Primary Evaluator	William Cutchin, Chemist HED/SIMB (7509C)	Date: 7/19/04
Reviewer	Richard Loranger, Chemist HED/RAB2 (7509C)	
Contractor	Dynamac Corporation 20440 Century Blvd., Suite 100 Germantown, MD 20874	

STUDY REPORT

45830713 Smith, J.; Savides, M. (2002) Nature of Residue Study in the Lactating Goat Using (Carbon 14)-XDE-638: Lab Project Number: 000277: 012559. Unpublished study prepared by Dow AgroSciences LLC. 127 p.

Addendum to 45830713 Smith, J; Dow AgroSciences LLC and Plant Sciences Inc., 5/4/04 (Attachment).

EXECUTIVE SUMMARY

Dow AgroSciences LLC has submitted a study investigating the metabolism of [triazolopyrimidine-2-^{14}C]penoxsulam and [phenyl-U-^{14}C]penoxsulam in goats. Radiolabeled penoxsulam was administered orally to a single lactating goat for each label, at an average of 10.1 ppm (TP label) or 12.4 ppm (PH label) in the diet. The goats were dosed once per day for five consecutive days. Milk was collected twice daily throughout the study, and tissues (muscle, fat, liver, and kidney) were collected at sacrifice. The in-life phase of the study was conducted by Ricerca LLC (Painesville, OH), and the analytical phase of the study was conducted by Dow AgroSciences (Indianapolis, IN).

Total radioactive residues (TRR) were 0.002-0.008 ppm in milk, nondetectable in muscle and fat (<0.006 and <0.004 ppm, respectively), 0.038 ppm in kidney, and 0.071 ppm in liver from a single goat dosed orally with **[triazolopyrimidine-2-^{14}C]penoxsulam**, and were <0.001-0.007 ppm in milk, nondetectable in muscle and fat, 0.051 ppm in kidney, and 0.058 ppm in liver from a single goat dosed orally with **[phenyl-U-^{14}C]penoxsulam**. Because the TRR in milk, muscle, and fat were <0.01 ppm, only the kidney and liver samples (both labels) were extracted for metabolite characterization. The majority of the TRR (~94-108% TRR) was extracted from goat kidney using ACN/water and ACN/HCl, but only 42-50% TRR was extracted from liver using these solvents. Base hydrolysis of the nonextractable residues of liver released additional radioactivity (~36-37% TRR). These methods adequately extracted residues from goat matrices. Material balances, based on solvent extractions were 97-122% for kidney and liver. The petitioner has provided data to indicate that the samples did not degrade over the duration of the goat metabolism study.

Total residues amounting to 77-92% and 24-33% TRR were identified in kidney and liver, respectively. Parent penoxsulam was the only residue identified in kidney, at 77-92% TRR (0.029-

0.047 ppm), and was the major residue identified in liver, at 24-31% TRR (0.017-0.018 ppm). The 5-OH XDE-638 metabolite was tentatively identified in PH-label liver as a minor residue (3% TRR, 0.002 ppm). An unknown was also characterized as a minor residue (<5% TRR, ≤0.002 ppm) in kidney (TP label) and liver (TP and PH labels). Base hydrolysis released a significant amount of radioactivity (36-37% TRR, 0.021-0.024 ppm) from liver samples; however, further partitioning was unsuccessful, and no further identification of the hydrolysates was performed.

The petitioner proposed that penoxsulam is primarily excreted and not significantly metabolized in goats. Because no significant differences were observed between the two labels, the sulfonanilide bridge in penoxsulam does not appear to be cleaved as a result of goat metabolism. The petitioner concluded that the low levels of residues observed in milk and tissues, combined with the rapid excretion of residues, demonstrated that penoxsulam would not be expected to bioconcentrate in ruminants.

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS

Under the conditions and parameters used in the study, the livestock metabolism data are classified as scientifically acceptable.

The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document, DP Barcode D288152.

COMPLIANCE

Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided. No deviations from regulatory requirements were reported.

A. BACKGROUND INFORMATION

Penoxsulam (company code XDE-638; PC Code 119031) is an herbicide intended for the control of *Echinochloa* grasses, broadleaf weeds, and sedge weeds in both water-injected (transplanted paddy) and postemergence (direct-seeded) rice. A single postemergence application of penoxsulam is to be made to rice from the one-leaf growth stage (7-12 days after seeding) to 60 days prior to rice harvest. The application is to be made by aerial or ground equipment once per growing season at a maximum rate of 0.045 lb ai/A (50 g ai/ha). Penoxsulam is to be formulated as a granular (for water-seeded rice) or suspension concentrate (for direct-seeded rice) formulation.

