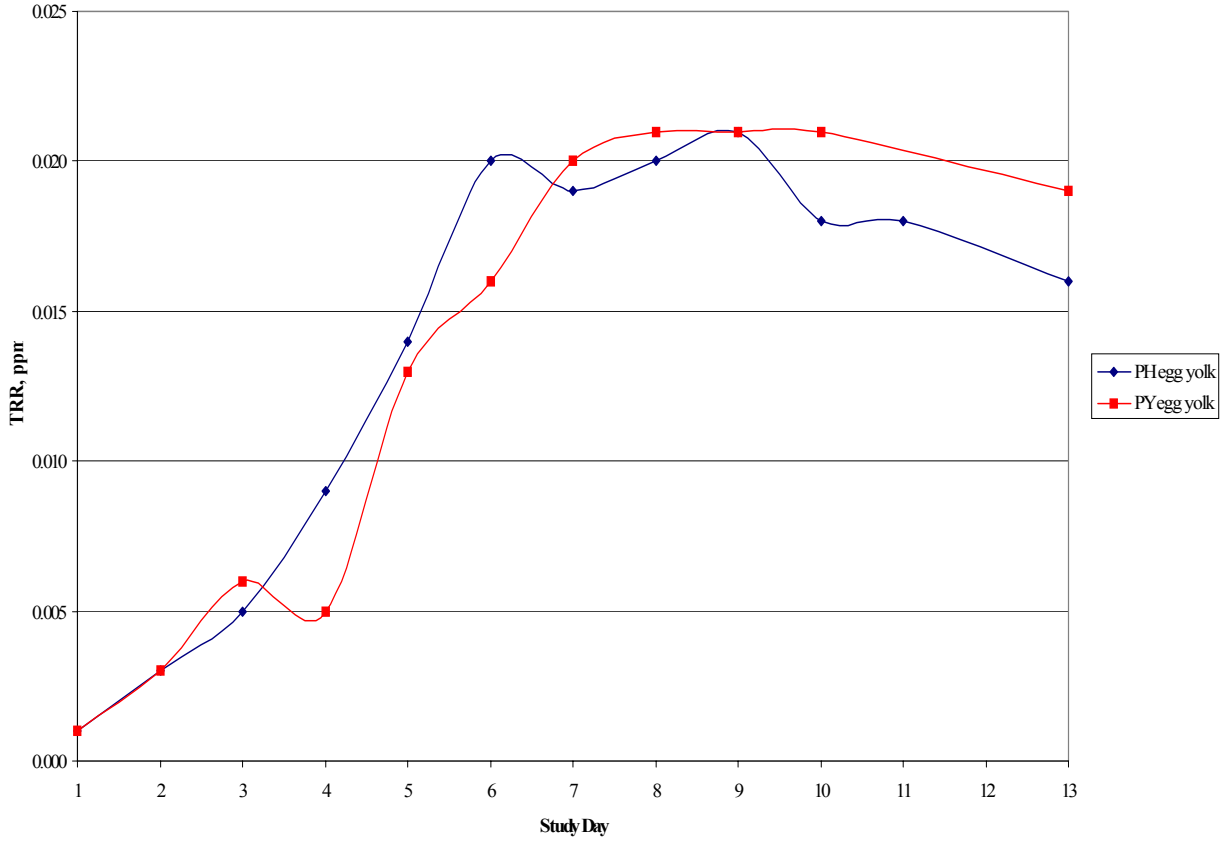


Table 3.12.a. Summary of Characterization and Identification of Radioactive Residues in Livestock Matrices Following Dosing with [Phenyl-^{14}C]Fluazifop-butyl at 2.6 ppm in the Diet [1].

Compound	Muscle		Fat		Kidney		Liver		Egg, yolk (Day 8)		Egg, albumen (Day 8)	
	TRR = 0.005 ppm		TRR = 0.043 ppm		TRR = 0.056 ppm		TRR = 0.027 ppm		TRR = 0.020 ppm		TRR = 0.003 ppm	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	%TRR	ppm	%TRR	ppm
Fluazifop: free	51.3	0	--	--	57.6	0.032	69.7	0.019	6.4 (+~6) [3]	~0.002	85.1	0.003
lipophilic conjugates [2]	--	--	70.8	0.03	--	--	--	--	41.3 (+~6) [3]	~0.009	--	--
Unknown	--	--	--	--	10.3	0.006	--	--	--	--	--	--
Aqueous soluble	15.6	0	2.1	0.001	5.2	0.003	2.4	0.001	3.4	<0.001	2.3	0
Hexane extract/phases	10.2	0	--	--	7.4	0.004	9.4	0.003	--	--	--	--
Ether phases not analyzed	0.9	<0.0001	2.9	0.001	--	--	0.6	<0.001	6.8 [4]	0	1.9	0
ACN phase	--	--	--	--	--	--	2.7	0.001	--	--	--	--
Florisil eluates	–	–	–	–	–	–	–	–	4.4	0	--	--
Total identified	51.3	0	70.8	0.03	57.6	0.032	69.7	0.019	~59.7	~0.012	85.1	0.003
Total characterized	26.7	0	5	0.002	22.9	0.013	15.1	0.004	14.6	0	4.2	0
Total extractable	82	0	93.5	0.04	93.5	0.052	94.9	0.026	92.4	0.018	89.3	0.003
Unextractable (PES) [5]	18	0	7.7	0.003	6.5	0.004	5.1	0.001	7.6	0	10.7	0
Accountability [6]	100		101.2		100		100		100		100	

