UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

MEMORANDUM:

Date: 2/14/2007

Subject: Orthosulfamuron. First Food Use Petition for the Establishment of Tolerances on the Raw Agricultural Commodities of Rice. Summary of Analytical Chemistry and Residue Data. PP#5F6957.

DP Barcode:	D332290	Decision Number:	358188
PC Code:	108209	MRID Nos.:	46578960-46578966, 46578969, 46578974-46578976, 46578982, 46578983, 46578986, & 46578988
40 CFR 180.	Not Established		
Chemical Class:	Sulfamoylurea		

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This document was originally prepared under contract by Dynamac Corporation (2275 Research Blvd, Suite 300; Rockville, MD 20850; submitted 06/12/2006). The document has been reviewed by the Health Effects Division (HED) and revised to reflect current Office of Pesticide Programs (OPP) policies.

Executive Summary

Orthosulfamuron is a postemergence herbicide that the petitioner, Isagro S.p.A., is proposing for use on rice grown in the United States for the control of annual and perennial broadleaf weeds, sedges, and barnyard grass. The CAS name of orthosulfamuron is: 2-[[[[[(4, 6-dimethoxy-2-pyrimidinyl)-amino]carbonyl]amino]sulfonyl]amino]-N,N-dimethylbenzamide. Orthosulfamuron belongs to the sulfamoylurea class and reportedly acts by inhibiting the plant enzyme acetolactate synthase, which is active in the biosynthesis of valine, leucine, and isoleucine.

Isagro S.p.A. proposes the establishment of tolerances for residues of orthosulfamuron *per se* in/on the following rice commodities:

Rice, grain	0.05 ppm
Rice, straw	0.05 ppm

Concurrently, the petitioner is seeking the registration of two orthosulfamuron formulations for use on rice: (i) a water dispersible granular (WG) formulation containing 51.5% active ingredient (Product Name = IR5878 50 WG); and (ii) a granular (GR) formulation containing 0.51% ai (Product Name = IR5878 0.5 GR). Both formulations are proposed at a maximum application rate of 0.066-0.069 lb ai/A, and may be applied only once per growing season when the rice crop is in the 2-4 leaf stage (IR5878 50 WG) or the 1-2 leaf stage (IR5878 0.5 GR). It may be applied with aerial or ground equipment. No rotational crop restrictions are listed on the specimen labels.

The nature of the residue in rice is adequately understood. In an acceptable rice metabolism study using two radiolabels and an application rate reflecting 1x, the parent was identified as a minor component (≤0.001-0.003 ppm) along with four metabolites. The nonextractable residues were shown to be incorporated into natural constituents. The nature of the residue in rice for both tolerance expression and risk assessment is parent orthosulfamuron *per se*.

The nature of the residue in lactating goats is adequately understood pending submission of confirmatory storage stability data/information. The reviewed study showed low levels of total radioactive residues (TRR) in goat milk and tissues following oral dosing of goats with [^{14}C]orthosulfamuron at feeding levels equivalent in the diet to 10.26-13.11 ppm (approximately 500-650x the theoretical dietary burden of 0.020 ppm for dairy cattle). The study found that the parent was degraded to metabolites both with the molecule bridge intact or broken between the pyrimidinyl and phenyl rings, and a significant amount of the residue in liver was eventually bound to protein.

The nature of the residue in rotational crops is adequately understood. TRR ranged from 0.0007 to 0.8730 ppm in/on representative rotational crop commodities planted at various plantback intervals following treatment of soil with [^{14}C]orthosulfamuron at 1x. As with the rice metabolism study, the parent was identified as a minor component along with other metabolites.

The petitioner has submitted data waiver requests for the conduct of a poultry metabolism study, a poultry feeding study, and a ruminant feeding study. HED concludes that the proposed use of

orthosulfamuron on rice is considered to fall under Section 3 of 40 CFR §180.6(a) (no expectation of finite residues in animal commodities). Therefore, tolerances for meat, milk, poultry, and eggs are not required for the purposes of this petition only. At the present time, HED recommends that the Agency grant the waiver requests for the poultry metabolism study, the poultry feeding study, and the ruminant feeding study. HED also concludes that residue analytical methods and storage stability data for animal commodities are not required. This determination is based on the results of the goat metabolism study, the rice field trials (performed at a 1x application rate), and processing studies (performed at up to a 3x application rate) which showed that residues of orthosulfamuron were below the method LOQ (<0.05 ppm) in/on all samples of rice grain, straw, and processed commodities. The decision is also based on the low dietary burdens of orthosulfamuron to dairy and beef cattle (0.020 ppm), poultry (0.022 ppm), and swine (0.013 ppm). The Agency reserves the right to require these waived studies if the petitioner seeks to register additional feed crops in the future.

There are adequate residue analytical methods for data collection and for tolerance enforcement. The petitioner has submitted an LC/MS/MS method (Report ISA-0102V) and proposed it as the tolerance enforcement method. This method was also the data-collection method used in the analysis of samples collected from the rice field trial, storage stability, and processing studies. Adequate method and concurrent recovery data were provided for the LC/MS/MS method (Report ISA-0102V), and the fortification levels used in method and concurrent validation are adequate to bracket expected residue levels in rice commodities. The LOQ is 0.05 ppm for all rice matrices, and the reported LOD is 0.01 ppm. The registrant submitted an independent laboratory validation (ILV) for the enforcement method. The Analytical Chemistry Branch (ACB) of the Biological and Economic Analysis Division (BEAD) reviewed the method and the ILV. The method was deemed to be acceptable for enforcement purposes. The ILV satisfied Agency requirements. Radiovalidation data are not required for the use on rice. The extraction procedures of the enforcement method and metabolism study are similar.

The registrant also submitted an LC/MS method (Report 2305) for the determination of residues of orthosulfamuron in/on rice grain and straw. The LC/MS method (Report 2305) was also adequately validated by the petitioner. For this method, the LOQ is 0.05 ppm for all rice matrices and the reported LOD is 0.03 ppm.

The requirement for data on multiresidue methods is not fulfilled. The petitioner has submitted validation data for a QuEChERS multiresidue method, based on a published journal, for the determination of orthosulfamuron residues in/on rice grain. However, the QuEChERS method does not conform to the FDA multiresidue methods data requirements under OPPTS 860.1360.

There are adequate magnitude of the residue data for rice grain and straw. Geographic representation of field trial data is in accordance with that specified in Guideline OPPTS 860.1500. Following application of the two proposed formulations (WG and G) to rice plants according to the maximum proposed use pattern, residues of orthosulfamuron were below the LOQ (<0.05 ppm) in all treated samples (n = 32) of rice grain and straw. The field residue studies are supported by adequate storage stability data which indicate that residues of orthosulfamuron are reasonably stable under frozen storage conditions and intervals used for sample storage. HED concludes that the proposed tolerance levels (0.05 ppm each) for rice grain and straw are appropriate.

An acceptable rice processing study is available. Residues of orthosulfamuron did not appear to concentrate in samples of polished rice, bran, and hulls processed from rice grain treated at a 3x application rate and bearing nonquantifiable orthosulfamuron residues. These data suggest that tolerances for the processed commodities of rice are not needed.