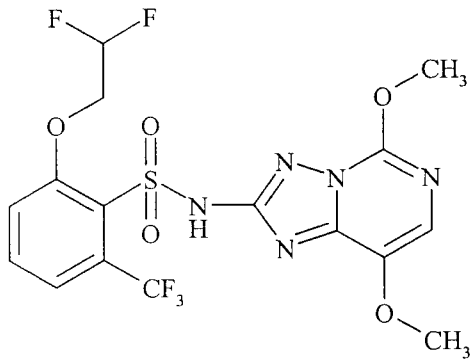
TABLE A.1. Penoxsulam Nomenclature.	
Compound	
Common name (proposed)	Penoxsulam
Company experimental name	XDE-638
IUPAC name	6-(2,2-Difluoroethoxy)-N-(5,8-dimethoxy-s-triazolo[1,5-c]pyrimidin-2-yl)-α,α,α-trifluoro-o-toluenesulfonamide
CAS name	2-(2,2-difluoroethoxy)-N-(5,8-dimethoxy[1,2,4]triazolo[1,5-c] pyrimidin-2-yl)-6-(trifluoromethyl)benzenesulfonamide
CAS #	219714-96-2
End-use product/EP	GF-443 SC SF (File Symbol 62719-LNN); GF-947 Granule SF (File Symbol 62719-LNG); GF-947 Granule CA (File Symbol 62719-LNR).

TABLE A.2. Physicochemical Properties of Technical Grade Penoxsulam.			
Parameter	Value		Reference
Melting point/range	Not available		
pH	Not available		
Density	Not available		
Water solubility	pH	Solubility (mg/L)	MRID 45830720
	(unbuffered)	4.91	
	5	5.66	
	7	408	
	9	1460	
Solvent solubility	Solvent	Solubility (g/L)	MRID 45830720
	DMSO	78.4	
	NMP	40.3	
	DMF	39.8	
	acetone	20.3	
	acetonitrile	15.3	
	ethyl acetate	3.23	
	methanol	1.48	
	octanol	0.035	
	xylene	0.017	
	heptane	<1 µg/mL	
Vapor pressure	7.16×10^{-16} mm Hg at 25 °C		MRID 45830720
Dissociation constant, pK_a	5.1		MRID 45830720

TABLE A.2. Physicochemical Properties of Technical Grade Penoxsulam.			
Parameter	Value		Reference
Octanol/water partition coefficient, Log(K_{OW})	pH	Log(K_{OW})	MRID 45830720
	(unbuffered)	-0.354	
	5	1.137	
	7	-0.602	
	9	-1.418	

B. EXPERIMENTAL DESIGN

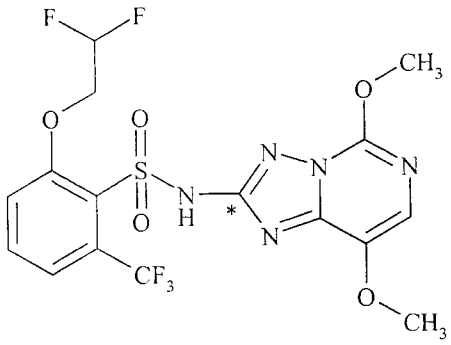
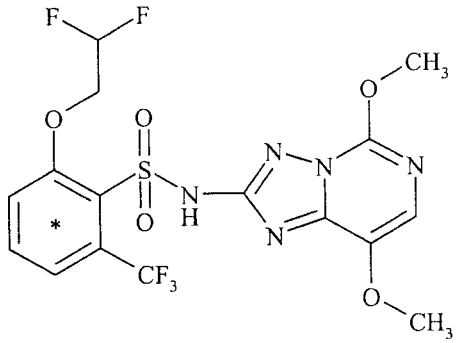
B.1. Livestock

TABLE B.1.1. General Test Animal Information.					
Species	Breed	Age	Weight at study initiation (kg)	Health Status	Description of housing/holding area
Lactating goat (*Capra hircus*)	Not provided	1-2 years	38.80, 43.80	Appeared healthy throughout study	Stainless steel stanchions at Ricerca, LLC (Painesville, OH), at 16-27 °C, and 12 hour light/dark cycle.

TABLE B.1.2. Test Animal Dietary Regime.			
Diet	Water	Acclimation period	Predosing
Purina Rumilab® Diet (1.5 kg/day) and Purina Goat Chow ® milking ration (200-250 g/milking)	Tap water, *ad libitum*	13 days; goats were free-ranged upon receipt, and caged for increasing periods of time. Goats were not caged for more than 5 straight days during the acclimation period.	None

TABLE B.1.3. Test Animal Dosing Regime.					
Treatment Type	Level of administered dose (mg/day)	Food consumption (g/day)	Residue intake in diet (ppm)	Vehicle	Timing/Duration
Oral	TP goat: 19.8	1922-2000	9.9-10.3 (10.1 average)	Gelatin capsule with cellulose, via bolus gun	Once per day after the morning milking for five consecutive days
	PH goat: 22	1648-1856	11.9-13.3 (12.4 average)		

B.2. Test Materials

TABLE B.2.1. Test Material Characteristics.		
Chemical structure		
Radiolabel position	2-triazolopyrimidine labeled (TP)	Uniformly labeled on the phenyl ring (PH)
Lot No.	INV1456	INV1475
Purity	99%	98.4%
Specific activity	28.9 mCi/mmole; 18.02 µCi/mg (test substance)	24.6 mCi/mmole; 18.06 µCi/mg (test substance)
Code	N/A	N/A

The radiolabeled materials were diluted with nonlabeled penoxsulam and shipped to Ricerca, LLC.

