UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

Date: 8/11/04

Subject: Penoxsulam. Petition for the Establishment of Permanent Tolerances for the Use on Rice. Summary of Analytical Chemistry and Residue Data. PP#3F6542.

DP Barcode: D288152
PC Code: 119031
40 CFR 180. N/A

MRID Nos.: 45830712-45830717, 45830719-20, 46267601

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Executive Summary

Dow AgroSciences LLC has proposed, in PP#3F6542, the establishment of permanent tolerances for residues of the herbicide penoxsulam [2-(2,2-difluoroethoxy)-N-(5,8-dimethoxy[1,2,4] triazolo[1,5-c]pyrimidin-2-yl)-6-(trifluoromethyl)benzenesulfonamide] in/on the following raw agricultural commodities:

Rice grain	0.01 ppm
Rice straw	0.50 ppm
Rice hull	0.01 ppm
Rice bran	0.01 ppm
Polished rice	0.01 ppm

Penoxsulam is a sulfonamide herbicide intended for postemergence application to rice for selective control of grass, broadleaf, and sedge weeds.

In conjunction with the subject tolerance petition, Dow has submitted an application for Section 3 registration of two 0.24% granular (G) formulations (GF-947 Granule SF, EPA File Symbol No. 62719-LNG; and GF-947 Granule CA, EPA File Symbol No. 62719-LNR) and a 2 lb/gal soluble concentrate (SC) formulation (GF-443 SC SF, EPA File Symbol No. 62719-LNN). The penoxsulam formulations are to be applied as a single postemergence broadcast spray to water- or dry-seeded rice using ground or aerial equipment. Applications are to be made at rates of 0.027-0.044 lb ai/A, at the one-leaf stage up to 60 days before harvest.

Based on the submitted rice metabolism study, penoxsulam primarily degrades to its 5-OH metabolite (5-OH XDE-638) and at least two minor unknown metabolites in rice matrices; little translocation of penoxsulam residues or its metabolites into the grain was observed. The available goat and poultry metabolism data indicate that penoxsulam is primarily excreted and not significantly metabolized in either goats or poultry. 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. Adequate storage stability information/data are available to support the rice, goat, and poultry metabolism studies.

Adequate field trial data are available for rice; although the field trial data reflect exaggerated application rates, additional data will not be required unless the petitioner wishes to lower the recommended tolerances. Residues were generally below the method limit of quantitation in rice grain samples; quantifiable residues were observed in rice straw samples.

Adequate processing data have been submitted. Ruminant and poultry feeding study data are not required to support this petition. The available analytical methodology (LC/MS/MS method) is tentatively considered to be adequate for tolerance enforcement, pending completion of petition method validation (PMV) by EPA's Analytical Chemistry Branch (ACB/BEAD). HED's Metabolism Assessment Review Committee (MARC) determined that for the tolerance expression and risk assessment the residue of concern for penoxsulam in plants, livestock, and rotational crops is parent only. The available rotational crop data indicate that tolerances for rotational crop commodities are not required. There are currently no U.S. or international Codex tolerances established for penoxsulam.

Recommendations

Pending the results of the forthcoming human health risk assessment, a successful PMV, and receipt of a revised Section F, there are no deficiencies precluding the registration of penoxsulam in/on rice at 0.02 ppm for rice, grain and 0.50 ppm for rice, straw.

Residue Chemistry Deficiencies

OPPTS 860.1340 Residue Analytical Methods

1. The submitted LC/MS/MS method is adequate for tolerance enforcement purposes for plant commodities, pending completion of PMV at ACB/BEAD. We note that in step 9.3.9 of the method, there is an instruction to "Dilute" with no identification of what

should be diluted or what solvent should be used; presumably the word "Dilute" is a typo and should be deleted. In addition, the laboratory that conducted the independent laboratory validation for the method recommended some changes/clarifications to the method procedures. Unless ACB concludes differently, the modifications recommended by the independent laboratory will have to be made to the method prior to its acceptance as a tolerance enforcement method; any additional changes recommended by ACB will also have to be incorporated.

860.1380 Storage Stability

2. The final report of the ongoing storage stability study must be submitted. Storage stability data for future uses will require the receipt and acceptance of the final rice report as well as any data required for the additional use.

860.1550 Proposed Tolerances

3. The available crop field trial data for rice grain do not support the proposed tolerance of 0.01 ppm; a tolerance of 0.02 ppm must be proposed for rice grain. The rice processing data indicate that tolerances for rice processed commodities are not needed. In addition, the proposed tolerances should be revised to reflect the correct commodity definitions as specified in Table 8.

Background

The subject petition, PP#3F6542, represents the first food/feed use of penoxsulam proposed in the U.S. The PC Code and nomenclature of penoxsulam is listed below in Table 1. The physicochemical properties of penoxsulam are listed in Table 2. The chemical names and structures of penoxsulam and its transformation products are presented in Table 3.