Tolerances are not needed for rotational crops. Field rotational crop studies were not submitted and none are required at this time. Based on the results of the confined rotational crop studies, it is permissible to rotate to any crop after 30 days.

Residues are not expected in irrigated crops, fish, shellfish, and crustaceans (e.g., crayfish) from the proposed use on rice.

Samples of analytical standard for orthosulfamuron are currently not available in the EPA National Pesticide Standards Repository. The registrant needs to submit a sample to the Repository

Regulatory Recommendations and Residue Chemistry Deficiencies

HED recommends in favor of the proposed tolerances of 0.05 ppm for rice grain and rice straw. The data deficiencies discussed below should be considered conditions of registration.

860.1300 Nature of the Residue - Livestock

For the submitted goat metabolism study (MRIDs 46578962 and 46578963), the petitioner needs to provide the dates of sample extraction, initial TLC analysis, and metabolite identification analyses in order to determine sample storage intervals. If the initial quantitative TLC analyses were conducted within 6 months of sample collection, then supporting storage stability data will not be required to support the additional analyses for metabolite identification in goat matrices.

860.1360 Multiresidue Methods

The petitioner needs to follow specific directions for each multiresidue method used by FDA published in that Agency's Pesticide Analytical Manual, Vol. I (PAM Vol. I) and provide recovery data for orthosulfamuron through these methods.

860.1650 Submittal of Analytical Reference Standards

Analytical standards for orthosulfamuron are not currently available in the National Pesticide Standards Repository. Analytical reference standards of orthosulfamuron need to be supplied and supplies need to be replenished as requested by the Repository. The reference standards should be sent to the Analytical Chemistry Lab, which is located at Fort Meade, to the attention of either Theresa Cole or Frederic Siegelman at the following address:

USEPA
National Pesticide Standards Repository/Analytical Chemistry Branch/OPP
701 Mapes Road
Fort George G. Meade, MD 20755-5350

Note that the mail will be returned if the extended zip code is not used.

Background

Orthosulfamuron is an herbicide that was developed by Isagro S.p.A. for the control of various weeds in rice fields. Orthosulfamuron belongs to the sulfamoylurea class of pesticides. It acts by inhibiting the plant enzyme acetolactate synthase, which is active in the biosynthesis of valine, leucine, and isoleucine. The nomenclature and chemical structure of orthosulfamuron are listed in Table 1. The physicochemical properties of orthosulfamuron are listed in Table 2.

Table 1. Nomenclature of Orthosulfamuron.

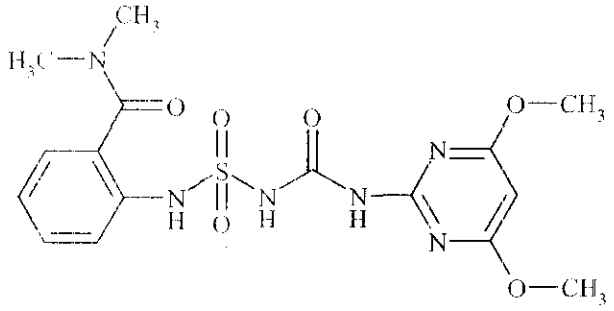
Compound	
Common name	Orthosulfamuron
Company experimental name	IR5878
IUPAC name	1-(4,6-dimethoxypyrimidin-2-yl)-3-[2-(dimethylcarbamoyl)phenylsulfamoyl]urea
CAS name	2-[[[[[(4,6-dimethoxy-2-pyrimidinyl)-amino]carbonyl]amino]sulfonyl]amino]-N,N-dimethylbenzamide
CAS registry number	213464-77-8
End-use product (EP)	0.51% GR formulation (IR5878 0.5 GR; EPA Co. No. 80289) 51.5% WG formulation (IR5878 50 WG; EPA Co. No. 80289)

Table 2. Physicochemical Properties of the Technical Grade of Orthosulfamuron.

Parameter	Value	Reference (MRID)
Color	White	46219004
Physical State	Fine Powder at 20°C	46219005
Odor	Odorless	46219006
pH	4.35 at 25°C (1% aqueous dispersion)	46219013
Density	1.45 g/mL at 20°C	46219008
Water solubility at 20°C	pH 4 buffer: 0.062 g/L pH 7 buffer: 0.63 g/L pH 8.5 buffer: 39 g/L	46219009

Table 2. Physicochemical Properties of the Technical Grade of Orthosulfamuron.		
Parameter	Value	Reference (MRID)
Solvent solubility at 20°C	n-heptane: 0.23 mg/L xylene: 130 mg/L acetone: 20 g/L ethyl acetate: 3.3 g/L dichloromethane: 56 g/L methanol: 8.3 g/L	Electronic communication, J. Messina to E. Kraft, 9/6/2006
Vapor pressure	1.1×10^{-7} at 20°C	46219010
Dissociation constant, pK_a	The test material becomes increasingly less soluble in water as the pH is lowered and undergoes degradation (hydrolysis) at neutral to acidic pHs. The test material is predicted to have 5 overlapping dissociation constants.	46219011
Octanol/water partition coefficient, $Log(K_{OW})$	pH 4: 2.0 pH 7: 1.3	46219012
UV/visible absorption spectrum	at pH 6.9, A=0.49 and $\varepsilon = 2.1 \times 10^4$ at 238 nm	46219001

860.1200 Directions for Use

Table 3. Summary of Proposed End-Use Products.						
Trade Name	Reg. No.	ai (% of formulation)	Formulation Type	Target Crops	Target Pests	Label Date
IR5878 0.5GR	80289-A(6)	0.51%	Granular (G)	Rice (permanently flooded)	several annual and perennial broadleaf weeds and sedges	Not specified
IR5878 50 WG	80289-L(5)	51.5%	Water dispersible granule (WG)	Rice (wet-seeded or dry-seeded)	several annual and perennial broadleaf weeds and sedges	Not specified

Table 4. Summary of Directions for Use of Orthosulfamuron.

Applic. Timing, Type [Equipment]	Formulation	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Rice						
Broadcast foliar (early growth stage; 1-2 leaves) to permanent flooded rice only [Ground or aerial]	0.51% G	0.066	1	0.066	Not specified (NS)	Application is to be made dry (without dilution in water). Application through any type of irrigation equipment is prohibited.
Broadcast foliar (early growth stage; 2-4 leaves) to wet-seeded or dry-seeded rice [Ground or aerial]	51.5% WG	0.069	1 (implied)	0.069	NS	For dry-seeded rice, application may be made from early postemergence to pre-flood. For water-seeded rice, application may be made from early postemergence to middle-late postemergence. Application may be made in a minimum of 10 gal/A using ground equipment or a minimum of 5 gal/A using aerial equipment. A spray adjuvant (organo siliconic or nonionic surfactant) at the rate of 0.1-0.2% v/v is recommended. Application may be made alone or as a tank mix with other herbicides registered for use on rice.

Conclusions. The submitted product labels for IR5878 50 WG and IR5878 0.5 GR are adequate to allow evaluation of the residue data relative to the proposed use on rice.