B.3. Sampling Information

TABLE B.3.1. Sample Collection Information.			
Milk collected	Urine, feces and cage wash collected	Interval from last dose to sacrifice	Tissues harvested and analyzed
Milk was collected twice daily. During the dosing period 743-899 (814 average) g/day/goat and 1086-1226 (1184 average) g/day/goat were collected (TP and PH label, respectively). During the acclimation period 645-1038 (813 average) g/day/goat and 822-1332 (996 average) g/day/goat were collected (TP and PH label, respectively).	Urine, feces, and cage washes collected daily	22 ± 2 hours	Kidney, liver, fat (composite of omental and perirenal), and muscle (composite of triceps, longissimus dorsi, and semimembranosus)

B.4. Identification/Characterization of Residues

B.4.1. Sample Preparation

Milk was collected twice daily, in the morning prior to dosing and in the afternoon; morning and afternoon milk samples were kept separate and frozen (<-15 C) if not radioassayed immediately following collection. Tissue samples were chopped if necessary and were stored frozen (<-15 C) prior to homogenization for radioassay. Following radioassay, frozen samples of milk and homogenized tissues were shipped to Dow AgroSciences LLC, Regulatory Laboratories (Indianapolis, IN), where they were stored frozen (-20 °C) prior to residue characterization. Only

the kidney and liver samples (both labels) were extracted for characterization of residues, because all milk, fat and muscle samples contained <0.01 ppm radioactivity.

Subsamples of liver and kidney were extracted with acetonitrile:water (50:50, v:v) at reflux for one hour, and the extract was isolated by centrifugation. The remaining nonextractable residues were extracted at reflux with acetonitrile:0.01 N HCl (90:10, v:v) for one hour; the extract was isolated by centrifugation. The acetonitrile/water extract was concentrated and diluted with 1% acetic acid for reverse phase C-18 solid phase extraction cleanup. Residues were eluted with acetonitrile (ACN), concentrated, and centrifuged for HPLC analysis. The ACN/HCl extract was not further characterized.

For liver, the solids remaining after extraction were subjected to base hydrolysis with 5 N NaOH; the conditions of hydrolysis were not described. The hydrolysate was partitioned with dichloromethane or dichloromethane:ACN (50:50, v:v), and the remaining aqueous phase was acidified with concentrated HCl and partitioned with dichloromethane.

B.4.2. Analytical Methodology

Total radioactive residues (TRR) in milk samples were determined by LSC, and TRR in kidney, liver, and muscle samples were determined by combustion/LSC. Fat samples were solubilized with 10% sodium hydroxide:methanol:triton (8:1:1, v:v:v) overnight at 60 °C prior to TRR determinations by LSC. The reported limit of detection for TRR determinations was 0.001-0.0013 ppm in milk and 0.004-0.007 ppm in tissues. Extracts and hydrolysates were radioassayed by LSC, and nonextractable residues were radioassayed by combustion/LSC.

ACN/water extracts of kidney and liver were analyzed by HPLC using a system equipped with a C-18 column, a UV detector, and a radiodetector; a gradient mobile phase of water and ACN, each containing 1.0% acetic acid, was used. Metabolites were identified by co-chromatography and/or retention time comparisons with those of unlabeled reference standards of penoxsulam and its 5-OH metabolite (5-OH XDE-638). Radioactivity was quantified by fraction collection/LSC.

LC/MS analyses were used to confirm the identification of penoxsulam in the ACN/water extract of liver (PH-label). Both the sample and reference standard were analyzed using the HPLC conditions described above with MS and MS/MS detection using electrospray ionization.

C. RESULTS AND DISCUSSION

Total radioactive residues (TRR) in goat milk and tissues are reported in Table C.2.1. TRR were 0.002-0.008 ppm in milk, nondetectable in muscle and fat (<0.006 and <0.004 ppm, respectively), 0.038 ppm in kidney, and 0.071 ppm in liver from a single goat dosed orally with **[triazolopyrimidine-2-^{14}C]penoxsulam** at 10.1 ppm in the diet for 5 consecutive days. TRR were <0.001-0.007 ppm in milk, nondetectable in muscle and fat, 0.051 ppm in kidney, and 0.058 ppm in liver from a single goat dosed orally with **[phenyl-U-^{14}C]penoxsulam** at 12.4 ppm in the diet for 5 consecutive days. For both labels, radioactivity was highest in liver and lowest in muscle and fat; very low levels were observed in milk collected throughout the dosing period, and residues appeared

to plateau in milk within the first day of dosing. The majority of the administered dose was excreted; urine, feces, and cage wash accounted for ~99-101% of the administered dose.