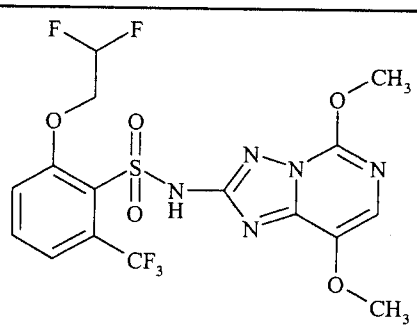
Table 1. Penoxsulam Nomenclature.	
Chemical structure	
Common name	Penoxsulam
Company experimental name	XDE-638
IUPAC name	6-(2,2-Difluoroethoxy)-N-(5,8-dimethoxy-s-triazolo[1,5-c]pyrimidin-2-yl)-α,α,α-trifluoro-o-toluenesulfonamide

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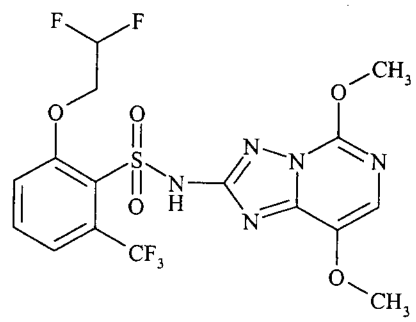
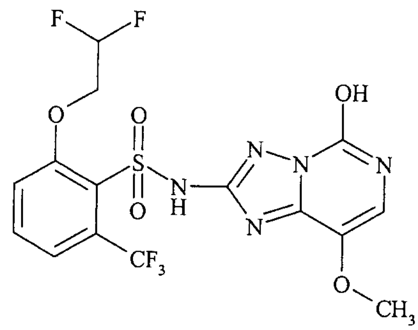
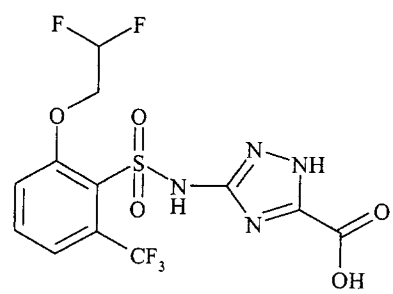
Table 1. Penoxsulam Nomenclature.	
CAS name	2-(2,2-difluoroethoxy)-N-(5,8-dimethoxy[1,2,4]triazolo[1,5-c] pyrimidin-2-yl)-6-(trifluoromethyl) benzenesulfonamide
CAS #	219714-96-2
End-use formulations (EUP)	GF-443 SC SF (File Symbol 62719-LNN) GF-947 Granule SF (File Symbol 62719-LNG) GF-947 Granule CA (File Symbol 62719-LNR)

Table 2. Physicochemical Properties of Penoxsulam.

Parameter	Value		Reference
Melting point/range	Not available		
pH	Not available		
Density	Not available		
Water solubility	pH	Solubility (mg/L)	45830720
	(unbuffered)	4.91	
	5	5.66	
	7	408	
	9	1460	
Solvent solubility	Solvent	Solubility (g/L)	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		45830720
Dissociation constant, pK_a	5.1		45830720
Octanol/water partition coefficient, $Log(K_{OW})$	pH	$Log(K_{OW})$	45830720
	(unbuffered)	-0.354	
	5	1.137	
	7	-0.602	
	9	-1.418	

Table 3. Chemical Name and Structure of Penoxsulam and its Transformation Products.		
Company Name	Chemical Name	Structure
Penoxsulam	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) benzenesulfonamide	
BSTCA	3-[[[2-(2,2-difluoroethoxy)-6-(trifluoromethyl) phenyl]sulfonyl]amino]-1H-1,2,4-triazole-5-carboxylic acid	

860.1200 Directions for Use

Table 4. Summary of End-Use Products.						
Trade Name	File Symbol No.	ai (% of formulation)	Formulation Type	Target Crops	Target Pests	Label Version
GF-947 Granule SF	62719-LNG	0.24%	G	Water-seeded rice	Grass, broadleaf and sedge weeds (selective control)	Draft, dated 11/18/02
GF-947 Granule CA	62719-LNR	0.24%	G	Water-seeded rice		Draft, dated 11/18/02
GF-443 SC SF	62719-LNN	21.7%; 2 lb ai/gal	suspension concentrate	Water- and dry-seeded rice		Draft, dated 11/18/02

Table 5. Summary of Directions for Use of Penoxsulam.

Trade 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
Rice						
GF-947 Granule SF	Postemergence (1-leaf stage up to 60 days prior to harvest) Broadcast Ground or aerial equipment	0.031-0.044	1	0.044	60	Restricted to use in AR, FL, LA, MS, MO, TN, and TX. Apply to shallow flooded water-seeded rice; field water depth at application (and for 10 days following application) should be 2-4 inches.
GF-947 Granule CA	Postemergence (1- to 3-leaf stage) Broadcast Ground or aerial equipment	0.036-0.044	1	0.044	60	Restricted to use in CA. Apply to shallow flooded water-seeded rice; field water depth at application (and for 10 days following application) should be 2-4 inches.
GF-443 SC SF	Postemergence (1-leaf stage up to 60 days prior to harvest) Broadcast Ground or aerial equipment	0.027-0.044	1	0.044 (first and ratoon crops combined)	60	Restricted to use in AR, FL, LA, MS, MO, TN, and TX. For water-seeded rice, fields must be partially drained prior to application. For dry-seeded rice, use is recommended as a preflood application. Postflood applications to dry-seeded rice may be made to partially drained fields (1-2 inches water depth). Re-flooding of fields should begin 24-48 hours after application. Application must be made with an agriculturally approved crop oil concentrate (1 qt/A) in a minimum of 10 GPA (ground and aerial equipment). Use of organosilicone surfactants is prohibited. May be applied as a tank mix with compatible materials with postemergence uses on rice.