860.1300 Nature of the Residue – Plants (46578961.der.doc)

Isagro S.p.A. has submitted a study investigating the metabolism of [^{14}C-5-pyrimidinyl]orthosulfamuron (PY label) and [^{14}C-U-phenyl]orthosulfamuron (PH label) in rice. Each radiolabeled test substance was formulated as a WG using formulation blank, suspended in water with a nonionic surfactant, and applied as a single foliar application to rice plants at the 2-leaf growth stage (grown outdoors in minipaddies) at 0.070 lb ai/A (PY label) or 0.066 lb ai/A (PH label). Separate plots were treated at an exaggerated rate in case additional material was required for metabolite identification. These samples were not used in the study. Samples of mature whole grain (kernel plus hulls) and straw were collected 112 days after treatment. Subsamples of whole grain were separated into husked rice and hulls to investigate residue concentration. The in-life and analytical phases of the study were conducted by Isagro Ricerca Srl (Novara, Italy).

Total radioactive residues (TRR) in rice matrices, determined by combustion/LSC, were 0.0632 ppm and 0.0898 ppm in samples of rice whole grain and straw, respectively, treated with PY-labeled orthosulfamuron. TRR were 0.0368 ppm and 0.1101 ppm in samples of rice whole grain and straw, respectively, treated with PH-labeled orthosulfamuron. In both PY- and PH-label grain, TRR appear to be concentrated in the hull of rice grain; TRR were 0.0584 ppm and 0.1128 ppm in PY-label husked rice and hulls, and 0.0330 ppm and 0.0502 ppm in PH-label husked rice and hulls, respectively.

The distribution of radioactivity was similar between the two labels. Samples of rice grain were first extracted with hexane, which only released ~1-2% TRR. A large amount of radioactivity was released from both rice grain (~21-29% TRR; 0.008-0.018 ppm) and straw (~48-49% TRR; 0.043-0.054 ppm) with solvent extraction (ACN/NH_4OH). Partitioning of the solvent extract separated the organic and aqueous soluble residues, respectively as 13.0% TRR (0.008 ppm) and 15.7% TRR (0.010 ppm) in PY-label grain; 5.4% TRR (0.002 ppm) and 16.0% TRR (0.006 ppm) in PH-label grain; 21.2% TRR (0.019 ppm) and 27.3% TRR (0.025 ppm) in PY-label straw; and 7.5% TRR (0.008 ppm) and 41.5% TRR (0.046 ppm) in PH-label straw. Additional extraction with aqueous sodium bicarbonate at reflux released only ≤6% TRR (<0.006 ppm) from rice grain and straw. The majority of the radioactivity (62-71% TRR, <0.04 ppm) in rice grain remained nonextractable, and was subjected to various enzyme hydrolyses, which released an additional 40-48% TRR. Nonextractable radioactivity (41-42% TRR, <0.05 ppm) in rice straw following solvent extraction was subjected to base and acid hydrolyses to precipitate cellulose and lignin (25% TRR).

Nonextractable residues were not reported following hydrolysis procedures; however, accountabilities were >68-95.1% for rice grain and straw, and uncharacterized nonextractable residues were ≤0.02 ppm in rice grain and straw. These procedures adequately extracted and characterized the majority of residues from rice grain and straw. Residues were identified and quantitated by normal and reverse phase TLC. Since all samples of rice grain and straw were stored frozen and analyzed within 124 days (4.1 months) of harvest, no supporting storage stability data are needed.

The metabolite profile differed between the PY and PH labels, demonstrating cleavage of the molecule between the two rings. Parent, orthosulfamuron, was not identified in PY-label grain and straw, and was only identified in PH-label grain and straw at trace levels (1.6% TRR, <0.001 ppm and 2.5% TRR, 0.003 ppm, respectively).

DOP urea was the only residue identified in PY-label grain and straw at 13.0% TRR (0.008 ppm) and 21.2% TRR (0.019 ppm), respectively. DOP urea was not identified in PH-label matrices. The metabolite DBS acid was the major metabolite identified in PH-label straw at 34.8% TRR (0.038 ppm); DBS acid was identified in PH-label grain, but at lower levels (6.8% TRR, 0.003 ppm). Metabolites DB amine and DBS amide were also identified in both grain and straw at minor levels (<4% TRR, <0.005 ppm). The remaining unknowns, present at 15.7% TRR in PY-label grain, 27.3% TRR in PY-label straw, 9.2% TRR in PH-label grain and 6.8% TRR in PH-label straw, were characterized as organic or aqueous soluble and individually accounted for <0.01 ppm. Nonextractable residues were characterized as natural components accounting for: 22-25% TRR as cellulose, 6-9% TRR as starch, 3-4% TRR as pectin, 3-4% TRR as protein, and 1-2% TRR as lignin in grain (both labels); and 9-11% TRR as cellulose and 14-15% TRR as

lignin in straw (both labels).

TRR levels were extremely low in rice matrices, and no significant degradation compounds were present in either grain or straw. The majority of the residue was bound, and the radioactivity was incorporated into natural components.

The chemical names and structures of metabolites identified in the rice metabolism study, goat metabolism study, and confined rotational crop study are listed in Appendix I.

Conclusions. The nature of the residue in plants is adequately understood based on an acceptable rice metabolism study using two radiolabels and an application rate reflecting 1x. The parent was identified as a minor component (≤0.001-0.003 ppm) along with four metabolites. The nonextractable residues were shown to be incorporated into natural constituents. Based on the results of the study, parent orthosulfamuron is the residue of concern in rice for both tolerance expression and risk assessment (Memo, K. Bailey, *et al.*, D319264, 2/14/2007). Orthosulfamuron appeared in rice grain at a very low level. DOP urea and DBS acid appeared in straw at 0.02 ppm and 0.04 ppm, respectively. Rice straw is not a human food commodity, however.

860.1300 Nature of the Residue - Livestock

Goat: (46578962.der.doc)

Isagro S.p.A. has submitted a study investigating the metabolism of [^{14}C-5-pyrimidinyl]orthosulfamuron (PY label) and [^{14}C-U-phenyl]orthosulfamuron (PH label) in lactating goats. The radiolabeled test substances were administered orally to separate goats at 18.09 mg/day (PY label) or 22.66 mg/day (PH label) for five consecutive days. Based on the daily dietary intake, the dosage corresponded to 10.26 ppm (PY label) and 13.11 ppm (PH label) in the feed. Milk was collected twice daily during the dosing period, and the test goats were sacrificed 23 hours after the last dose administration. Tissues collected at animal sacrifice include both kidneys, liver, omental fat, renal fat, and skeletal muscle (hind and fore quarters). The in-life phase was conducted by Inveresk Research (Tranent, Scotland) whereas the analytical phase was performed by Isagro Ricerca Srl (Novara, Italy).

Total radioactive residues (TRR) were determined at the in-life facility. TRR were 0.005-0.014 ppm in milk, <0.002 ppm in muscle, 0.003 ppm in omental and renal fat, 0.125 ppm in liver, and 0.090 ppm in kidney from the goat orally dosed with PY-labeled orthosulfamuron. TRR were 0.004-0.016 ppm in milk, 0.007 ppm in muscle, 0.003 ppm in omental and renal fat, 0.131 ppm in liver, and 0.144 ppm in kidney from the goat orally dosed with PH-labeled orthosulfamuron. TRR was highest in liver and kidney, and <0.01 ppm in muscle and fat; the TRR were consistently low in milk but appear to plateau at 72 hours for the PY label goat and 48 hours for the PH label goat. The majority (90-97%) of the administered dose was excreted: ~50% in the feces, ~32-40% in the urine, and ~8% in the cage washes.