[1] Ppm values were calculated by the study reviewer and may vary from Table C.2.2.1. due to rounding.
[2] Determined as fluazifop upon base hydrolysis; co-chromatographed with the isomeric dipalmityl triglyceride esters of fluazifop in egg yolk.
[3] The registration only provided estimated values for these compounds in one fraction (hexane phase following partitioning of the combined ACN phases).
[4] A large portion (up to 4.4% TRR) is probably due to fluazifop; because of poor chromatography the TLC peak could not be quantitated.
[5] Residues remaining after exhaustive extractions.
[6] Accountability = (Total extractable + Total unextractable)/(TRR from combustion analysis; see TABLE C.2.1) * 100.

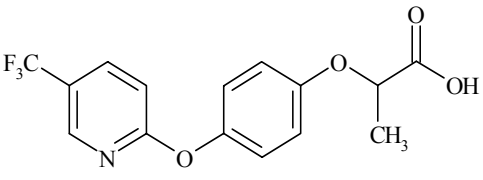
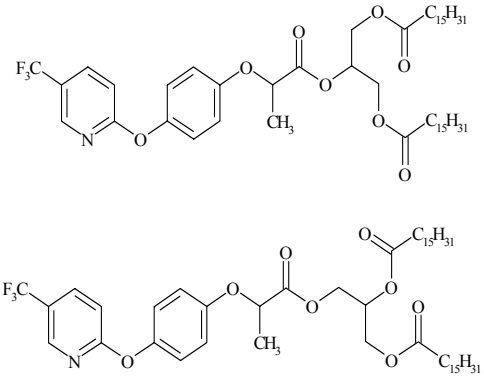
Table 3.12.b. Summary of Characterization and Identification of Radioactive Residues in Livestock Matrices Following Dosing with [Pyridyl-^{14}C]Fluazifop-butyl at 2.2 ppm in the Diet [1].

Compound	Muscle		Fat		Kidney		Liver		Egg, whole (Day 6)	
	TRR = 0.010 ppm		TRR = 0.034 ppm		TRR = 0.437 ppm		TRR = 0.077 ppm		TRR = 0.007 ppm	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	%TRR	ppm
Fluazifop**:** free	68	0.007	--	--	54.1	0.236	65.9	0.051	15.3	0.001
lipophilic conjugates [2]	--	–	65.3	0.022	--	--	--	--	40.5	0.003
Aqueous soluble	10.5	0.001	3.8	0.001	13.8	0.06	4.6	0.004	6.3	<0.001
Hexane extract/phases	6.8	0.001	--	--	0.9	0.004	8.3	0.006	2.1	<0.001
Ether phases not analyzed	--	--	1.9	0.001	4.8	0.021	0.6	<0.001	1.4	<0.001
ACN phase	--	--	--	--	--	--	2	0.002	--	--
Florisil eluates/losses	--	--	12	0.004	--	--	--	--	16.6	0.001
Total identified	68	0.007	65.3	0.022	54.1	0.236	65.9	0.051	55.8	0.004
Total characterized	17.3	0.002	17.7	0.006	19.5	0.085	15.5	0.012	26.4	0.002
Total extractable	90.6	0.009	90.3	0.031	88.4	0.386	93	0.072	85.3	0.006
Unextractable (PES) [3]	9.4	0.001	9.7	0.003	11.6	0.051	7	0.005	14.7	0.001
Accountability [4]	100		100		100		100		100	

[1] Ppm values were calculated by the study reviewer and may vary from Table C.2.2.2. due to rounding.
[2] Determined as fluazifop upon base hydrolysis; co-chromatographed with the isomeric dipalmityl triglyceride esters of fluazifop in whole egg and fat.
[3] Residues remaining after exhaustive extractions.
[4] Accountability = (Total extractable + Total unextractable)/(TRR from combustion analysis; see TABLE C.2.1) * 100.

FIGURE 3.7. Proposed Metabolic Profile of Fluazifop-butyl in Poultry and Egg

No metabolic pathway was proposed for fluazifop-butyl in poultry.