The proposed general use directions (for all end-use product labels) specify a restricted entry interval (REI) of 12 hours and include the following restrictions:

- treated land may not be rotated to crops other than rice for 3 months following application;
- fishing or commercial growing of fish, shellfish, or crustaceans, other than crayfish, may not be conducted in treated areas during the year of treatment;
- application may not be made where runoff or irrigation water may flow directly onto agricultural land other than rice fields;
- application may not be made through any type of irrigation system.

Conclusions. The proposed use directions are adequate to allow RAB2 an assessment of whether the submitted residue data reflect the maximum residues likely to occur in rice.

We note that the proposed use directions only allow penoxsulam application to rice grown in AR, CA, FL, LA, MS, MO, TN, and TX. Because these states represent the major growing regions for rice (Regions 4, 5, 6, and 10), the proposed tolerances do not need to be established with regional registration.

860.1300 Nature of the Residue - Plants

45830712.der.wpd
MARC Decision Memo TXR No. 0052740, DP Barcode: D305542, W. Cutchin, 7/19/04

Dow AgroSciences LLC has submitted a study investigating the metabolism of [triazolopyrimidine-2-^{14}C]penoxsulam and [phenyl-U-^{14}C]penoxsulam in rice. Each radiolabeled test substance was formulated as a suspension concentrate formulation and applied as a foliar broadcast spray to rice plants at the 5- to 6-leaf growth stage at 0.089 lb ai/A (100 g ai/ha). Rice plants were grown in galvanized steel tubs maintained in outdoor screenhouses; water levels in the rice plots were maintained at 2.5-5 inches depending on the growth stage of the rice crop. Approximately 4 weeks prior to mature harvest, a plot dry-back period was initiated, with no further irrigation until harvest. Immature rice shoots were harvested at posttreatment intervals (PTIs) of 0, 3, 7, 14, and 30 days, and mature rice straw and grain were harvested 134 days posttreatment. The in-life phase was conducted by Plant Sciences (Manteca, CA), and the analytical phase of the study was conducted by Dow AgroSciences, Global Environmental Chemistry Laboratory (Indianapolis, IN).

The total radioactive residues (TRR) were 0.021 and 0.003 ppm in mature rice straw and grain, respectively, following treatment with [triazolopyrimidine-2-^{14}C]penoxsulam (TP) at 0.083 lb ai/A (1.9x the proposed maximum seasonal rate). TRR were 5.166 ppm in immature rice shoots collected on the day of treatment and declined with each subsequent sampling interval to 0.048 ppm at the 30-day PTI.

In rice matrices harvested at maturity following treatment with [phenyl-U-^{14}C]penoxsulam (PH) at 0.095 lb ai/A (2.2x the proposed maximum seasonal rate), TRR were 0.023 and 0.004 ppm in mature rice straw and grain, respectively. TRR were 3.990 ppm in immature rice shoots collected on the day of treatment and declined with each subsequent sampling interval to 0.056 ppm at the 30-day PTI.

The majority of the TRR (~63-160% TRR) was extracted from rice matrices (immature shoots, and mature rice straw and grain) using acetonitrile/water. Nonextractable residues were <10% TRR or <0.05 ppm in all samples of immature shoots (0.7-24.7% TRR, 0.012-0.051 ppm) and mature straw (19.6-40.5% TRR, 0.005-0.008 ppm); material balances ranged 87-110% for rice shoots and straw. Nonextractable residues in mature rice grain samples were not determined due to very low levels of radioactivity. Residues were characterized/identified by HPLC analysis with confirmatory analysis by TLC. These methods successfully identified the predominant residues in rice matrices.

In general, identification of residues was most successful in immature rice shoots and mature straw and was less successful in rice grain due to very low levels of radioactivity. No significant differences were observed between the two labels. Total identified residues ranged from 46-102% TRR in immature shoots, 35-38% TRR in straw, and 9-11% TRR in grain. Parent penoxsulam was the major component identified in immature rice shoots (both labels) harvested at 0-, 3-, 7-, and 14-day PTIs, ranging from 94.4-99.9% TRR (3.831-5.161 ppm) at the 0-day PTI to 53.5-62.0% TRR (0.197-0.227 ppm) at the 14-day PTI. Penoxsulam remained the major component identified in PH-label 30-day PTI immature shoots, at 41.3% TRR (0.023 ppm), but was present in TP-label 30-day PTI immature shoots at lower levels (12.3% TRR, 0.006 ppm). Penoxsulam was also identified as a minor component in mature rice straw and grain (both labels), at 4.2-8.9% TRR (<0.001-0.003 ppm). The metabolite 5-OH XDE-638 was identified as the major component in 30-day PTI immature rice shoots and mature rice straw (both labels) at 16.2-33.5% TRR (0.009-0.016 ppm) and 29.5-30.4% TRR (0.007-0.009 ppm), respectively. The 5-OH XDE-638 metabolite was also identified as a minor component in immature rice shoots harvested at 0-, 3-, 7-, and 14-day PTIs (both labels), at 1.8-14.2% TRR (0.043-0.209 ppm), and in mature rice grain, at 2.2-3.3% TRR (<0.001 ppm). In addition, two unknowns, present individually at levels of 1-23% TRR, were characterized by HPLC in rice matrices as being more polar than penoxsulam and 5-OH XDE-638. Because of the low levels of the unknowns in mature straw samples, no attempts were made to further identify these residues; however, the petitioner stated that one of the unknowns was likely comprised of conjugates of less polar metabolites.