Muscle and fat were not extracted for metabolite identification because the TRR was <0.01 ppm. The majority of the radioactivity was released with solvent extraction; ~95-103% TRR from milk with methanol, and ~93% TRR from kidney and ~48-69% TRR from liver with ACN/ammonium

bicarbonate. Additional radioactivity was released from the nonextractable residues of liver with chemical or enzyme hydrolyses; protease hydrolysis released the largest amount (45% TRR from PY label liver and 23% from PH label liver). Nonextractable residues were nondetectable in milk and ≤5% TRR (≤0.005 ppm) in kidney (both labels). Nonextractable residues remaining in liver after enzyme hydrolysis were not determined; however, based on the total radioactivity released, the nonextractable residues would be <10% TRR in liver (both labels). These procedures adequately extracted and characterized the majority of residues from goat milk and tissues; accountabilities ranged from 92% to 100%.

Residues were quantitated by TLC, and identified with goat urine metabolites using TLC, HPLC, and/or LC/MS. Sample integrity was maintained by appropriate freezer storage prior to residue analysis; however, actual extraction and analysis dates were not provided. Goat milk, kidney, and liver samples may have been stored for up to 5.5 months based on the initial dosing date (11/14/02) and a statement by the petitioner that analysis was completed April 2003. No storage stability data are available to support the storage intervals and conditions of samples from the goat metabolism study. The petitioner should submit the dates of extraction, initial TLC analysis, and metabolite identification analyses.

The metabolite profile differed somewhat between the PY and PH labels, demonstrating possible cleavage of the molecule between the two rings. Parent, orthosulfamuron, was identified in all goat milk and tissue samples. The parent was present at low levels in milk, accounting for 8.9-11.2% TRR (0.001 ppm) in PY label milk, and 7.9-16.6% TRR (0.001-0.002 ppm) in PH label milk. The parent was identified as a major residue in tissues, accounting for 26.4% TRR (0.024 ppm) in PY label kidney, 27.8% TRR (0.037 ppm) in PH label kidney, 12.7% TRR (0.016 ppm) in PY label liver, and 20.5% TRR (0.030 ppm) in PH label liver.

Pyr-O-Sulf DOP urea was identified as the major metabolite in PY label milk and kidney accounting for 59.1-76.4% TRR (0.005-0.011 ppm) in milk and 25.7% TRR (0.023 ppm) in kidney; Pyr-O-Sulf DOP urea was also identified in PY label liver as a minor metabolite (3.3% TRR, 0.004 ppm). Pyr-O-Sulf DOP urea only contains the parent pyrimidinyl ring and, therefore, was not identified in any PH label goat matrices. DOP urea, another pyrimidinyl ring metabolite, was only identified in liver at 3.8% TRR (0.005 ppm).

Metabolites N-desm-O-desm IR5878, N-desm IR5878, and O-desm IR5878, each with the molecule bridge between the two rings intact, were identified in both PY and PH label goat matrices. N-desm IR5878 accounted for 9.4-17.0% TRR (0.001-0.002 ppm) in PY label milk, 13.3% TRR (0.012 ppm) in PY label kidney, and 7.3% TRR (0.009 ppm) in PY label liver; and 21.9-34.9% TRR (0.004-0.005 ppm) in PH label milk, 17.7% TRR (0.023 ppm) in PH label kidney, and 10.9% TRR (0.016 ppm) in PH label liver. O-desm IR5878 was identified as a minor residue in all milk and tissue samples: 2.7-8.2% TRR (≤0.001 ppm) in milk, 3.4-4.0% TRR (≤0.005 ppm) in kidney, and 4.1-7.0% TRR (≤0.010 ppm) in liver (both labels). N-desm-O-desm IR5878 was also identified as a minor residue, accounting for 2.5-7.2% TRR (≤0.001 ppm) in PH label milk, 1.8-2.5% TRR (0.002 ppm) in PY and PH label kidney, and 1.4% TRR (0.002 ppm) in PY label liver; N-desm-O-desm IR5878 was not detected in PY label milk or PH label liver.

Metabolites DBS acid, N-desm DB amine, and DBS amide were only identified in PY label milk and tissues, because each contains only the parent phenyl ring. DBS acid accounted for 8.6-15.2% TRR (≤0.002 ppm) in milk, 11.4% TRR (0.015 ppm) in kidney, and 4.6% TRR (0.007 ppm) in liver; N-desm DB amine accounted for 9.4-16.3% TRR (≤0.002 ppm) in milk, 13.8% TRR (0.018 ppm) in kidney, and 8.0% TRR (0.012 ppm) in liver; and DBS amide accounted for 10.6-14.1% TRR (≤0.002 ppm) in milk, 4.5% TRR (0.006 ppm) in kidney, and 3.9% TRR (0.006 ppm) in liver.

A significant amount of radioactivity in goat liver was characterized as protein bound residues (45.5% TRR, 0.057 ppm in PY label liver and 22.6% TRR, 0.032 ppm in PH label liver). The remaining residues in goat milk and tissues were characterized as unknowns totaling 2.7-15.9% TRR in milk and 11.8-20.4% TRR in kidney and liver, with individual peaks accounting for <0.01 ppm.

Based on the goat metabolism study, the petitioner states that the radioactivity in goat milk, muscle, and fat is negligible, and very low in the liver and kidneys. The parent is metabolized to metabolites both with the molecule bridge intact or broken between the pyrimidinyl and phenyl rings, and a significant amount of the residue in liver is eventually bound to protein. The metabolic pathway for orthosulfamuron in goats is similar to that in rats.

The chemical names and structures of metabolites identified in the rice metabolism study, goat metabolism study, and confined rotational crop study are listed in Appendix I.

Conclusions. The nature of the residue in lactating goats is adequately understood pending submission of confirmatory storage stability data/information. The petitioner is required to provide the dates of sample extraction, initial TLC analysis, and metabolite identification analyses in order to determine sample storage intervals. If the initial quantitative TLC analyses were conducted within 6 months of sample collection, then supporting storage stability data will not be required to support the additional analyses for metabolite identification in goat matrices. The reviewed study showed low levels of total radioactive residues (TRR) in goat milk and tissues following oral dosing of goats with [^{14}C]orthosulfamuron at feeding levels equivalent in the diet to 10.26-13.11 ppm (approximately 500-650x the theoretical dietary burden of 0.020 ppm for dairy cattle). The study found that the parent was degraded to metabolites both with the molecule bridge intact or broken between the pyrimidinyl and phenyl rings, and a significant amount of the residue in liver was eventually bound to protein. Based on the results of the study, determinations do not need to be made regarding residues of concern in ruminants. The theoretical dietary burdens for beef and dairy cattle are both 0.020 ppm. The dosing rates used in the PY and PH label studies were 10.3 and 13.1 ppm, respectively. Although residues of parent and some metabolites appear at levels slightly over 0.01 ppm in liver and kidney, the levels of these compounds are below 0.0001 ppm when adjusted for the exaggeration rates. As a result, there is no expectation of quantifiable residues in ruminant tissues or milk.