TABLE 3.13. Identification of Compounds from Metabolism Study		
Common name/code	Chemical name	Chemical structure
Fluazifop	2-(4-[5-(trifluoromethyl-2-pyridinyloxy]phenoxy)propionic acid	
Compound XVI	1,2 and 1,3 dipalmityl triglyceride esters of fluazifop	

Summary of Confined Rotational Crop Data

The qualitative nature of the residue in rotational crops is not understood. New confined rotational crop studies must be submitted. The confined rotational crop study has been determined to be inadequate to satisfy data requirements.

Currently, the following plantback interval exists on the product labels for EPA Reg. Nos. 100-994, 100-1003, 100-1059, 100-1069, and 100-1070: a 60-day plantback interval for rotational crops such as corn, sorghum, and cereals. The following plantback intervals exist on the product labels for EPA Reg. Nos. 100-1071 and 100-1116 (MAIs with sodium salt of fomesafen): a 4-month plantback interval for small grains such as wheat, barley, and rye; a 10-month plantback interval for beans, peas, corn, cotton, peanuts, and rice; and an 18-month plantback interval for alfalfa, seed corn, sunflowers, sugar beets, sorghum, or any other crop.

Confined Rotational Crops **(MRID 00093850).** ^{14}C-Phenyl labeled fluazifop-butyl (Ia) and ^{14}C-pyridyl labeled fluazifop-butyl (Ib) were applied at 250g/ha to a sandy loam soil and incorporated into the top 5 cm. Lettuce, wheat and sugar beet seeds were sown 30, 121, and 351 days after incorporation of Ia and 29 and 119 days after incorporation of Ib. Crops were grown to maturity and analyzed for total radioactivity content by combustion

analysis.

Radioactive residues (expressed as fluazifop-butyl equivalents) were <0.01 ppm in all crops grown to maturity in ^{14}C-Phenyl labeled fluazifop-butyl treated soil. Radioactive residues (expressed as fluazifop-butyl equivalents) were also <0.01 ppm in lettuce, wheat grain and sugar beet root in ^{14}C-pyridyl labeled fluazifop-butyl treated soil; however, in wheat straw and sugar beet foliage residues were 0.10 ppm and 0.03 ppm respectively.

Table 3.14.a. Summary of Radioactive Residues in Rotational Crop Matrices Following Application of ^{14}C-Phenyl labeled fluazifop-butyl at 250g/ha.

Crop		30 Days	121 Days	351 Days
		ppm	ppm	ppm
Lettuce		0.002	0.001	<0.001
Wheat	Straw	0.004	0.007	0.003
	Grain	0.004	0.002	0.001
	Husk	0.001	0.002	0.001
Sugar Beet	Foliage	0.002	0.002	<0.001
	Beet	<0.001	0.001	0.001
	Peel	0.002	0.002	0.002

Table 3.14.b. Summary of Radioactive Residues in Rotational Crop Matrices Following Application of ^{14}C-pyridyl labeled fluazifop-butyl at 250g/ha.

Crop		29 Days	119 Days
		ppm	ppm
Lettuce		0.004	0.005
Wheat	Straw	**0.098**	**0.078**
	Grain	0.006	0.003
	Husk	**0.080**	**0.021**
Sugar Beet	Foliage	**0.025**	**0.017**
	Beet	0.005	0.002
	Peel	0.006	0.002

Figure 3.8. Relative Distribution and Metabolite Levels in Rotational Crops Following Treatment with Fluazifop-butyl.

This information was not available.

FIGURE 3.9. Proposed Metabolic Profile of Fluazifop-butyl in Rotational Crops.

No metabolic pathway was proposed for fluazifop-butyl in rotational crops**.**

TABLE 3.15. Identification of Compounds from the Confined Rotational Crop Study		
Common name/code Figure 3.9 ID No.	Chemical name	Chemical structure
Not Available.		

Summary of Analytical Methods

Neither of the enforcement methods distinguish the optical isomers of fluazifop-butyl or fluazifop.

Crop Matrices **(MRIDs 92068020 92068041 92068043).** A GC/MS method (RR 91-014B) and an HPLC/UV method (modification of ICI Method #62) were used for the determination of total fluazifop residues in asparagus. These methods are similar to PAM Vol. II Method II.

Five methods for the determination of total fluazifop residues in plant commodities were addressed in the 2/26/91 Phase 4 Review. All methods involve acid or base extraction/hydrolysis of the crop sample, with residue determination by HPLC or ^{19}F-NMR. Residues may be confirmed using GC/MS after derivatization with diazomethane. None of the methods distinguish the optical isomers of fluazifop-butyl or fluazifop.

For enforcement of tolerances for fluazifop-P-butyl residues of concern in crop matrices, PAM Vol. II lists Method II for oily and non-oily crops. The stated detection limits are 0.02-0.05 ppm for crops. Residues of fluazifop-butyl, fluazifop, and any ester or acid conjugates are extracted from crop samples using acetonitrile and hydrochloric acid. Residues are then hydrolyzed to fluazifop and cleaned up using a coagulation procedure, solvent partitioning, and silica column chromatography for determination by HPLC/UV. Residues may be confirmed by GC/MS, following methylation with diazomethane.