The distribution of radioactivity in goat commodities is reported in Tables C.2.2.1 (TP label) and C.2.2.2 (PH label). Because the TRR in milk, muscle, and fat were <0.01 ppm, only the kidney and liver samples (both labels) were extracted for metabolite characterization. The majority of the TRR (~94-108% TRR) was extracted from goat kidney using ACN/water and ACN/HCl, but only 42-50% TRR was extracted from liver using these solvents. Base hydrolysis of the nonextractable residues of liver released additional radioactivity (~36-37% TRR). These methods adequately extracted residues from goat matrices. Nonextractable residues accounted for 14-15% TRR (0.007-0.010 ppm) in goat kidney and were not reported for liver samples following base hydrolysis; however, material balances, based on solvent extractions, were 97-122% for kidney and liver.

The characterization and identification of radioactive residues is summarized in Tables C.2.3.1 (TP label) and C.2.3.2 (PH label). Total residues amounting to 77-92% and 24-33% TRR were identified in kidney and liver, respectively. Parent penoxsulam was the only residue identified in kidney, at 77-92% TRR (0.029-0.047 ppm), and was the major residue identified in liver, at 24-31% TRR (0.017-0.01[illegible] ppm). The 5-OH XDE-638 metabolite was tentatively identified in PH-label liver as a minor residue (3% TRR, 0.002 ppm). An unknown was also characterized as a minor residue (<5% TRR, ≤0.002 ppm) in kidney (TP label) and liver (TP and PH label).

For liver, base hydrolysis released a significant amount of radioactivity (36-37% TRR, 0.021-0.024 ppm). However, no radioactivity partitioned into dichloromethane or dichloromethane/ACN from the base hydrolysate, and no radioactive residues were liberated from the aqueous phase of the base hydrolysate when acidified and partitioned with dichloromethane. No further attempts were made to characterize the nonextractable residues.

C.1. Storage Stability

Total radioactive residues were determined for milk and tissue samples at the in-life facility prior to shipment to the analytical laboratory, within 21 days following sacrifice, and only kidney and liver samples were further analyzed. The study dates included in the submission indicated that initial extraction and analysis of samples was conducted within 135 days of sample collection, and final extraction or analysis of samples was conducted within 300 days of sample collection. Samples were kept frozen at either <-15 or 20 °C. Comparative analyses were conducted on Sample A extracts, those with sufficient radioactivity for further processing, at 135 (within the recommended 4-6 month storage interval) and 300 days after sample collection. Results of the two analyses were similar. No additional storage stability data are required to support this study.

TABLE C.1. Summary of Storage Conditions.			
Matrix	Storage Temp. (°C)	Actual Storage Duration	Limit of Demonstrated Storage Stability
Goat, milk, muscle, and fat	<-15	<1 month	Samples stable up to 300 days
Goat, kidney	-20	Initial analysis: 135 days (4.4 months) Final analysis: 300 days (9.9 months)	
Goat, liver			

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

TABLE C.2.1. Total Radioactive Residues (TRR) in Goat Milk, Tissue and Excreta.					
Matrix	Collection Timing	TP label		PH label	
		ppm	% Administered Dose	ppm	% Administered Dose
Urine	Day 1	5.81	7.49	6.91	10.4
	Day 2	5.22	8.04	4.90	8.46
	Day 3	5.13	8.68	6.14	9.14
	Day 4	3.76	6.24	6.52	7.74
	Day 5	5.13	8.55	5.59	10.9
Feces	Day 1	4.29	6.92	5.36	7.78
	Day 2	7.79	13.4	6.10	8.72
	Day 3	8.23	12.7	8.62	11.6
	Day 4	7.96	12.5	9.04	12.0
	Day 5	9.21	15.4	6.47	11.3
Cage Washes	Day 1	0.554	0.15	0.930	0.25
	Day 2	2.42	0.62	0.541	0.12
	Day 3	0.756	0.13	1.70	0.09
	Day 4	0.428	0.14	0.794	0.21
	Day 5	0.301	0.19	0.414	0.29
Total Excreta	Study duration	--	101.15	--	99
Muscle	At termination	<0.006	0.00	<0.006	0.00
Fat	At termination	<0.004	0.00	<0.004	0.00
Kidney	At termination	0.038	0.00	0.051	0.01
Liver	At termination	0.071	0.06	0.058	0.04

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

Matrix	Collection Timing	TP label		PH label	
		ppm	% Administered Dose	ppm	% Administered Dose
Milk	Day 1, PM	0.008	0.001	0.007	0.002
	Day 1, AM	0.002	0.001	0.001	0.001
	Day 2, PM	0.006	0.002	0.005	0.002
	Day 2, AM	0.006	0.004	<0.001 (0.001)	0.001
	Day 3, PM	0.008	0.002	0.005	0.002
	Day 3, AM	0.002	0.001	0.001	0.001
	Day 4, PM	0.008	0.002	0.006	0.002
	Day 4, AM	0.003	0.002	0.002	0.001
	Day 5, PM	0.006	0.001	0.007	0.002
	Day 5, AM	0.004	0.003	0.002	0.002
Total	Study duration/termination	--	101.23	--	99.07

FIGURE C.2.1. Pharmacokinetics of Penoxsulam in Milk of Lactating Goat.