Poultry

The petitioner has submitted a data waiver request (MRID 46578975) for the conduct of a poultry metabolism study based on the following rationale: No quantifiable residues were found in the magnitude of the residue study for processed rice commodities, including poultry

feedstuffs, at either 1x or 3x the proposed application rate. Therefore, there is no possibility of quantifiable residues in poultry eggs and tissues. As a result, negligible dietary exposure potential is expected. Also, a ruminant study demonstrated very little transfer of orthosulfamuron residue to the tissue and milk of goats at a dose rate considerably higher than the calculated dietary burden.

Conclusions: HED concludes that the proposed use of orthosulfamuron on rice is considered to fall under Section 3 of 40 CFR §180.6(a) (no expectation of finite residues in animal commodities). Therefore, tolerances for poultry and eggs are not required for the purposes of this petition only. This determination is based on the results of the rice field trials in which residues of orthosulfamuron were below the method LOQ of 0.05 ppm in/on all samples of rice grain that were treated at a 1x application rate. The decision is also based on the relatively low poultry dietary burden of 0.022 ppm and the low transfer of residues observed in the goat metabolism study. At the present time, HED recommends that the Agency grant the waiver request for a poultry metabolism study. However, the Agency reserves the right to require a poultry metabolism study if the petitioner seeks to register additional feed crops in the future.

860.1340 Residue Analytical Methods (46578960.der.doc (Includes MRID 46578983))

Isagro S.p.A. has submitted an LC/MS/MS method (referenced as Report ISA-0102V) and an LC/MS method (referenced as Report 2305) for the determination of residues of orthosulfamuron in/on rice grain and straw.

The LC/MS/MS method (Report ISA-0102V) was the data-collection method used in the analysis of samples collected from the rice field trial, storage stability, and processing studies. The method was based on the "Enforcement Method (including Validation) for the Determination of Residues of IR5878 in Rice Grain, Rice Green Plant and Rice Straw" as presented in Report ISA-0102V, Dr. Specht & Partner, 2002. Method descriptions along with validation data were included as an attachment to the storage stability study (MRID 46578983).

The petitioner has also submitted a similar LC/MS method (Report 2305, MRID 46578960) with validation data for rice RAC and processed commodities, which includes an additional optional cleanup step. For both methods, the LOQ is 0.05 ppm for all rice matrices, and the reported LOD is 0.01 ppm for Method Report ISA-0102V and 0.03 ppm for Method Report 2305.

Using the LC/MS/MS method (Report ISA-0102V), homogenized rice samples were extracted twice with acetonitrile (ACN):0.02 M triethylamine (4:1, v:v) and then filtered. Sodium chloride was added to the filtrate to induce separation of the aqueous and ACN phases. An aliquot of the ACN layer was brought to volume with additional ACN and partitioned with hexane. The resulting ACN phase was evaporated to dryness, and residues were redissolved in methanol and water for LC/MS/MS analysis. The ions monitored for orthosulfamuron are 425→199 amu (for quantitation) and 425→227 amu (for qualitative confirmation).

Using the LC/MS method (Report 2305), the ACN extract (after the addition of sodium chloride) was partitioned with hexane pre-saturated with ACN. The concentrated ACN phase was then redissolved in dichloromethane, filtered, and dried again for further cleanup (if necessary) through an alumina/activated charcoal column. The eluate was dried, and residues were

redissolved in ACN for LC/MS analysis. The ion monitored for orthosulfamuron is 425 amu (for quantitation), and the transition ions are 199 and 227 amu (for qualitative confirmation).

Both methods are adequate for data collection based on acceptable method recoveries. Using the LC/MS/MS method (Report ISA-0102V), recoveries of orthosulfamuron averaged 70% with a standard deviation (s.d.) of 5% for green plants and 80% (s.d. 8%) for grain following fortification of rice samples at 0.05 and 0.50 ppm. Acceptable concurrent validation recoveries were also obtained with LC/MS/MS method (Report ISA-0102V) for rice grain and straw fortified at 0.05 ppm from the field trials, and for rice grain, polished rice, bran, and hulls fortified at 0.05 ppm from the processing study. Using the LC/MS method (Report 2305), recoveries of orthosulfamuron averaged 96% (s.d. 7%) for plants, 79% (s.d. 8%) for grain, 88% (s.d. 13%) for straw, 103% (s.d. 8%) for husked rice, and 83% (s.d. 15%) for hulls following fortification of rice samples at 0.05 and 0.50 ppm. The fortification levels used in method and concurrent validation are adequate to bracket expected residue levels in rice grain, straw, hulled rice, and hulls.

The registrant proposed the LC/MS/MS method (ISA-0102V) as the tolerance enforcement method. The registrant submitted an ILV for this method. The ACB reviewed the method and the ILV (C. Stafford, 1/31/2007, Attachment C). The method was deemed to be acceptable for enforcement purposes. The ILV satisfied Agency requirements. Radiovalidation data (using samples from the rice metabolism study) for the proposed enforcement method are not required for the use on rice. The extraction solvent in the method (4:1 ACN:0.02M triethylamine) is similar to that employed in the rice metabolism study (1:1 ACN:ammonium hydroxide, pH 8.5).

Conclusions. There are adequate residue analytical methods for both data collection and tolerance enforcement. The petitioner has submitted an LC/MS/MS method (Report ISA-0102V) and an LC/MS method (Report 2305) for the determination of residues of orthosulfamuron in/on rice grain and straw. The LC/MS/MS method (Report ISA-0102V) was the data-collection method used in the analysis of samples collected from the rice field trial, storage stability, and processing studies. Adequate method and concurrent recovery data were provided for the LC/MS/MS method, and the fortification levels used in the method and concurrent validation are adequate to bracket expected residue levels in rice commodities. The LC/MS method (Report 2305) was also adequately validated by the petitioner. For both methods, the LOQ is 0.05 ppm for all rice matrices, and the reported LOD is 0.01 ppm for the LC/MS/MS method (Report ISA-0102V) and 0.03 ppm for the LC/MS method (Report 2305). ACB/BEAD has determined that Method ISA-0102V is adequate for tolerance enforcement.

860.1360 Multiresidue Methods (46578969.der.doc)

Isagro S.p.A. has submitted validation data for a QuEChERS multiresidue method for the determination of orthosulfamuron residues in/on rice grain (matrix with low water content). The QuEChERS multiresidue method used in the validation study is based on:

M. Anastassaides, S.J. Lehotay, D. Stajnbaher, and F.J. Schenck (2003). "Fast and easy multiresidue method employing acetonitrile extraction/partitioning and "dispersive solid-phase extraction" for the determination of pesticide residues in produce." Journal of AOAC International 86(2): 412-431.

The petitioner stated that the study was conducted according to the guidance documents of: (i) SANCO/825/00 (rev. 7 of March 17, 2004) and SANCO3029/99 (rev. 4 of July 11, 2000) of the European Commission; (ii) BBA Guideline: Residue Analytical methods for Post-registration Control Purposes of July 21, 1983; and (iii) U.S. EPA Residue Chemistry Test Guidelines, OPPTS 860.1340.