Livestock Matrices **(MRIDs 92068021 92068040).** For enforcement of tolerances for fluazifop-P-butyl residues of concern in livestock matrices, PAM Vol. II lists Method I for animal tissues and milk. The stated detection limits are 0.01 ppm for milk, and 0.02 ppm for animal tissues. Samples (except fat) are extracted with acetonitrile/acetone/hexane, which separates residues of fluazifop and fluazifop-butyl (found in the acetonitrile/acetone layer) from residues of fluazifop lipophilic conjugates (found in the hexane layer). Fluazifop and fluazifop-butyl are determined in milk by HPLC/UV; in tissue samples, fluazifop-butyl is converted to fluazifop via hydrolysis, and then fluazifop residues are methylated, using diazomethane, and determined by GC/MS. Fluazifop lipophilic conjugates (for both milk and tissue samples) are cleaned up by Florisil chromatography, hydrolyzed to fluazifop, and determined by HPLC/UV. For fat, samples are extracted with chloroform/methanol at reflux (2 hours) and residues of fluazifop and lipophilic conjugates are hydrolyzed to fluazifop, methylated, and determined by GC/MS.

***Multiresidue Methods* (MRID 41041501).** The FDA PESTDATA database dated 11/01 (PAM Volume I, Appendix I) indicates that fluazifop-butyl is completely recovered using Multiresidue Methods Sections 302 (Luke Method; Protocol D) and 303 (Mills, Onley, and Gaither Method; Protocol E, nonfatty food); recovery using Section 304 (Mills Method; Protocol F, fatty food) is variable.

Summary of Magnitude of the Residue Studies – Crops

The reregistration requirements for magnitude of the residue in plants are not fulfilled for asparagus, carrot, cotton seed, cotton gin byproducts, and dry bulb onion. Pending determination of the adequacy of the available crop field trial data during Phase 5 review, reregistration requirements are fulfilled for coffee bean, endive, macadamia nut, pecan, rhubarb, soybean seed and aspirated grain fractions, stone fruit group, sweet potato, and tabasco pepper. When the required data for dry bulb onion have been submitted, they may be translated to support fluazifop-P-butyl use on garlic.

Summary of Magnitude of the Residue Studies – Livestock

Pending determination of the adequacy of the available livestock feeding studies during Phase 5 review, the reregistration requirements for magnitude of the residue in meat, milk, poultry, and eggs are satisfied.

Currently, there are no registered direct animal treatments of fluazifop-P-butyl to livestock. However, fluazifop-P-butyl is registered for use on the following crops with animal feedstuffs: carrot, cotton, and soybean. Tentative maximum theoretical dietary burdens of fluazifop-P-butyl to livestock have been calculated (the diet was reviewed by Jerry Stokes 01/22/04); however, we note that these calculations are tentative because plant and animal metabolism studies remain outstanding, and several crop field trial studies have not undergone Phase 5 review. It should also be noted that there are currently label restrictions against the grazing or harvesting of soybean forage and hay; these restrictions are appropriate, according to Table 1 of 860.1000.

***Cattle* (MRID).** A summary of the available cattle feeding study was evaluated in the 2/26/91 Phase 4 Review; it was concluded that the study was acceptable for review. In the study, four cows were dosed with fluazifop-butyl for 28 days at 0.2, 0.8, 3.0, and 12.0 ppm in the diet. It was noted that results for residues in muscle were not presented; it was not clear whether the data were simply not included in the summary document or muscle samples were not analyzed. The registrant should note that residue data for cattle muscle tissue are required to support fluazifop-P-butyl reregistration.

***Poultry* (MRID).** A summary of the available poultry feeding study was evaluated in the 2/26/91 Phase 4 Review; it was concluded that the study was acceptable for review. Three groups of chickens were dosed with fluazifop-butyl for 28 days at 0.5, 2.5, and 12.5 ppm in the diet. It was noted that results were presented for combined fat and muscle tissues, instead of separate analyses of these tissues. In addition, storage stability data for poultry commodities must be submitted.

International Considerations

No Codex MRLs have been established for residues of fluazifop-P-butyl or fluazifop-butyl; therefore, issues of compatibility do not exist.

The following Canadian MRLs have been established for residues of fluazifop-butyl, calculated as the acid:

soybeans, strawberries	1 ppm
mustard	0.3 ppm
flax, solin	0.2 ppm
eggs, meat, meat by-products and fat of cattle, goats, hogs, horses, poultry and sheep	0.05 ppm
milk	0.01 ppm

No Mexican MRLs have been established for residues of fluazifop-P-butyl.