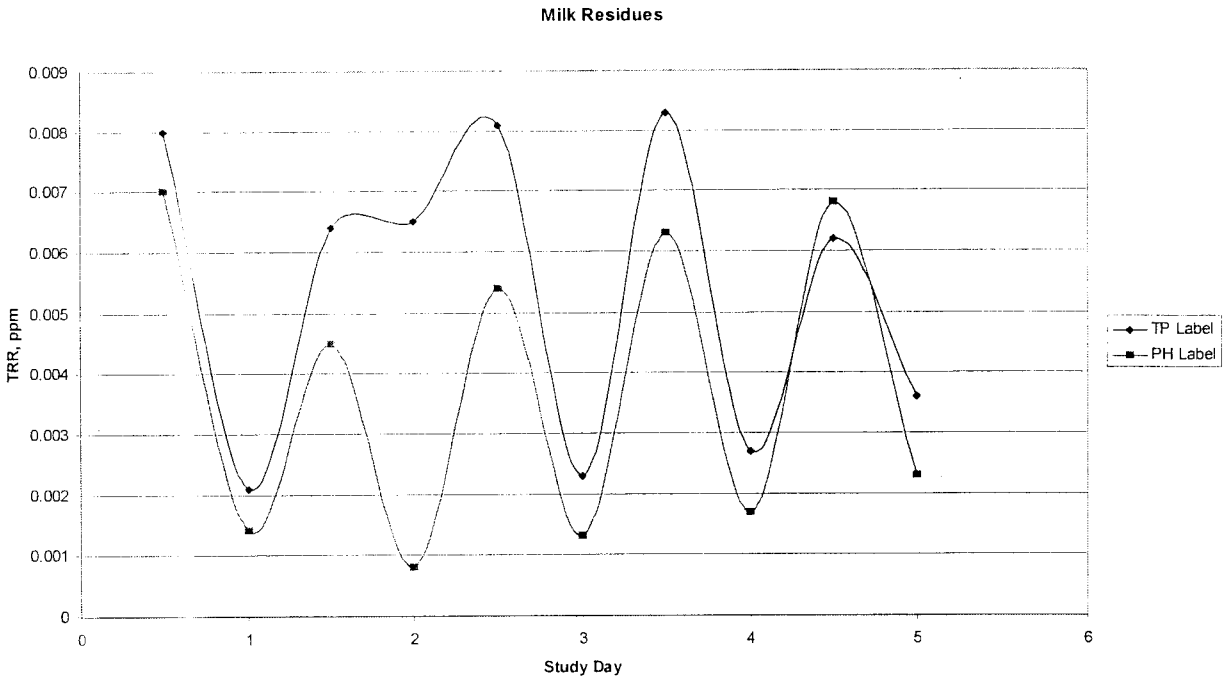


FIGURE C.2.1. Pharmacokinetics of Penoxsulam in Excreta of Lactating Goat.