Briefly, the QuEChERS method uses a single-step buffered ACN extraction and salting out liquid-liquid partitioning from the water in the sample with magnesium sulfate and sodium acetate. The sample is cleaned up using dispersive solid phase extraction (SPE) to remove organic acids, excess water, and other components with primary secondary amine (PSA) and magnesium sulfate. An aliquot of the supernatant is diluted with 0.1% formic acid for HPLC/MS/MS analysis. The limit of quantitation (LOQ) is 0.01 ppm. Adequate recoveries ranging from 70% to 105% were obtained for rice grain samples fortified with orthosulfamuron at the LOQ of 0.01 ppm and 10x the LOQ.

Conclusions. The QuEChERS method does not conform to the FDA multiresidue methods data requirements under OPPTS 860.1360. To fulfill these data requirements, the petitioner needs to follow specific directions for each multiresidue method used by FDA published in that Agency's Pesticide Analytical Manual, Vol. I (PAM Vol. I) and provide recovery data for orthosulfamuron through these methods.

860.1380 Storage Stability (46578982.der.doc)

Isagro S.p.A. has submitted storage stability studies with orthosulfamuron in rice. Untreated samples of rice green plant, grain, and straw from the orthosulfamuron rice field trials were fortified with orthosulfamuron standard at 0.5 ppm. Samples were stored at -20°C in the dark and analyzed at storage intervals of approximately 0, 1, 3, 6, and 12 months. The study on rice green plants (MRID 46578982) was conducted by Isagro Ricerca S.r.l. (Novara, Italy), and the study on rice grain and straw (MRID 46578983) was conducted by PTRL West, Inc. (Hercules, CA). The results indicate that residues of orthosulfamuron are stable at -20°C for up to 368 days (12 months) in/on rice grain and straw, and for up to 408 days (13 months) in/on rice green plants.

Rice samples were analyzed for residues of orthosulfamuron using an LC/MS/MS method which is the same method that was used for data collection for the magnitude of the residue trials. Based on the concurrent method recovery data, the LC/MS/MS analytical method is adequate for the determination of residues of orthosulfamuron in rice matrices. The validated LOQ was 0.05 ppm in/on rice grain, straw, and green plant.

The maximum storage intervals of RAC samples reported in MRID 46578964 were 97 days (3.2 months) for rice grain and 113 days (3.7 months) for rice straw. The maximum storage intervals of crop samples reported in MRID 46578986 were 78 days (2.6 months) for rice grain and 79 days (2.6 months) for rice straw. These storage conditions and intervals are supported by adequate storage stability data.

The maximum storage interval of processed commodity samples reported in MRID 46578965 was 49-56 days. No storage stability data were submitted for processed rice commodities.

Conclusions. There are adequate storage stability data for rice grain and straw but not for processed rice commodities. The available data indicate that residues of orthosulfamuron are reasonably stable under frozen storage conditions in/on fortified samples of rice grain and straw for up to 12 months. Although no storage stability data for processed commodities were submitted, none are needed. The processed commodities were stored frozen for up to 1.8 months. In storage stability studies conducted on rice grain and straw, residues were stable for up to 12 months. These data will be translated to the processed commodities of rice.

860.1400 Water, Fish, and Irrigated Crops

It is possible that orthosulfamuron will be used on rice fields where runoff or irrigation water can flow directly into agricultural land other than rice fields. The proposed use of orthosulfamuron is an early season use when plants are in their early growth stages. As a result, residue decline will occur before rice field water will be used for irrigation to other crops. In addition, the orthosulfamuron labels permit only one application at a low rate (0.07 lb ai/acre). For these reasons, residues will not be expected in irrigated crops. With respect to crayfish, the petitioner has submitted a rationale that residues are not expected based on the timing of production (field stocked after rice harvest in the fall), the results of the bluegill sunfish study (bioconcentration factor reported to be less than one), and the factors cited above for irrigated crops. HED concludes that residues of orthosulfamuron are not expected to be present in fish, shellfish, or crustaceans as a result of the proposed use on rice

860.1480 Meat, Milk, Poultry, and Eggs

There are animal feedstuffs associated with the proposed use on rice. Rice grain, straw, hulls, and bran are feed items for beef and dairy cattle. Rice grain, hulls, and bran are feed items of poultry. Rice grain and bran are feed items for swine. The theoretical dietary burdens (TDBs) for livestock are presented below in Table 5. The animals' nutritional needs are a major factor in selecting feed items. In order for an animal's diet to be nutritious it must contain a grain (carbohydrate), a source of protein, and a source of roughage. To construct the animal diets, lists of all of the potential animal feed items associated with the tolerance requests were prepared for dairy cattle, beef cattle, hogs, and poultry. The lists were examined by J. Stokes and B. Schneider of HED who selected the feed items that they felt were most likely to be used to provide a nutritious diet. In Table 5, the sources of roughage, carbohydrate, and protein are designated as [R], [C], and [P], respectively.

Table 5. Calculation of Livestock Maximum Theoretical Dietary Burdens.

Feedstuff	% Dry Matter[1]	% Diet[1]	Recommended Tolerance (ppm)	Dietary Contribution (ppm)[2]
Beef Cattle				
Rice grain [C]	88	20	0.05	0.011
Rice straw [R]	90	10	0.05	0.006
Rice hulls [R]	90	5	0.05	0.003
TOTAL BURDEN		35		**0.020**

Table 5. Calculation of Livestock Maximum Theoretical Dietary Burdens.				
Feedstuff	% Dry Matter[1]	% Diet[1]	Recommended Tolerance (ppm)	Dietary Contribution (ppm)[2]
Dairy Cattle				
Rice grain [C]	88	20	0.05	0.011
Rice straw [R]	90	10	0.05	0.006
Rice hulls [R]	90	5	0.05	0.003
TOTAL BURDEN		35		**0.020**
Poultry				
Rice grain [C]	88	20	0.05	0.010
Rice bran [R]	90	25	0.05	0.012
TOTAL BURDEN		45		**0.022**
Swine				
Rice grain [C]	88	20	0.05	0.01
Rice bran [R]	90	5	0.05	0.0025
TOTAL BURDEN		25		**0.0125**

[1] Table 1 (OPPTS Guideline 860.1000).

[2] Contribution = [(tolerance) x (% DM)] x [% in diet] for beef and dairy cattle; contribution = [(tolerance) x (% in diet)] for poultry and swine.

Data Waiver Requests for the Conduct of Ruminant and Poultry Feeding Studies

The petitioner has submitted a data waiver request (MRID 46578975) for the conduct of a poultry feeding study (MRID 46578976) and a ruminant feeding study (MRID 46578974). The justifications provided by the petitioner to support these requests are similar to those presented in the data waiver request for a poultry metabolism study (see OPPTS GLN 860.1300).