TOXICOLOGY

Most of the toxicity studies were conducted on the [RS] enantiomer mixture, fluazifop-butyl, which has a complete toxicity data base, except there no acceptable carcinogenicity study in mice. The purified [R] enantiomer, fluazifop-P-butyl, toxicity data base consists of acute studies, 4 developmental toxicity studies in rats and 1 study in rabbits, 90-day studies in rats and hamsters and a carcinogenicity study in hamsters. In addition, there are several mutagenicity studies conducted on the purified [R] enantiomer and absorption and excretion studies conducted in the hamster with the purified [R] enantiomer. Thus the toxicity data base for fluazifop-P-butyl is adequate for reregistration.

Acute oral, dermal LD50 and inhalation LC50 are high. Chronic toxicity shows a much lower effect level. Fluazifop-butyl is a teratogen at high dose levels, and other developmental effects at lower doses, which are not maternally toxic. Reproduction studies show testicular weight decrement at low dose levels. There are no sperm count studies. See below.

Toxicological Endpoints from the HIARC Report on fluzifop-butyl/fluazifop-P-butyl of June 14, 2004 (TXR# 0052611)

SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

Summary of Toxicological Dose and Endpoints for Fluazifop-butyl & Fluazifop-P-butyl

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 years of age)	NOAEL = **50** mg/kg/day UF = 100 **Acute RfD** = **0.50** mg/kg	FQPA SF = **1X** **aPAD** = acute RfD / FQPA SF = 0.50 mg/kg/	**Developmental Toxicity in rats** LOAEL = 200 mg/kg/day based on diaphragmatic hernia
Acute Dietary (General population including infants and children)	An appropriate endpoint attributable to a single dose was not identified in the available studies including the developmental toxicity studies.		
Chronic Dietary (All populations)	NOAEL= **0.74** mg/kg/day UF = 100 **Chronic RfD** = **0.0074** mg/kg/day	FQPA SF = **1X** **cPAD** = chronic RfD / FQPA SF = **0.0074** mg/kg/day	**Two-Generation Reproduction in rats** LOAEL = 5.8 mg/kg/day in males and 7.1 in females based on decreased spleen, testes & epididymal weights in males and uterine & pituitary weights in females
Short-Term Incidental Oral (1-30 days)	Maternal NOAEL = 100 mg/kg/day	**Residential** LOC for MOE = 100 **Occupational** = NA	**Developmental Toxicity Study in rats** LOAEL = 300 mg/kg/day based on maternal body weight decrement during GD 7-16.
Intermediate-Term Incidental Oral (1- 6 months)	Parental/ Systemic NOAEL= 0.74 mg/kg/day	**Residential** LOC for MOE = 100 **Occupational** = NA	**Two-Generation Reproduction in rats** LOAEL = 5.8 mg/kg/day in males and 7.1 in females based on decreased spleen, testes & epididymal weights in males and uterine & pituitary weights in females
Short-Term Dermal [a] (1 to 30 days) **(Females 13-49)**	Developmental NOAEL= 2.0 mg/kg/day	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	**Developmental Toxicity Study in rats** LOAEL = 5.0 mg/kg/day based on fetal weight, hydroureter and delayed ossification

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Short-Term Dermal [a] (1 to 30 days) (**General Population including Infants & children)**	Maternal NOAEL= 100 mg/kg/day	**Residential** LOC for MOE = **[100]**	**Developmental Toxicity Study in rats** LOAEL = 300 mg/kg/day based on maternal body weight decrements during GD 7-16.
Intermediate & Long-Term Dermal [a] (1 to >6 months)	Parental/ Systemic NOAEL= 0.74 mg/kg/day	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	**Two-Generation Reproduction in rats** LOAEL = 5.8 mg/kg/day in males and 7.1 in females based on decreased spleen, testes & epididymal weights in males and uterine & pituitary weights in females
Short-Term Inhalation [b] 1 to 30 days) **(Females 13-49)**	Developmental NOAEL= 2.0 mg/kg/day	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	**Developmental Toxicity Study in rats** LOAEL = 5.0 mg/kg/day based on fetal weight, hydroureter and delayed ossification
Short-Term Dermal [a] (1 to 30 days) (**General Population including Infants & children)**	Maternal NOAEL= 100 mg/kg/day	**Residential** LOC for MOE = **[100]**	**Developmental Toxicity Study in rats** LOAEL = 300 mg/kg/day based on maternal body weight decrements during GD 7-16.
Intermediate & Long-Term Inhalation [b] (1 to >6 months)	Parental/ Systemic NOAEL= 0.74 mg/kg/day	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	**Two-Generation Reproduction in rats** LOAEL = 5.8 mg/kg/day in males and 7.1 in females based on decreased spleen, testes & epididymal weights in males and uterine & pituitary weights in females
Cancer (oral, dermal, inhalation)	"Not likely to be carcinogenic to humans."		