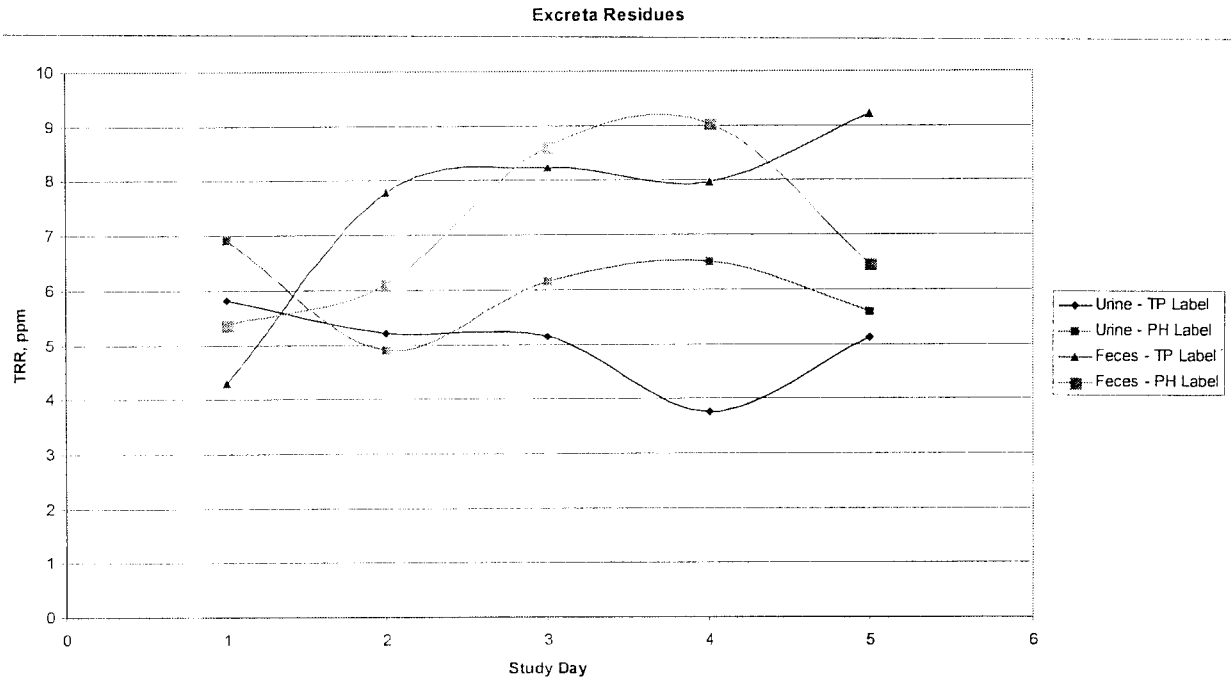


TABLE C.2.2.1. Distribution of the Parent and the Metabolites in Livestock Matrices Following Dosing with [Triazolopyrimidine-2-^{14}C]Penoxsulam at 10.1 ppm in the Diet.[1]

Metabolite Fraction	Kidney		Liver	
	TRR = 0.038 ppm		TRR = 0.071 ppm	
	%TRR	ppm	%TRR	ppm
ACN/water extract	83.8	0.031	29.3	0.021
Penoxsulam	76.6	0.029	24.3	0.017
Unknown	4.3	0.002	2.4	0.002
ACN/HCl extract	10.6	0.004	12.2	0.009
Extracted solids			55.9	0.040
Base hydrolysate			35.8	0.026
Total extractable	94.4	0.035	77.3	0.056
Total identified	76.6	0.029	24.3	0.017
Total unidentified	14.9	0.006	50.4	0.036
Total bound residues (PES)	14.5	0.010	NR	NR
% Accountability	108.9		97.4 [2]	

[1] NR = Not reported. Shading indicates that the extraction step and/or characterization analysis was not conducted for the matrix in question. Ppm values for penoxsulam and the unknown were recalculated by the study reviewer because the values reported by the petitioner appeared to have been calculated incorrectly.
[2] Accountability for liver was calculated using extractable and nonextractable residues prior to base hydrolysis.

TABLE C.2.2.2. Distribution of the Parent and the Metabolites in Livestock Matrices Following Dosing with [Phenyl-U-^{14}C]Penoxsulam at 12.4 ppm in the Diet.[1]

Metabolite Fraction	Kidney		Liver	
	TRR = 0.051 ppm		TRR = 0.058 ppm	
	%TRR	ppm	%TRR	ppm
ACN/water extract	94.9	0.049	38.2	0.022
Penoxsulam	91.5	0.047	30.6	0.018
5-OH XDE-638	--	--	2.7	0.002
Unknown	--	--	2.3	0.001
ACN/HCl extract	13.1	0.007	11.4	0.007
Extracted solids			53.2	0.031
Base hydrolysate			36.5	0.021
Total extractable	108.0	0.056	86.1	0.050
Total identified	91.5	0.047	33.3	0.020
Total unidentified	13.1	0.007	50.2	0.029
Total bound residues (PES)	14.3	0.007	NR	NR
% Accountability	122.3		102.8 [2]	

[1] NR = Not reported. Shading indicates that the extraction step and/or characterization analysis was not conducted for the matrix in question. Ppm values for penoxsulam and the unknown were recalculated by the study reviewer because the values reported by the petitioner appeared to have been calculated incorrectly.
[2] Accountability for liver was calculated using extractable and nonextractable residues prior to base hydrolysis.

TABLE C.2.3.1. Summary of Characterization and Identification of Radioactive Residues in Livestock Matrices Following Dosing with Triazolo-Pyrimidine-2-^{14}C]Penoxsulam at 10.1 ppm in the Diet.