Conclusions: The proposed use of orthosulfamuron on rice is considered to fall under Section 3 of 40 CFR §180.6(a) (no expectation of finite residues in animal commodities). Therefore, tolerances for meat, milk, poultry, and eggs are not required for the purposes of this petition only. HED also concludes that residue analytical methods and storage stability data for animal commodities are not required. This determination is based on the results of the goat metabolism study, the rice field trials, and processing studies which showed that residues of orthosulfamuron were below the method LOQ (<0.05 ppm) in/on all samples of rice grain and straw that were treated at a 1x application rate. The decision is also based on the low orthosulfamuron dietary burdens for dairy and beef cattle (0.020 ppm), poultry (0.022 ppm), and swine (0.013 ppm). HED reserves the right to require these waived studies if the petitioner seeks to register additional feed crops in the future.

860.1500 Crop Field Trials

The petitioner has submitted two studies (one for each formulation class being supported) depicting the magnitude of the residues of orthosulfamuron in/on rice grain and straw.

Rice Field Trials Using WG Formulation (46578964.der.doc)

Isagro S.p.A. has submitted field trial data for orthosulfamuron on rice. Fourteen field trials were conducted in the United States in Zones 4 (AR, LA, MS; 9 trials), 5 (MO; 1 trial), 6 (TX; 2 trials), and 10 (CA; 2 trials) during the 2003 growing season. At each test location, a single broadcast spray application of the 50% water-dispersible granular (WG) formulation was made at 0.066-0.070 lb ai/A (73.6-78.0 g ai/ha) to moist/wet soil (not flooded) when rice was in the 2-3 leaf stage. Application was made using ground equipment in ~15-21 gal/A with an adjuvant added to the spray mixture. Samples of mature rice grain and straw were harvested from all test sites 91-119 days after application.

Samples of rice grain and straw were analyzed for residues of orthosulfamuron using an LC/MS/MS method based on the "Enforcement Method (including Validation) for the Determination of Residues of IR 5878 in Rice Grain, Rice Green Plant and Rice Straw" as presented in Report ISA-0102V, Dr. Specht & Partner, 2002. This method is adequate for data collection based on acceptable concurrent method recoveries. The validated LOQ was 0.05 ppm in/on rice grain and straw, and the limit of detection was 0.02 ppm.

The maximum storage interval of crop samples from harvest to analysis was 97 days (3.2 months) for rice grain and 113 days (3.7 months) for rice straw. The results of a storage stability study were submitted (refer to the 860.1380 DER for MRID 46578983) and indicate that residues of orthosulfamuron are stable under frozen storage conditions in/on fortified samples of rice grain and straw for up to 12 months. These data are adequate to support the storage intervals of samples from the rice field trials.

Residues of orthosulfamuron were each below the LOQ (<0.05 ppm) in/on all samples (n = 28) of rice grain and straw harvested at maturity following a single broadcast application of the 50% WG formulation at 0.066-0.070 lb ai/A to rice grown in un-flooded fields; see Table 6. No residue decline data were included in the submission. These data are not required because application was made prior to the formation of the edible portion of the crop.

Table 6. Summary of Residue Data from Crop Field Trials with Orthosulfamuron (WG Formulation).

Commodity	Total Applic. Rate (lb ai/A) [g ai/ha]	PHI (days)	Residue Levels (ppm) [1]						
			N	Min.	Max.	HAFT [2]	Median (STMdR)	Mean (STMR)	Std. Dev.
Rice grain	0.066-0.070 [73.6-78.0]	91-119	28	<0.05	<0.05	<0.05	<0.05	<0.05	N/A
Rice straw		91-119	28	<0.05	<0.05	<0.05	<0.05	<0.05	N/A

[1] The method LOQ was <0.05 ppm. The median, mean, and standard deviation were calculated using half the LOQ (<0.025 ppm) for all residues reported as ND in Table C.3 of the DER.
[2] HAFT = Highest Average Field Trial

Rice Field Trials Using GR Formulation (46578986.der.doc)

Isagro S.p.A. has submitted field trial data for orthosulfamuron on rice. A total of two field trials were conducted in the United States in Zone 10 (CA) during the 2004 growing season. At each test location, a single broadcast application of the 0.5% granular formulation was made to emerged rice (3 leaf stage) growing in flooded rice paddies at 0.067 lb ai/A (75.0-75.1 g ai/ha).

Application was made using ground equipment without an adjuvant. Samples of mature rice grain and straw were harvested 116-136 days after application.

Samples of rice grain and straw were analyzed for residues of orthosulfamuron using an LC/MS/MS method based on the "Enforcement Method (including Validation) for the Determination of Residues of IR 5878 in Rice Grain, Rice Green Plant and Rice Straw" as presented in Report ISA-0102V, Dr. Specht & Partner, 2002. This method is adequate for data collection based on acceptable concurrent method recoveries. The validated LOQ was 0.05 ppm in/on rice grain and straw, and the limit of detection was 0.02 ppm.

The maximum storage interval of crop samples from harvest to analysis was 78 days (2.6 months) for rice grain and 79 days (2.6 months) for rice straw. The results of a storage stability study were submitted (refer to the 860.1380 DER for MRID 46578983) and indicate that residues of orthosulfamuron are stable under frozen storage conditions in/on fortified samples of rice grain and straw for up to 12 months. These data are adequate to support the storage intervals of samples from the rice field trials.

Residues of orthosulfamuron were each below the LOQ (<0.05 ppm) in/on all four samples of rice grain and straw harvested at maturity following a single broadcast application of the 0.5% GR formulation at 0.067 lb ai/A to rice in flooded rice paddies; see Table 7. No residue decline data were included in the submission. These data are not required because application was made prior to the formation of the edible portion of the crop.

Table 7. Summary of Residue Data from Crop Field Trials with Orthosulfamuron (G Formulation).

Commodity	Total Applic. Rate (lb ai/A) [g ai/ha]	PHI (days)	Residue Levels (ppm) [1]						
			N	Min.	Max.	HAFT [2]	Median (STMdR)	Mean (STMR)	Std. Dev.
Rice grain	0.067 [75.0-75.1]	116-136	4	<0.05	<0.05	<0.05	<0.025	<0.025	0.0
Rice straw		116-136	4	<0.05	<0.05	<0.05	<0.025	<0.025	0.0

[1] The method LOQ was <0.05 ppm. The median, mean, and standard deviation were calculated using half the LOQ (<0.025 ppm) for all residues reported as ND in Table C.3 of DER.
[2] HAFT = Highest Average Field Trial

Conclusions. There are adequate magnitude of the residue data for rice grain and straw. Geographic representation of field trial data is in accordance with that recommended in Guideline OPPTS 860.1500. Following application of the two proposed formulations (WG and GR) to rice plants according to the maximum proposed use pattern, residues of orthosulfamuron were below the LOQ (<0.05 ppm) in all treated samples (n = 32) of rice grain and straw. The field residue studies are supported by adequate storage stability data which indicate that residues of orthosulfamuron are reasonably stable under frozen storage conditions and at intervals used for sample storage. HED concludes that the proposed tolerance levels (0.05 ppm each) for rice grain and straw are appropriate.

860.1520 Processed Food and Feed

Rice: (46578965.der.doc)

Isagro S.p.A. submitted a rice processing study. In two trials conducted in AR and CA, mature rice grain was harvested 103 or 105 days after a single broadcast application of the 50% water-dispersible granular (WG) formulation made at either 0.066-0.067 lb ai/A (73.9-74.9 g ai/ha; 1x the field trial application rate) or 0.200 lb ai/A (223.7-224.5 g ai/ha; ~3x the field trial application rate) to moist/wet soil (not flooded) when rice was in the 2-3 leaf stage. The harvested rice grain samples were processed into polished rice, bran, and hulls using simulated commercial processing procedures.