Residues of penoxsulam were highest in earlier sampled immature shoot samples. The metabolite patterns in subsequent immature shoot samples indicated that residues of the parent declined, and levels of the 5-OH metabolite increased with increasing posttreatment intervals.

The petitioner proposed that penoxsulam primarily degrades to its 5-OH metabolite and at least two minor unknown metabolites in rice matrices; little translocation of penoxsulam residues or its metabolites was observed into the grain.

All samples were extracted within 6-55 days of harvest and subjected to acid hydrolysis within 21-27 days of harvest. Samples were stored frozen at -20 °C. All samples were analyzed within 2 months of harvest. The petitioner conducted a repeat extraction and analysis of 14-day PTI immature rice shoots several weeks after the initial extraction and analysis and similar metabolite profiles were observed. The storage stability data provided by the petitioner are sufficient to fulfill data requirements for this study.

Conclusions. Because the petitioner is only proposing use of penoxsulam on one crop, rice, no additional plant metabolism studies are required at this time. The MARC determined that for the tolerance expression and risk assessment the residue of concern for penoxsulam in/on rice is parent only. Any future uses of penoxsulam, including those on cereal grains, will require additional nature of the residue data. As an alternative to metabolism data on other cereal crops, the registrant may submit crop field trial data which include residue data for the metabolite 5-OH XDE-638 as well as parent.

860.1300 Nature of the Residue - Livestock

Ruminants

45830713.der.wpd
MARC Decision Memo TXR No. 0052740, DP Barcode: D305542, W. Cutchin, 7/19/04

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; 180x the maximum theoretical dietary burden; see Table 6) or 12.4 ppm (PH label; 220x the maximum theoretical dietary burden) 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 0.0021-0.0083 ppm in milk, nondetectable in muscle and fat (<0.0065 and <0.0044 ppm, respectively), 0.0375 ppm in kidney, and 0.0712 ppm in liver from a single goat dosed orally with [triazolopyrimidine-2-^{14}C]penoxsulam, and were <0.0010-0.0070 ppm in milk, nondetectable in muscle and fat, 0.0512 ppm in kidney, and 0.0581 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.

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.

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.

Poultry

46267601.der.wpd
MARC Decision Memo TXR No. 0052740, DP Barcode: D305542, W. Cutchin, 7/19/04

Dow AgroSciences LLC has submitted a study investigating the metabolism of [triazolopyrimidine-2-^{14}C]penoxsulam and [phenyl-U-^{14}C]penoxsulam in laying hens. 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 of the dietary burden(1800x the maximum theoretical dietary burden; see Table 6) once daily for seven consecutive days to two groups of ten laying hens. A third group of ten laying hens served 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 total radioactive residues 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 normally required for samples stored more than 4-6 months. However, since virtually all the radioactivity was recovered from the excreta and very low total radioactivity was observed in tissues and eggs from a highly exaggerated dose, the lack of formal storage stability data will not affect the results of the study.

Conclusions. The submitted goat and poultry metabolism studies are adequate. The test substance was rapidly excreted by animals. The MARC determined that for the tolerance expression and risk assessment the residues of concern for penoxsulam in ruminants is parent only. A decision was not made on the residue of concern in poultry.

860.1340 Residue Analytical Methods

45830714.der.wpd (also includes review of MRID 45830715)
PP# 3F6542, DP Barcode: D303172, W. Cutchin, 7/19/04

Enforcement method: Dow AgroSciences LLC has proposed an LC/MS/MS method, GRM 01.25, for the enforcement of tolerances for residues of penoxsulam in/on rice commodities.

Briefly, samples of rice matrices are homogenized/extracted with acetonitrile/water, shaken for 60 minutes, and centrifuged. An aliquot of the supernatant is diluted with water and cleaned up on a mixed-mode polymeric-anion exchange solid phase extraction (SPE) plate. Residues are eluted with ACN:formic acid (99.9:0.1, v:v), evaporated to dryness, and redissolved in mobile phase. Residues are quantitated by LC/MS/MS using a C8 column, a gradient mobile phase of ACN/methanol and water, each containing 0.1% acetic acid, and electrospray ionization in the positive ion mode. Residues are quantified using external standards. The validated limit of quantitation (LOQ) and calculated limit of detection (LOD) for penoxsulam were 0.01 and 0.002 ppm, respectively, in/on rice forage, straw, grain, hulls, bran, and polished rice.

Adequate method recoveries were obtained for rice commodities at the LOQ (0.01 ppm) and up to 100x the LOQ.

A successful independent laboratory validation (ILV) of the LC/MS/MS method has been completed with rice grain and straw. Although extraction efficiency data were submitted, penoxsulam residues in the samples examined were too low to allow determination of the ability of the residue analytical method to extract aged residues. However, because the extraction procedures of the method are very similar to those used in the metabolism study, no additional extraction efficiency data will be required. The LC/MS/MS method has been submitted to ACB/BEAD for regulatory method validation.

Data collection method: Samples of rice commodities (forage, grain, straw, hulls, bran, and polished rice) from the storage stability, crop field trial, and processing studies with penoxsulam submitted in conjunction with this petition were analyzed using the proposed enforcement method, GRM 01.25. Adequate concurrent method validation data were submitted in conjunction with the storage stability, crop field trial, and processing studies.