Compound	Kidney		Liver	
	TRR = 0.038 ppm		TRR = 0.071 ppm	
	% TRR	ppm	%TRR	ppm
Penoxsulam	76.6	0.029	24.3	0.017
Unknown	4.3	0.002	2.4	0.002
ACN/HCl extract	10.6	0.004	12.2	0.009
Base Hydrolysate	--	--	35.8	0.026
Total identified	76.6	0.029	24.3	0.017
Total characterized	14.9	0.006	50.4	0.036
Total extractable	94.4	0.035	77.3	0.056
Total bound	14.5	0.010	NR	NR

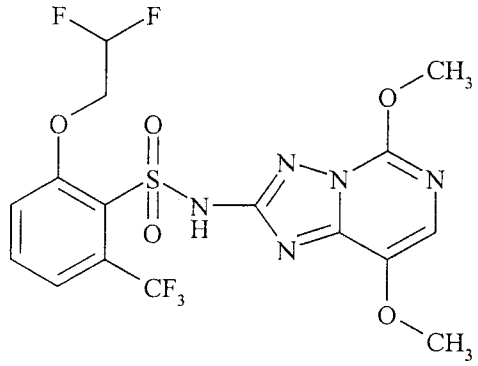
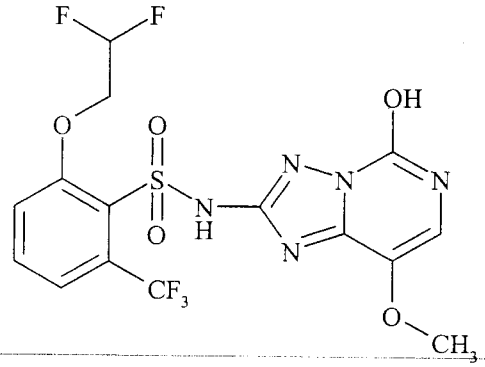
TABLE C.2.3.2. Summary of Characterization and Identification of Radioactive Residues in Livestock Matrices Following Dosing with [Phenyl-U-^{14}C]Penoxsulam at 12.4 ppm in the Diet.

Compound	Kidney		Liver	
	TRR = 0.051 ppm		TRR = 0.058 ppm	
	% TRR	ppm	%TRR	ppm
Penoxsulam	91.5	0.047	30.6	0.018
5-OH XDE-638	--	--	2.7	0.002
Unknown	--	--	2.3	0.001
ACN/HCl extract	13.1	0.007	11.4	0.007
Base Hydrolysate	--	--	36.5	0.021
Total identified	91.5	0.047	33.3	0.020
Total characterized	13.1	0.007	50.2	0.029
Total extractable	108.0	0.056	86.1	0.050
Total bound	14.3	0.007	NR	NR

C.3. Proposed Metabolic Profile

FIGURE C.3.1. Proposed Metabolic Profile of Penoxsulam in Lactating Goat.

The petitioner did not propose a metabolic pathway for penoxsulam in goats.

TABLE C.3.1. Identification of Compounds from Metabolism Study.		
Common name/code Figure C.3.1 ID No.	Chemical name	Chemical structure
Penoxsulam: XDE-638	2-(2,2-difluoroethoxy)-N-(5,8-dimethoxy[1,2,4]triazolo[1,5-c]-pyrimidin-2-yl)-6-(trifluoromethyl)-benzenesulfonamide	
5-OH XDE-638	2-(2,2-difluoroethoxy)-N-(5,6-dihydro-8-methoxy-5-oxo[1,2,4]triazolo[1,5-c]-pyrimidin-2-yl)-6-(trifluoromethyl) benzensulfonamide	

D. CONCLUSIONS

Total radioactive residues (TRR) were 0.002-0.008 ppm in milk, nondetectable in muscle and fat (<0.006 and <0.004 ppm, respectively), 0.038 ppm in kidney, and 0.071 ppm in liver from a single goat dosed orally with **[triazolopyrimidine-2-^{14}C]penoxsulam** at 10.1 ppm in the diet for 5 consecutive days. TRR were <0.001-0.007 ppm in milk, nondetectable in muscle and fat, 0.051 ppm in kidney, and 0.058 ppm in liver from a single goat dosed orally with **[phenyl-U-^{14}C]penoxsulam** at 12.4 ppm in the diet for 5 consecutive days. The majority of the administered dose was excreted; urine, feces, and cage wash accounted for ~99-101% of the administered dose.

The majority of the TRR (~94-108% TRR) was extracted from goat kidney using ACN/water and ACN/HCl, but only 42-50% TRR was extracted from liver using these solvents. Base hydrolysis of the nonextractable residues of liver released additional radioactivity (~36-37% TRR). The reported accountability, based on solvent extractions, ranged 97-122% for kidney and liver.

Total residues amounting to 77-92% and 24-33% TRR were identified in kidney and liver, respectively. Parent penoxsulam was the major residue identified in kidney and liver. The 5-OH XDE-638 metabolite was tentatively identified in PH-label liver as a minor residue. An unknown was also characterized as a minor residue in kidney (TP label) and liver (TP and PH labels). Base

hydrolysis released a significant amount of radioactivity from liver samples, but residues could not be further characterized/identified.

The petitioner proposed that penoxsulam is primarily excreted and not significantly metabolized in goats. Because no significant differences were observed between the two labels, the sulfonanilide bridge in penoxsulam does not appear to be cleaved as a result of goat metabolism. The petitioner concluded that the low levels of residues observed in milk and tissues, combined with the rapid excretion of residues, demonstrated that penoxsulam would not be expected to bioconcentrate in ruminants.

