Primary Evaluator	William Cutchin, Chemist HED/SIMB (7509C)	Date: 7/28/04
Peer Reviewer	Michael Doherty, Chemist HED/RAB2 (7509C)	

STUDY REPORTS:

MRID No. 46267601 Smith, J. K., Savides, M. C. (2001) Nature of Residue Study in the Laying Hen Using [^{14}C]XDE-638: Lab Project Number: 000371. Unpublished study prepared by Regulatory Laboratories - Indianapolis Lab Dow AgroSciences LLC. 112 pages.

EXECUTIVE SUMMARY:

Radiolabelled penoxsulam, diluted using nonradiolabeled analytical-grade penoxsulam to a specific activity of 17.98 μCi/mg and 18.01 μCi/mg, for the triazolopyrimidine (TP) and phenyl (PH) ring labels, respectively, was orally administered at approximately 11 ppm in the diet once daily for seven consecutive days to two groups of ten laying hens. A third group of ten laying hens served as a control. Beginning on the day before the first dose, egg samples were collected twice daily, and excreta samples were collected daily. A cage wash was collected after the last excreta collection. Each animal was sacrificed within 22 ± 2 hours of the last dose, and the liver, samples of fat, muscle, and the skin were collected. All of these samples were analyzed for their ^{14}C content.

The test substance was rapidly excreted by the animals, with >92% of the administered radioactivity recovered in the excreta. The egg samples contained less than the limit of detection (LOD, <0.002 ppm) at each sampling interval. The muscle, fat and skin all contained <LOD (0.003 ppm for muscle and skin, and 0.001 ppm for fat). No additional work was performed on those samples. Total residues in the TP and PH liver were 0.017 ppm and 0.006 ppm, respectively. The livers were extracted by refluxing with acetonitrile (extract A) followed by 90:10 acetonitrile:0.01 N HCl (extract B). The radioactive residues recovered in extract A (0.007 ppm) from the TP treated hens were analyzed by HPLC. Identification was made by co-injecting analytical standards. The bulk of the residues eluted in the same region as the XDE-638 reference standard (22.9% of the TRR or 0.004 ppm), while a smaller portion (9.7% of the TRR or 0.002 ppm) eluted as a highly polar unknown. None of the other liver extracts were further analyzed due to the low levels of radioactivity (≤0.002 ppm) accounted for in the samples.

All materials were stored frozen at -20°C for up to 8 months during the study. The registrant did not provide any storage stability data as required for samples stored more than 4-6 months. However, since virtually all the radioactivity was recovered from the excreta, the lack of formal storage stability data will not affect the results of the study.

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the livestock metabolism data are classified as scientifically acceptable. As noted above, formal storage stability data was not provided. Based on the weight of the evidence, storage stability data are not required in order to validate the study.

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.

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.

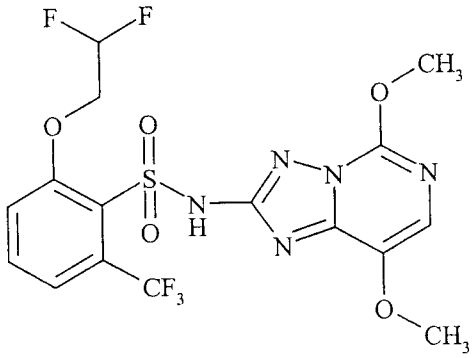
Compound	
Common name (proposed)	Penoxsulam
Company experimental name	XDE-638
IUPAC name	6-(2,2-Difluoroethoxy)-N-(5,8-dimethoxy-s-triazolo[1,5-c]pyrimidin-2-yl)-α,α,α-trifluoro-o-toluenesulfonamide
CAS name	2-(2,2-difluoroethoxy)-N-(5,8-dimethoxy[1,2,4]triazolo[1,5-c] pyrimidin-2-yl)-6-(trifluoromethyl)benzenesulfonamide
CAS #	219714-96-2

TABLE A.1. Penoxsulam Nomenclature.	
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
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 (yr)	Weight at study initiation (kg)	Health Status	Description of housing/holding area
chicken (Gallus domesticus)	white leghorn	1-2	1.6	good	individual galvanized wire cages