Conclusions. The submitted LC/MS/MS method is adequate for tolerance enforcement purposes for plant commodities, pending completion of regulatory method validation at ACB/BEAD. We note that in step 9.3.9 of the method, there is an instruction to "Dilute" with no identification of what should be diluted or what solvent should be used; presumably the word "Dilute" is a typo and should be deleted. In addition, the laboratory that conducted the ILV for the method recommended some changes/clarifications to the method procedures. Unless ACB concludes differently, the modifications recommended by the ILV laboratory will have to be made to the method prior to its acceptance as a tolerance enforcement method; any additional changes recommended by ACB will also have to be incorporated.

860.1360 Multiresidue Methods

45830716.der.wpd
PP# 3F6542, DP Barcode: D305554, W. Cutchin, 7/19/04

Penoxsulam was analyzed according to the FDA Multi-Residue Method Test guidelines in PAM Vol. I, Appendix II (1/94). Testing using Protocols B and G was not required because penoxsulam is not an acid, phenol, or substituted urea. When tested, penoxsulam did demonstrate natural fluorescence; however, no peak above the baseline was observed using the HPLC/UV system described under Section 401 DL2; therefore, Protocol A testing was terminated. Testing using Protocol C indicated that further testing through Protocols D, E, and F was required; poor sensitivity observed during the testing indicated that Florisil column cleanup would be required for Protocol D. Penoxsulam could not be recovered using the Florisil column cleanup test in Protocols E and F, and testing under these protocols was terminated. Because the Florisil column cleanup steps in Protocol D are similar to those of Protocols E and F, testing under Protocol D was not conducted.

Conclusions. The multiresidue method data indicate that penoxsulam is not adequately recovered using any of the multiresidue methods. These data have been forwarded to FDA for further evaluation.

860.1380 Storage Stability

45830717.der.wpd

Dow AgroSciences LLC has submitted the interim results of a 24-month storage stability study with penoxsulam. Untreated samples of homogenized rice grain, straw, immature forage, bran, hulls, and polished rice were fortified with penoxsulam at 0.10 ppm. The fortified samples were stored at -20 °C for up to 197 days (processed rice commodities) or 210 days (rice forage, grain, and straw). Under these conditions, residues of penoxsulam were relatively stable in rice grain, straw, immature forage, and processed rice commodities (bran, hulls, and polished rice).

The maximum storage intervals of samples from the crop field trial and processing studies submitted in conjunction with this petition were 68-101 days (2.2-3.3 months) for rice grain, straw, and immature forage, and 135 days (4.4 months) for rice processed commodities.

Conclusions. The interim storage stability data indicate that residues of penoxsulam are stable under frozen storage conditions in rice grain, straw, immature forage, bran, hulls, and polished rice for up to 7 months. The petitioner stated that the full study will include storage intervals of up to 24 months for rice commodities. Although the interim data support the storage intervals of samples from the crop field trial and processing studies, the interim study did not include a signed QA statement. Therefore, the study will be considered "interim" data until the full, final report is submitted. Storage stability data for future uses will require the receipt and acceptance of the final rice report as well as any data required for the additional use.

860.1400 Water, Fish, and Irrigated Crops

MRID: 45831101, DP Barcode: D288160, L. Shanaman, 4/22/04
EFED, D298489, L. Shanaman, 7/8/04

Dow AgroSciences LLC has submitted a study investigating the residues of penoxsulam in crayfish. The petitioner has proposed that fishing or commercial growing of fish, shellfish, or crustaceans, other than crayfish, may not be conducted in treated areas during the year of treatment. The bioaccumulation of [het-2-^{14}C]-labeled 3-(2,2-difluoroethoxy) -N-(5,8-dimethoxy[1,2,4] triazolo[1,5-c]pyrimidin-2-yl)-α,α,α-trifluorotoluene-2-sulfonamide (penoxsulam; XDE-638) was studied in crayfish (*Procambarus clarkii*) using a nominal concentration of 0.494 mg/L (494 ppb) under flow-through aquarium conditions. The test system consisted of two 200-L glass aquaria fitted with overflows to maintain a volume of 135 L (average flow rate of 94 mL/minute) at a loading rate of 70 crayfish per vessel. One aquaria was treated and the second was used as a solvent control. The exposure period was 14 days, and the subsequent depuration period was 7 days. During 14 days of exposure, the pH of the aquaria water was 7.3-8.1, the dissolved oxygen 7.1-8.7 mg/L, and the temperature 21.4-22.5°C. During the 7 days of depuration, the pH of the aquaria water was 7.7-7.9, the dissolved oxygen 8.0-8.4 mg/L, and the temperature 21.5-22.4°C. Crayfish (3) samples were collected on days 0, 1, 3, 5, 7, 11, and 14 during exposure and after 1, 3, 5, and 7 days of depuration. Aliquots of the aquaria water and portions of solubilized crayfish tail tissue were analyzed for total radioactivity using LSC. Water (days 6 and 13) was analyzed for penoxsulam and it's transformation products directly by reverse-phase HPLC. The identity of residue was established by comparison to reference standards.

The maximum concentration of total [^{14}C]residues in crayfish tail muscle was 14.4 μg/kg at 11 days. The average steady-state calculated bioconcentration factor (BCF) was 0.02 mL/g. [^{14}C]Residues in the tissues were not characterized. After 1 day of depuration, total [^{14}C]residues in crayfish tissues (7.4 μg/kg) was similar to the day 14 exposure value (7.3 μg/kg). After 5 days of depuration, total [^{14}C]residues were not detected in the crayfish tissue. [^{14}C]Residues in the crayfish during depuration were not characterized. [^{14}C]Residues in the water were only characterized on days 6 and 13. Based on the day 6 chromatogram, only 1 peak was detectable. The peak eluted with the retention time of penoxsulam. After 6 hours of depuration, [^{14}C]residues decreased to <2% of the exposure levels and by day 2 were below the limit of detection.