[a] Use either 9% (low exposure scenario) or 2% (high exposure scenario) for route-to-route extrapolations
[b] Absorption via the inhalation route is presumed to be equivalent to oral absorption.

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

NOTE: The Special FQPA Safety Factor recommended by the HIARC **assumes** that the exposure databases (dietary food, drinking water, and residential) are complete and that the risk assessment for each potential exposure scenario includes all metabolites and/or degradates of concern and does not underestimate the potential risk for infants and children.

Metabolism in the rat and hamster

There is no evidence for a difference in the toxicity of fluazifop-butyl and fluazifop-P-butyl (the pesticide being reregistered) in the studies submitted.

The metabolism data on fluazifop-butyl and fluazifop-P-butyl shows the reason for the similarity in toxicity. Rat metabolism data showed that [RS] fluazifop-butyl is converted in the blood to [R] fluazifop acid within a short time period. Fluazifop-butyl is rapidly hydroyzed to fluazifop acid by blood esterases and the [S] enantiomer is rapidly converted to the [R] enantiomer; apparently the [R] enantiomer is the preferred configuration. Whether rats are administered [RS] fluazifop-butyl (50:50 mixture) or [R] fluazifop-P-butyl (purified, 90%:10%= [R]:[S]) a ratio of [R]:[S]= 97%:3% for fuazifop acid was identified within a hour in the blood of rats.

The only significant metabolite in urine or feces is fluazifop acid. The only significant metabolite isolated from urine was fluazifop acid with minor amounts of conjugates and traces (<1%) of a cleavage product (2-[4-phenoxy]propionic acid) at the ether linkage of the parent (Table 1 and 2). No parent was isolated from the urine of male or female rats.

Biliary uptake of the parent in male rats resulted in about one-half of the material administered being excreted in the feces of males (about one-quarter of the material administered was fluazifop acid and conjugates and a similar percentage of the dose administered was excreted as the parent). In female feces, about 3% of the dose administered was fluazifop acid and conjugates and about 5% was the parent (Table 1 and 2). No cleavage products at the ether linkage were identified in the feces.

Excretion is essentially complete within 7 days in female rats and within 10 days in male rats. Female rats retained 0.4% to 1.0% of the administered dose in the carcass. Male rats retained 5% to 8% of the dose administered in the carcass (believed to be retained in the residual carcass fat and speculated to be esterified to mono- or diglycerides). One male rat retained 18% in the carcass, 10 days after dosing when excretion product were undetectable (MRID# 00093824). Minor amounts were retained by other tissue with only slightly larger amounts being retained by the kidneys, liver (about <1% of the dose administered) and fat.

There was considerable individual animal variation in the rate of excretion of fluazifop acid from rats, dogs and humans with one-half lifes varying two to three fold among individuals. In multi-dosed studies in rabbits, rats, mice, dogs and hamsters, some animals appeared to be more susceptible to the toxic effects of the test material. This susceptibility was expressed by death is some animals on study with little or no toxicity in the surviving animals. In male rats, the lower excretion rate was associated with greater toxicity. In other species, males and females showed similar individual variation with marginal difference in toxicity between males and females.

The relative percentages of the excretion products are presented in Table 1 and 2. A diagram of the project main metabolic pathway is presented in Figure 3.10.

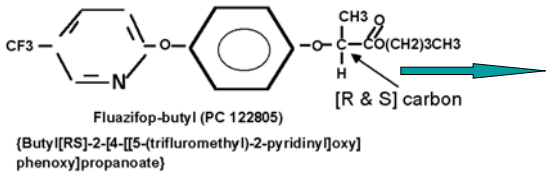
Table 3.16: Approximate percentage of dose excreted in the urine and feces of male and female rats administered 1 mg/kg in a single dose. Extracted from page 20 (bottom page#) of the report.

	Males (% of administered label excreted after 10 days)	Females (% of administered label excreted after 7 days)
Urine	43.6±6.3	89.1±1.3
Feces	52.1±5.2	8.2±1.5
Cage	0.4	-
Total	96	97

Table 3.17: Approximate % of components found in the urine and feces of male and female rats from single doses (1 mg/kg) during the first 48 hours. Data calculated on the bases of the recovery of the dose in the urine and feces in Table 1. Data extracted from page 26-28 (bottom page#) of MRID# 00093824.