TABLE B.1.2. Test Animal Dietary Regime				
Composition of Diet	Feed consumption (kg/day)	Water	Acclimation period	Predosing

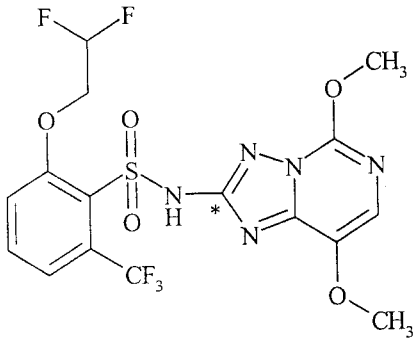
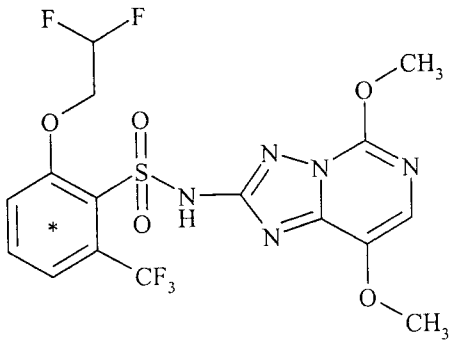
Purina Lab Cage Layer. Diet #5070 *ad libitum*	0.1	tap water *ad libitum*	14 days	no fasting

TABLE B.1.3. Test Animal Dosing Regime

Treatment Type	Feeding Level (ppm test material in food)	Vehicle	Timing/Duration
Oral	10-11	capsule	once daily/ 7 days

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	INV1573
Purity	>99 %	>99%
Specific activity	28.9 mCi/mmole	28.1 mCi/mmole

B.3. Sampling Information

TABLE B.3.1. Sample Collection Information

Eggs collected over 7 days (% of normal production)	Urine, feces and cage wash collected	Interval from last dose to sacrifice	Tissues harvested and analysed
PH label: 71 (101%)	excreta: once daily, cage wash: after last excreta collection	22 ± 2 hours	liver, fat, muscle, and skin
TP label: 72 (103%)			

B.4. Identification/ Characterization of Residues

B.4.1. Sample Handling and Preparation

Eggs from each group were collected twice daily. Evening and morning eggs were composited within day and treatment group. Eggs were cracked open into sample jars as whole eggs (yolk and white). After homogenizing by blending with an electric stirrer, subsamples were taken from the composite sample. Excreta were collected each day prior to dosing and pooled by group. Excreta samples were homogenized by thoroughly blending with a measured amount of deionized water using an electric stirrer. A cage wash was performed after the final excreta sample was collected. All cages were rinsed with water followed by a methanol rinse. These rinses were pooled by dose group and combined for analysis. The animals were sacrificed at 22 ± 2 hours after the administration of the last dose. The control hens were sacrificed first followed by the treated hens. Muscle (light meat and dark meat), liver, abdominal fat (all), and a skin sample from the back were collected. The liver, fat, skin and muscle were homogenized using a blender and dry ice.

The only extract samples with ^{14}C residue greater than 0.01 ppm penoxsulam-equivalents were from liver. A solution of acetonitrile:water (50:50) was added to a reflux flask and the tissue and extraction solution homogenized using a Polytron. The homogenized sample was then refluxed with stirring for approximately 1 hour. The extract and tissue was centrifuged. The supernatant, designated extract A, was collected and the extracted tissue was transferred to another reflux flask. A solution of acetonitrile:0.01 N HCl (90:10) was added to the flask and the tissue and extraction solution homogenized using a Polytron. The entire sample was refluxed with stirring, for approximately 1 hour. The extract and tissue was centrifuged. The supernatant, designated extract B, was collected and the extracted tissue, designated non-extractable residue (NER), was stored frozen.

Extracts were concentrated using a nitrogen evaporator and brought to final volume using a 1% aqueous acetic acid solution. Concentrated extracts were subjected to reverse phase solid phase extraction (SPE) cleanup. The eluted sample was then concentrated under a stream of nitrogen. The concentration steps were assayed for recovery.