Conclusions. Penoxsulam has very low potential to bioconcentrate in edible tissues of crayfish. Following exposure to 494 ppb penoxsulam in water (>10x the 45 ppb screening level recommended by EFED for the use in rice [L. Shanaman, 7/8/04], total radioactive residues in crayfish tail muscle were 14.4 ppb (0.014 ppm). The available data for crayfish indicate that tolerances for penoxsulam residues in crayfish are not required to support this petition.

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860.1480 Meat, Milk, Poultry, and Eggs

Table 6. Calculation of Maximum Theoretical Dietary Burdens of Penoxsulam to Livestock.

Feed Commodity	% Dry Matter[1]	% Diet[1]	Recommended Tolerance, ppm	Dietary Contribution, ppm[2]
Beef Cattle				
Rice, straw	90	10	0.50	0.056
TOTAL BURDEN		10		**0.056**
Dairy Cattle				
Rice, straw	90	10	0.50	0.056
TOTAL BURDEN		10		**0.056**
Poultry				
Rice, grain	NA	60	0.01	0.006
TOTAL BURDEN		60		**0.006**
Swine				
Rice, grain	NA	65	0.01	0.0065
TOTAL BURDEN		65		**0.0065**

1 Table 1 (OPPTS Guideline 860.1000).
2 Contribution = [tolerance / % DM (cattle)] x % diet). Poultry and swine diets are not corrected for % dry matter.

The petitioner did not submit any livestock feeding studies with this petition. The maximum residues of penoxsulam observed in any matrix in the goat metabolism study were 0.047 ppm in kidney from the goat dosed with [PH-^{14}C]penoxsulam. Based on a 220x dosing level for that goat, the expected residues of penoxsulam at a 10x dosing level are 0.002 ppm, which is less than the (plant) method LOQ of 0.01 ppm.

The maximum residues of penoxsulam observed in any matrix in the poultry metabolism study were 0.017 ppm in liver from the hens dosed with [TP-^{14}C]penoxsulam. Based on a 1800x dosing level for those hens, the expected residues of penoxsulam at a 10x dosing level are 0.00009 ppm, which is less than the (plant) method LOQ of 0.01 ppm.

Conclusions. RAB2 concludes that the proposed use of penoxsulam on rice results in a 40 CFR §180.6(a)(3) situation for ruminant and poultry commodities; i.e., there is no reasonable expectation of finite residues in ruminant and poultry commodities. Therefore, no ruminant or poultry feeding study need be submitted to support the subject petition. We note that if additional uses of penoxsulam with livestock feed items are proposed in the future, feeding studies may be required.

860.1500 Crop Field Trials

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Table 7.	Summary of Residues from the Crop Field Trials with Penoxsulam.						
Crop Matrix	Total Application Rate (lb ai/A); Formulation	PHI (days)	Residues (ppm)				
			Min.	Max.	HAFT	Mean	Std. Dev.
Rice (proposed use = 0.044 lb ai/A total application rate, 60-day PHI)							
Rice, grain	0.088-0.093; suspension concentrate	47-97	ND	0.013	0.013	0.006	0.002
	0.09; G	64-101	ND	ND	<0.01	0.005	0
Rice, straw	0.088-0.093; suspension concentrate	47-97	ND	0.484	0.463	0.066	0.116
	0.09; G	64-101	ND	0.008	<0.01	0.005	0.001

Dow AgroSciences LLC has submitted crop field trial data depicting the magnitude of the residue of penoxsulam in/on rice forage, straw, and grain following treatment with either a suspension concentrate or granular (G) formulation. The registrant conducted a total of 16 rice field trials in Regions 4 (AR, LA, MS; 11 trials), 5 (MO; 1 trial), 6 (TX; 2 trials), and 10 (CA; 2 trials) during the 2001 growing season. The number and location of field trials are adequate with respect to geographic representation of residue data for rice.

In separate plots at each field trial, a single application of the 2 lb/gal suspension concentrate or 0.11% G formulation was made to rice plants at 0.090 lb ai/A (2x the maximum proposed seasonal rate). Application of the suspension concentrate formulation was made to rice at the 30-32 Biologische Bundesanstalt, Bundessortenamt and CHemical (BBCH) growth stage to target a 60-day PHI; the suspension concentrate formulation was applied as a foliar broadcast spray in water with crop oil concentrate (2.5%). Application of the G formulation was made to rice ~40 days after seeding, when the permanent flood was established (21-23 BBCH); the G formulation was applied directly (broadcast) to flooded rice. Samples of mature rice grain and straw were collected from both plots at each trial site. To evaluate residue decline, samples of immature rice forage were collected 0, 1, 3, 7, 14, and 21 days following treatment at two field trial sites.

Residues of penoxsulam were less than the method LOQ (<0.01 ppm) to 0.013 ppm in/on rice grain samples and <0.01-0.484 ppm in/on rice straw samples harvested 47-97 days following a single application of the suspension concentrate formulation at 0.088-0.093 lb ai/A. Residues of penoxsulam were less than the method LOQ (<0.01 ppm) in/on rice grain and straw samples harvested 64-101 days following a single application of the G formulation at 0.09 lb ai/A.