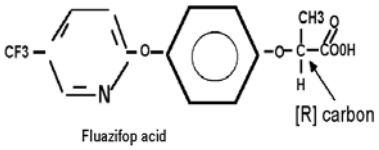
Metabolite/Component	Males	Females
Urine	% of dose in urine	% of dose in urine
Comp'd 1. fluazifop acid/taurine conjugate	0.35	0.09
Comp'd 2. (un-characterized)	0.92	<0.09
Comp'd 3. (un-characterized)	0.09	0.09
Comp'd 4. 2-(4-hydroxyphenoxy) propionate (2HPP)	<0.04	<0.09
Comp'd 5. fluazifop acid	42	88.6
Comp'd 6. fluazifop acid/methyl ester	0.09	0.5
Comp'd 7. fluazifop-butyl (parent)	Nil	Nil
Total in urine	43%	89%
Feces	% of dose in feces	% of dose in feces
Comp'd 1. fluazifop acid/taurine conjugate	4.7	0.098
Comp'd 5. fluazifop acid	19.8	2.8
Comp'd 6. fluazifop acid/methyl ester	0.21	0.008
Comp'd 7. fluazifop-butyl (parent)	26	5.2
Total in feces	50.7%	8.1%

Figure 3.10. Metabolism of Chemical Name in orally dosed rats (MRID).



Fluazifop-butyl (PC 122805)

{Butyl[RS]-2-[4-[[5-(trifluromethyl)-2-pyridinyl]oxy] phenoxy]propanoate}

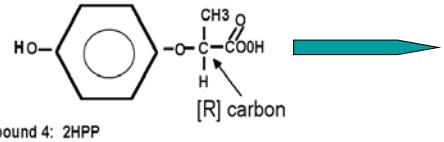


Fluazifop acid

{[R]-2-[4-[[5-(trifluromethyl)-2-pyridinyl]oxy] phenoxy]propionic acid}

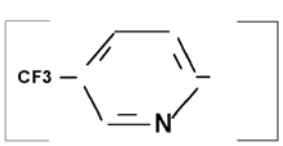
The 2-[4-hydroxyphenoxy]propionic acid was isolated and identified in male (<0.04%) and female (<0.09%) rat urine.

The 3-[trifluromethyl]pyridine residue was not identified, but must have been present.



Compound 4: 2HPP

{[R]-2-[4-hydroxyphenoxy]propionic acid}



{[[3-(trifluromethyl)-pyridine residue}

ENVIRONMENTAL FATE

Fluazifop-P-butyl, PC 122809, is considered in this assessment. This is the enantiomerically-enriched form (95% R-isomer) of this selective herbicide. The racemic mixture, which is no longer registered, was assigned PC 122805.

The uses considered here are the outdoor and agricultural uses. Cotton and soybeans account for over 90% of agricultural use of fluazifop-P-butyl.

Environmental Persistence

The dominant fate process for fluazifop-P-butyl in soil appears to be microbially-assisted hydrolysis to fluazifop acid. Aerobic soil metabolism (Addendum to MRID 92067032) studies show that the half-life of the parent ester is on the order of a few hours. Half-lives of the combined ester-plus-acid residues ranged from 11.2 to 26.4 days in three UK soils .

Anaerobic soil metabolism studies (Addendum to MRID 92067033) indicate that fluazifop-acid is stable (half-lives 315 to 1155 days) in flooded soil systems.

Hydrolysis of the parent ester is rapid at pH 9 (half-life 9 hours), slow at pH 7 (half-life 78 days) and stable at pH 5 (MRID 41598001). Theses rates, with the exception of pH 9, are exceeded by the micobially-assisted hydrolysis rate in soil. Fluazifop acid is the only product and is stable to further hydrolysis.

Rates of photolysis of the parent ester are disputed, with results ranging from a 6-day half-life in water (MRID 42543202) to a 195-day half-life in soil (MRID 41598002). However, both of these rates are exceeded by the dominant microbially-assisted hydrolysis rate in soil.

Expected Mobility

The Koc for fluazifop-P-butyl was not measured, presumably due to its rapid degradation in soil. EPISuite (PCKOCWIN v1.66) estimates the Koc to be 67,000, which would indicate strong binding to soil, and a tendency to be transported on soil particles rather than in solution.

The average Koc for fluazifop acid is 20, with a range of 8.3 to 51 in four UK soils (MRID 41900604). Koc was sensitive to pH, and was lowest (8.3) at the highest pH soil tested (pH 6.8). Based on its pKa of 2.8, fluazifop acid should have been the free anion at all soil pH tested (5.3 to 6.8). These results indicate that fluazifop acid is mobile. The degradate 5-trifluoromethyl-pyrid-2-one was found to not sorb to soil at all, indicating very high mobility.

Volatilization of the parent ester is not likely given its short half-life in soil and low volatility (Henry's law constant about 6.2 E-8 atm•m^3/mol). Volatilization of the acid is also not likely, since it will have a higher solubility and lower vapor pressure, both of which will reduce the Henry's law constant from the parent's value. The estimated value (EPISuite) is 3 E-9 atm•m^3/mol, about 1/20 that of the parent. If volatilized, the atmospheric half-lives of both the parent ester and acid are expected to be short (about 4

hours based on EPISuite estimates).