E. REFERENCES

None.

F. DOCUMENT TRACKING

RDI: R. Loranger (7/9/04)
Petition Number(s): 3F06542
DP Barcode(s): D288152
PC Code: 119031

Attachment: J. Smith. Dow AgroSciences,

IN RESPONSE TO: Errico.Philip@epamail.epa.gov
SENT: Tuesday, May 04, 2004 2:20 PM

SUBJECT: Response to Additional Information Requested by Residue Chemistry for Penoxsulam

STUDY IDENTIFICATION: 45830713 Smith, J.; Savides, M. (2002): Nature of Residue Study in the Lactating Goat Using (Carbon 14)-XDE-638: Lab Project Number: 000277; 012559.

REQUEST OF RESIDUE CHEMISTRY: "Total radioactive residues were determined for milk and tissue samples at the in-life facility prior to shipment to the analytical laboratory, within 21 days following sacrifice, and only kidney and liver samples were further analyzed. The study dates included in the submission indicated that initial extraction and analysis of samples was conducted within 135 days of sample collection, and final extraction or analysis of samples was conducted within 300 days of sample collection. No further extraction and analysis dates were provided, and the petitioner did not state which analyses were conducted on the "final" date. The petitioner must submit additional information pertaining to storage stability, including all extraction and analysis dates for each sample, and provide evidence that the identity of residues did not change during the period between collection and final analysis."

EPA Response:
RESPONSE OF PETITIONER:

Background: Samples collected from the lactating goat were milk, urine, feces, muscle, fat, liver and kidney. Only the liver and kidney tissues contained >0.01 ppm, and were subsequently analyzed.

The following tissue samples (135 days after collection for liver and 156 days for kidney) were initially extracted as summarized below:

Date	Sample	Extractions
15 Feb 01	Goat (TP label) liver	A, B, base hydrolysis and combustion
15 Feb 01	Goat (PH label) liver	A, B, base hydrolysis and combustion
8 Mar 01	Goat (TP label) kidney	A, B, base hydrolysis and combustion
8 Mar 01	Goat (PH label) kidney	A, B, base hydrolysis and combustion

Extract A-reflux with acetonitrile
Extract B-reflux with acetonitrile:0.01 N HCl (90:10)

Base hydrolysis- reflux of NER tissue with 5 N NaOH

Sample extracts A contained radioactivity in sufficient quantities for further processing. For both tissues, the sample extracts were processed by solid phase extraction (SPE) and concentration and analyzed by high performance liquid chromatography (HPLC) on March 13, 14 and 25, 2001. HPLC raw data results are summarized below:

Sample	Retention time (minutes)	Compound	% of HPLC (raw data)	% of TRR	ppm
Goat TP liver Extract A	35 31	penoxsulam 5-OH	87.4 9.1	32.8 3.4	0.009 0.001
Goat PH liver Extract A	35 32	penoxsulam Unknown	82.2 7.0	32.5 2.8	0.007 0.001
Goat TP kidney Extract A	35	penoxsulam	94.9	76.0	0.023
Goat PH kidney Extract A	35 31	penoxsulam 5-OH	93.3 3.5	78.4 2.9	0.034 0.001

Data presented in the report (300 days after collection) were for samples extracted and processed by SPE and concentrated on July 30 and 31, 2001. Analysis was performed on August 15 and 16, 2001. HPLC raw data results are summarized below:

Sample	Retention time (minutes)	Compound	% of HPLC (raw data)	% of TRR	ppm
Goat TP liver Extract A	35 32	penoxsulam unknown	82.9 8.1	24.3 2.4	0.005 0.001
Goat PH liver Extract A	35 32 31	penoxsulam Unknown 5-OH	80.2 5.1 7.1	30.6 2.3 2.7	0.007 <0.001 0.001
Goat TP kidney Extract A	35 32	penoxsulam Unknown	91.4 5.1	76.6 4.3	0.024 0.001
Goat PH kidney Extract A	35	penoxsulam	96.4	91.5	0.045

The Residue Chemistry Guidelines (OPPTS 860.1300 Nature of the Residue – Plants, Livestock, section (d)(7)) recommend that storage stability data should not normally be required for samples analyzed within 4 to 6 months of collection, provided evidence is given that attempts were made to limit degradation of residues by appropriate storage of matrices and extracts during the analytical portion of the study. Samples were stored at -20 °C (page 13, report 000277). Data presented shows that the distribution among residues is consistent between analyses performed on March 13, 14 and 25, 2001, compared to August 15 and 16, 2001. The major component of all analysis presented in the report was parent penoxsulam and all sample recoveries were between 84.7 and 100.2

% of applied (page 16, report 000277). This provides evidence that the identity of the residues did not change during the storage period.

Additional questions concerning the storage or any other aspect of this study may be directed to the study director:

Joelene Smith
Dow AgroSciences
(317) 337-3459
jksmith@dow.com