The registrant collected samples of immature rice forage at multiple posttreatment intervals in two field trials (one suspension concentrate treatment and one G treatment) to evaluate residue decline. The residue decline data indicate that residues of penoxsulam in/on immature rice forage decrease with increasing sampling intervals. The petitioner stated that the half-life of penoxsulam residues in rice forage was less than 1 day for both formulations. We note that residue levels were much higher in samples treated with the suspension concentrate formulation than in samples treated with the G formulation.

Conclusions. The submitted crop field trial data are adequate to satisfy data requirements. Although the use patterns of the crop field trials did not exactly reflect the proposed use pattern (field trials were conducted at 2x; samples from the trials with the G formulation were collected at posttreatment intervals longer than the proposed 60-day PHI), no additional crop field trial data will be required at this time because the trials were conducted at an exaggerated rate, result in low residues, and residue transfer to animals are expected to be minimal. The petitioner should note that if lower tolerances for rice grain and straw are desired, additional crop field trial data which accurately reflect the proposed use pattern would be required.

860.1520 Processed Food and Feed

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In rice processing studies conducted in MS and CA, mature rice grain was harvested 62 or 92 days following a single broadcast application of the 2 lb/gal suspension concentrate formulation (MS trial) or the 0.11% G formulation (CA trial), respectively, at 0.18 lb ai/A (4x the proposed maximum seasonal rate). The suspension concentrate formulation was applied as a broadcast foliar spray to rice at the 32 BBCH growth stage, using water containing a crop oil concentrate. The G formulation was applied directly to flooded rice, 40 days after seeding, when the permanent flood was established.

Residues of penoxsulam were nondetectable (<0.002 ppm) in/on rice grain treated with the suspension concentrate or G formulation, and residues were nondetectable in hulls, bran, and polished rice processed from treated rice grain. Processing factors could not be determined because the residue levels were nondetectable in both the RAC and processed commodities. The maximum theoretical concentration factor for rice is 8x (OPPTS 860.1520, Table 1), based on concentration factors of 5x for hulls and 7.7x for bran (OPPTS 860.1520, Table 3).

Conclusions. The submitted processing study data are adequate to satisfy data requirements. Tolerances are not required for the processed commodities of rice. Although the petitioner did not address the issue of conducting field trials on rice at higher rates, to potentially generate samples containing detectable or quantifiable residues, it was noted in the rice metabolism study (refer to the DER for MRID 45830712) that phytotoxic effects were observed in plants treated at 150 g ai/ha, which is equivalent to 0.13 lb ai/A.

860.1850 Confined Accumulation in Rotational Crops

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Dow AgroSciences LLC has submitted a confined rotational crop study with [triazolopyrimidine-2-^{14}C]penoxsulam and uniformly ring-labeled [phenyl-U-^{14}C]penoxsulam. The radiolabeled test substances were applied directly to sandy loam soil in pots maintained outdoors at 0.045-0.046 lb ai/A (1x the proposed maximum seasonal rate) or 0.090-0.093 lb ai/A (2x the proposed maximum seasonal rate), and rotational kale, potato, and wheat were planted 90 days after treatment. The in-life phase of the study was conducted by Research for Hire (Porterville, CA), and the analytical phase was conducted by Dow AgroSciences (Indianapolis, IN).

Total radioactive residues (TRR) accumulated at ≥0.01 ppm in certain rotated crops planted 90 days following a single soil application of [triazolopyrimidine-2-^{14}C]penoxsulam (TP) at 0.045 and 0.093 lb ai/A, or [phenyl-U-^{14}C]penoxsulam (PH) at 0.046 and 0.090 lb ai/A. At the 1x treatment rate, TRR were >0.01 ppm in potato foliage (0.024 ppm from the TP plot and 0.047 ppm from the PH plot), wheat hay (0.021 ppm, PH plot only), and wheat straw (0.011 ppm, TP plot; 0.024 ppm, PH plot). At the 2x treatment rate, TRR were >0.01 ppm in kale (0.014 ppm, TP plot only), potato foliage (0.038 ppm, TP plot; 0.062 ppm, PH plot), wheat hay (0.022 ppm, TP plot; 0.032 ppm, PH plot), and wheat straw (0.030 ppm, TP plot; 0.028 ppm, PH plot). TRR were <0.01 ppm in the following matrices: potato tuber (≤0.003 ppm), wheat forage (≤0.007 ppm), and wheat grain (<0.005 ppm) from both labels at both treatment rates; TP-treated kale (0.003 ppm) at the 1x treatment rate and PH-treated kale (≤0.008 ppm) at both treatment rates; and TP-treated wheat hay (0.009 ppm) at the 1x treatment rate. TRR were generally higher in PH-treated commodities than in TP-treated commodities.

Only crop samples with TRR ≥0.008 ppm were extracted. Solvent extraction released 62-97% TRR from rotational crop matrices. The majority of the extractable residues remained in the aqueous phase after partitioning with dichloromethane, and only the organic phase of potato foliage was subjected to further partitioning. Nonextractable residues in rotational crop commodities ranged 4-31% TRR (<0.001-0.009 ppm). The extraction procedures released sufficient residues from rotational crop matrices; material balances were 84-107%. Samples were analyzed within 5 months of harvest. All samples were stored frozen. No further storage stability data are required to support this study.