Environmental Metabolites

The major degradates (>10% of applied radiation in any fate study) are fluazifop-acid and 5-trifluoromethyl-2-pyridone. Fluazifop-acid is not very persistent in aerobic soil (half-lives 11 to 26 days) but is stable in flooded (anaerobic) soil, and in hydrolysis studies. No aqueous metabolism study was performed. Fluazifop-acid is considered to be mobile (Koc 8.3 to 51), and 5-trifluoromethypyrid-2-one is very mobile.

A minor degradate is 2-(4-hydroxyphenyl)-5-trifluromethylpyridine. There is no data on its mobility, but it is expected to be similar to that of fluazifop-acid.

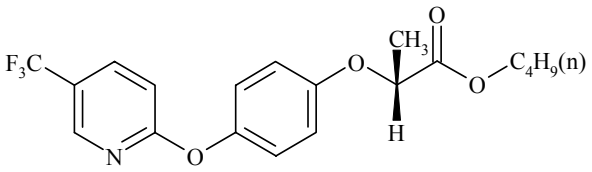
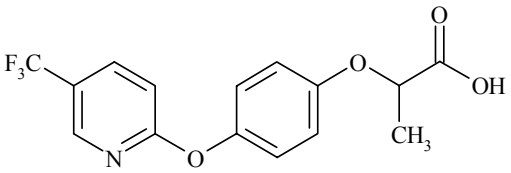
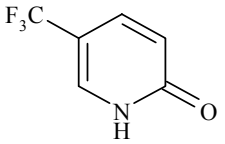
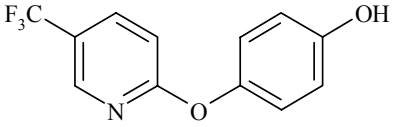
Water softening, in which the alkalinity is raised to pH 10 or 11 by the addition of lime or soda ash, will rapidly degrade the parent fluazifop-P-butyl to fluazifop-acid. Precipitation of particulates (coagulation and flocculation) is not expected to remove fluazifop-acid or 5-trifluoromethyl-2-pyridone because they are only weakly bound to soil particles.

No monitoring data was found.

See Table and structures below. Aqueous photolysis and terrestrial field dissipation studies were considered unacceptable, and are therefore not included. The degradation scheme is (I) parent > (II) fluazifop-acid > (III) 2-(4-hydroxyphenyl)-5-trifluoromethylpyridine > (IV) 5-trifluoromethyl-2-pyridone.

Table 3.18. Summary of Environmental Fate Studies for Fluazifop-butyl			
Degradate Name and Structure	Percent of Applied Dose	Study	Comments
Parent		Aerobic Soil Metabolism (MRID 92067032)	rapidly degraded to fluazifop-acid
		Anaerobic Soil metabolism (MRID 92067033)	rapidly degraded to fluazifop-acid
		Hydrolysis ((MRID 41598001)	Fluazifop-acid is sole product. Stable at pH5; half-life at pH 7, 78 days; at pH 9, 9 hours.
Degradate 1: fluazifop-acid	78-83% at 0.3 weeks 20-43% at 3 weeks <1% at 45 weeks	Aerobic Soil Metabolism (MRID 92067032)	Half-life of parent+acid is 35 to 59 days.
	24-65% at flooding 28-71% at 45 weeks	Anaerobic Soil metabolism (MRID 92067033)	fluazifop-acid is stable under these conditions
	9% at 239 hours continuous radiation	Soil Photolysis (MRID 41598002)	half-life 195 days
Degradate 2: 5-trifluoromethyl-2-pyridone	9.8-25% at 12-24 weeks	Aerobic Soil Metabolism (MRID 92067032)	
	<7.8% at all times (45 weeks)	Anaerobic Soil metabolism (MRID 92067033)	
	2.0% at 171 hours	Soil Photolysis (MRID 41598002)	
Degradate 3: 2-(4-hydroxyphenyl)-5-trifluoromethylpyridine	<3.3% at all times	Aerobic Soil Metabolism (MRID 92067032)	
	<3.8% at all times	Anaerobic Soil metabolism (MRID 92067033)	
	1.2% at 171 hours	Soil Photolysis (MRID 41598002)	

Overall Summary of Chemical Structures for **Fluazifop-butyl** Metabolism and Fate	
Name	Structure

Fluazifop-P-butyl butyl (R)-2-(4-((5-(trifluoromethyl)-2-pyridinyl)oxy)phenoxy)propanoate	
Degradate 1: fluazifop-acid 2-(4-[5-(trifluoromethyl-2-pyridinyloxy]phenoxy)propionic acid	
Degradate 2: 5-trifluoromethyl-2-pyridone	
Degradate 3: 2-(4-hydroxyphenyl)-5-trifluoromethylpyridine	

cc: Sherrie L. Kinard (RRB2), David G. Anderson (RRB2), William P. Eckel (EFED Reviewer), Diana Locke (RRB2).

Template Version September 2003