B.4.2. Analytical Methodology

Eggs, excreta, and tissues were analyzed for TRR by either direct liquid scintillation counting (LSC) or by combustion analysis followed by LSC. The LOD was 0.002 ppm for eggs, 0.003 ppm for muscle and skin and 0.001 ppm for fat. The NER was measured by oxidative combustion followed by LSC.

Liver extracts which contained sufficient ^{14}C (>0.01 ppm) were analyzed by RP-HPLC with a ^{14}C detector. Identification was made by co-injecting standards with identification by UV-254 detector. One-minute fractions of the mobile phase were collected and further analyzed by LSC and the results plotted.

C. RESULTS AND DISCUSSION

The final extraction and analysis of the nature of the residue study samples were conducted 8 months after sacrifice. All materials were stored frozen at -20°C during the study. The registrant did not provide any storage stability data as required for samples stored more than 4-6 months. However, since virtually all the radioactivity was recovered from the excreta, the lack of formal storage stability data will not affect the results of the study.

The test substance was rapidly excreted by the animals, with >92% of the administered radioactivity recovered in the excreta. The egg samples contained <0.002 ppm (LOD) at each sampling interval. The muscle, fat and skin all contained <0.003 ppm (LOD of 0.003 ppm for muscle and skin and 0.001 ppm for fat). No additional work was performed on those samples.

Total residues in the TP and PH liver were 0.017 ppm and 0.006 ppm, respectively. The radioactive residues recovered in extract A (0.007 ppm) from the TP treated hens were analyzed by HPLC. The bulk of the residues eluted in the same region as the XDE-638 reference standard (22.9% of the TRR or 0.004 ppm), while a smaller portion (9.7% of the TRR or 0.002 ppm) eluted as a highly polar unknown. None of the other extracts or NERs were further analyzed due to the low levels of radioactivity (≤0.002 ppm) accounted for in the samples.

C.1. Storage Stability

TABLE C.1. Summary of Storage Conditions

Matrix	Storage Temp.(°C)	Actual Storage Duration (months)	Interval of Demonstrated Storage Stability
eggs, muscle, liver, skin, fat, excreta	-20	8	not determined

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

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

Matrix	Collection Timing	TP label	PH label
		ppm	ppm
Excreta (pooled sample)	daily	82.1	134.4
Cage Wash	after last excreta collection	0.515	0.567
Muscle	22 ± 2 hours after last dose	<LOD	<LOD
Fat		<LOD	<LOD
Skin		<LOD	<LOD
Liver		0.017	0.006
Eggs	twice daily	<LOD	<LOD
% of Administered Dose		91.5	129.0

FIGURE C.2.1. Pharmacokinetics of Penoxsulam in Excreta and Eggs of Laying Hen.

The registrant did not propose a degradation pathway for penoxsulam in poultry.

TABLE C.2.2. Distribution of the Parent and the Metabolites in Laying Hens when Dosed with ^{14}C-labeled Penoxsulam.

Metabolite Fraction	Liver			
	TP Label		PH Label	
	%TRR	ppm	%TRR	ppm
Extract A	38.6	0.007	26.6	0.002
Parent	22.9	0.004	NA	NA
Unidentified compound	9.7	0.002	NA	NA
Extract B	14.2	0.002	7.7	<0.001
NER	60.8	0.010	113.4	0.007
Total identified	22.9	0.004	NA	NA
Total characterized	32.6	0.006	NA	NA
Total extractable	52.8	0.009	34.3	0.003
Unextractable (PES)[1]	60.8	0.010	113.4	0.007
Accountability[2]	113	0.019	148	0.010

[1] Residues remaining after exhaustive extractions.

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

D. CONCLUSION

The test substance was rapidly excreted by the animals, with >92% of the administered radioactivity recovered in the excreta. The eggs, muscle, fat and skin all contained <LOD for both radioactive labels. Total residues in the TP and PH liver were 0.017 ppm and 0.006 ppm, respectively. In liver, the majority of extractable residues were parent indicating that no significant metabolism of penoxsulam had occurred.

E. REFERENCES

F. DOCUMENT TRACKING

RDI: M. Doherty (7/23/04)
Petition Number(s): 3F06542
DP Barcode(s): D288152
PC Code: 119031