Only the extracts of PH-treated potato foliage were analyzed by HPLC for metabolite identification. In all other samples, because the aqueous extracts contained <0.03 ppm and the organic extracts contained <0.01 ppm, no further characterization was attempted. Total identified residues were 8.4% and 38.9% TRR in PH-label potato foliage at the 1x and 2x treatment rates, respectively. The 5-OH metabolite was identified at 8.4-13.9% TRR (0.004-0.009 ppm), and a single unknown was characterized at approximately the same level (8.9-11.8% TRR, 0.004-0.007 ppm) in both the 1x and 2x treatment rate potato foliage. In addition, the BSTCA metabolite was identified in potato foliage from the 2x treatment rate, at 25.0% TRR (0.015 ppm). Three unknowns were also characterized, each present at ≤18.0% TRR (≤0.011 ppm). Residues were characterized/identified in potato foliage by HPLC analysis, and, because no confirmatory method was used, the identifications are considered tentative. However, because no parent was detected and no single component was present at >0.015 ppm in potato foliage, RAB2 concludes that these methods successfully identified the predominant residues in rotational crop matrices.

The petitioner proposed that the penoxsulam is metabolized in rotated potato foliage to 5-OH XDE-638 and BSTCA, and that both 5-OH XDE-638 and BSTCA are then metabolized to unknowns and nonextractable residues.

Conclusions. Based on data from the confined rotational crop study, no quantifiable residues of penoxsulam or 5-OH XDE-638 are expected to be present in the raw agricultural commodities of small grains, leafy vegetables, and root crops planted 90 days following treatment with penoxsulam at 0.045 or 0.090 lb ai/A. The data also indicate that residues of BSTCA could be present at ≥0.01 ppm in the foliage of root crops planted 90 days following treatment at 0.090 lb ai/A (2x proposed rate). The MARC determined that for the tolerance expression and risk assessment the residue of concern for penoxsulam in rotated crops is parent only.

We note that the submitted confined rotational crop study only included one plantback interval, 90 days. If in the future plantback intervals other than 90 days are proposed, an additional confined rotational crop study reflecting the proposed plantback interval would be required.

860.1900 Field Accumulation in Rotational Crops

No field rotational crop studies have been submitted. The petitioner has proposed a 3-month plantback interval for all crops other than rice. Based on data from the confined rotational crop study, no quantifiable residues of penoxsulam, its 5-OH metabolite, or BSTCA are expected to be present in the raw agricultural commodities of small grains, leafy vegetables, and root crops planted 90 days following treatment with penoxsulam at 1x the maximum seasonal rate. Therefore, field rotational crop studies are not required to support this petition.

860.1550 Proposed Tolerances

The MARC determined that for the tolerance expression and risk assessment the residue of concern for penoxsulam in plants, ruminants and rotated crops is parent only. Dow AgroSciences LLC has proposed the establishment of permanent tolerances for residues of the herbicide penoxsulam [2-(2,2-difluoroethoxy)-N-(5,8-dimethoxy[1,2,4]triazolo[1,5-c]pyrimidin-2-yl)-6-(trifluoromethyl)benzenesulfonamide] in/on the raw agricultural and processed commodities of rice. The proposed tolerances are listed in Table 8.

There are currently no established Codex, Canadian, or Mexican MRLs for penoxsulam. An International Residue Limits Status (IRL) sheet is attached.

The available crop field trial data for rice grain do not support the proposed tolerance of 0.01 ppm; a tolerance of 0.02 ppm must be proposed. The rice processing data indicate that tolerances for rice processed commodities are not needed. In addition, the proposed tolerances should be revised to reflect the correct commodity definitions as specified in Table 8.

Table 8. Tolerance Summary for Penoxsulam.

Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments (correct commodity definition)
Rice grain	0.01	0.02	Rice, grain
Rice straw	0.50	0.50	Rice, straw
Rice hull	0.01	Not needed	Rice, hulls
Rice bran	0.01	Not needed	Rice, bran

Table 8. Tolerance Summary for Penoxsulam.			
Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments (correct commodity definition)
Polished rice	0.01	Not needed	Rice, polished rice

860.1650 Submittal of Analytical References

An analytical reference standard for penoxsulam is available at the EPA National Pesticide Standards Repository (expiration date January 2007). In addition, several metabolite standards are available.

Attachment: International Residue Limit Status (IRL)

Template Version April 2003

INTERNATIONAL RESIDUE LIMIT STATUS

Chemical Name: 2-(2,2-difluoroethoxy)-N-(5,8-dimethoxy[1,2,4]triazolo[1,5-c] pyrimidin-2-yl)-6-(trifluoromethyl) benzenesulfonamide	Common Name: Penoxsulam	X Proposed tolerance ☐ Reevaluated tolerance ☐ Other	Date: 08/21/03

Codex Status (Maximum Residue Limits)	U. S. Tolerances
X No Codex proposal step 6 or above ☐ No Codex proposal step 6 or above for the crops requested	Petition Number: PP#3F6542 DP Barcode: D288152 Other Identifier:
Residue definition (step 8/CXL): N/A	Reviewer/Branch: M.J. Nelson/RAB2 Residue definition: Penoxsulam *per se*

Crop (s)	MRL (mg/kg)	Crop(s)	Tolerance (ppm)
		Rice grain	0.01
		Rice straw	0.50
		Rice hull	0.01
		Rice bran	0.01
		Polished rice	0.01

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

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

Notes/Special Instructions:S.Funk, 08/26/03.

Rev. 1998