Samples of rice grain and its processed commodities (polished rice, bran, and hulls) were analyzed for residues of orthosulfamuron using an LC/MS/MS method based on the "Enforcement Method (including Validation) for the Determination of Residues of IR5878 in Rice Grain, Rice Green Plant and Rice Straw" as presented in Report ISA-0102V, Dr. Specht & Partner, 2002. This method is adequate for data collection based on acceptable method recoveries. The validated LOQ was 0.05 ppm and the limit of detection was 0.02 ppm.

The maximum storage interval of the study samples from collection/processing to analysis was 86 days (2.8 months) for rice grain and 49-56 days (1.6-1.8 months) for the processed rice commodities. To support sample storage conditions and intervals, the petitioner submitted the results of a storage stability study (refer to the 860.1380 DER for MRID 46578983) which indicate that residues of orthosulfamuron are stable under frozen storage conditions in/on fortified samples of rice grain and straw for up to 12 months. The available storage stability data support the storage intervals and conditions of the RAC (rice grain), but no storage stability data are available for the processed commodities of rice.

Residues of orthosulfamuron were less than the method LOD (<0.02 ppm) in/on rice grain from both treatment rates. Residues of orthosulfamuron were also less than the method LOD in all samples of polished rice, bran, and hulls processed from rice grain bearing nonquantifiable orthosulfamuron residues. Processing factors could not be calculated because residues were below the LOD in/on the RAC and the processed commodities.

The maximum theoretical concentration factor for rice is 8x (OPPTS GLN 860.1520; Table 1). According to Table 3 of OPPTS 860.1520, the theoretical concentration factors for rough rice grain commodities are 5.0x for hulls and 7.7x for bran.

Conclusions. The submitted rice processing study is acceptable. Residues of orthosulfamuron did not concentrate in samples of polished rice, bran, and hulls processed from rice grain treated at 3x and bearing nonquantifiable orthosulfamuron residues. These data indicate that tolerances for the processed commodities of rice are not needed. Although no storage stability data for processed commodities were submitted, none are needed. The processed commodities were stored frozen for up to 1.8 months. In storage stability studies conducted on rice grain and straw, residues were stable for up to 12 months. These data will be translated to the processed commodities of rice.

860.1650 Submittal of Analytical Reference Standards

Analytical standards for orthosulfamuron are not currently available in the National Pesticide Standards Repository (electronic communication, D. Wright, BEAD to D. Dotson, HED, 9/13/06). Analytical reference standards of orthosulfamuron need to be supplied, and supplies must be replenished as requested by the Repository. The reference standards should be sent to the Analytical Chemistry Lab, to the attention of either Theresa Cole or Frederic Siegelman at the following address:

USEPA
National Pesticide Standards Repository/Analytical Chemistry Branch/OPP
701 Mapes Road
Fort George G. Meade, MD 20755-5350

Note that the mail will be returned if the extended zip code is not used.

860.1850 Confined Accumulation in Rotational Crops

Study with [^{14}C-U-phenyl]orthosulfamuron (PH label) (46578988.der.doc)

Isagro S.p.A. submitted a confined rotational crop study with [^{14}C-U-phenyl]orthosulfamuron (PH label). The radiolabeled test substance was mixed with acetonitrile/water and applied micro-dropwise to sandy loam soil in plastic pots, maintained outdoors, at a nominal rate of 0.067 lb ai/A. Carrot (root vegetable), lettuce (leafy vegetable), and wheat (small grain) were planted in the treated soil as representative rotational crops at plantback intervals (PBIs) of approximately 30, 120, and 365 days. The in-life and analytical phases of the study were conducted at Isagro Ricerca (Novara, Italy).

Total radioactive residues (TRR) accumulated at ≥0.01 ppm in carrot top and wheat forage rotated crops planted 33/29 and 128/121 days, and wheat straw rotated crop planted 29, 121, and 365 days after a single application of [^{14}C-U-phenyl]orthosulfamuron (PH label) to bare soil at 0.073 lb ai/A. TRR were below 0.01 ppm in carrot root, lettuce, and wheat grain rotated crop matrices at all plantback intervals (PBIs), and in carrot tops and wheat forage planted at the 373/365-day PBI. In general, TRR were highest at the ~30 or 120-day PBI, and greatly reduced at the ~365-day PBI. Residues in carrot tops were 0.0442 ppm at the 33-day PBI, 0.0368 ppm at the 128-day PBI, and 0.0063 ppm at the 373-day PBI; residues in wheat forage were 0.0286 ppm at the 29-day PBI, 0.0310 ppm at the 121-day PBI, and 0.0019 ppm at the 365-day PBI; and residues in wheat straw were 0.5763 ppm at the 29-day PBI, 0.8730 ppm at the 121-day PBI, and 0.1458 ppm at the 365-day PBI.

Rotated crop matrices with TRR>0.01 ppm were extracted (carrot tops and wheat forage, 33/29- and 128/121-day PBIs, and wheat straw, all PBIs). The majority of the radioactivity (72-94% TRR) was extracted from the rotated crop matrices using ACN/ammonium bicarbonate; small amounts of radioactivity (1-5% TRR) were subsequently released with acetone. The ACN extracts were partitioned into DCM, ethyl acetate and aqueous soluble phases for metabolite analysis. The majority of the extractable residue was aqueous soluble. Nonextractable residues

in the extracted crop matrices were <0.01 ppm in carrot tops and wheat forage, and 0.031-0.074 ppm (7-21% TRR) in wheat straw; nonextractable residues were partially characterized as cellulose and lignin (see below) and accountabilities ranged from 89 to 101%. The extraction procedures extracted sufficient residues from all PBIs. Metabolites were quantitated and identified by co-chromatography with the respective radiolabeled standard using normal and reverse phase TLC.

Total identified residues ranged from 51% to 76% TRR in rotated carrot tops, wheat forage, and wheat straw. Parent orthosulfamuron, was only identified in rotated wheat straw (all PBIs) at trace levels (<1% TRR; 0.001-0.004 ppm).

The major metabolite identified in rotated crop matrices was DBS-acid. DBS-acid accounted for 63.2% and 75.7% TRR (0.028 ppm) in carrot tops from the 33- and 128-day PBIs, respectively; 50.8% and 51.1% TRR (0.015-0.016 ppm) in wheat forage from the 29- and 121-day PBIs, respectively; and 63.7%, 65.8%, and 44.8% TRR (0.066-0.575 ppm) in wheat straw from the 29-, 121-, and 365-day PBIs, respectively. DBS-amide was identified as a minor metabolite in wheat forage and straw accounting for 9.2-9.8% TRR (0.003 ppm) in wheat forage from the 29- and 121-day PBIs, and 3.2-4.1% TRR (0.005-0.028 ppm) in wheat straw from all PBIs; DBS-amide was not identified in carrot tops. DB-amine was identified as a minor residue present only in wheat straw (<1-2.6% TRR; 0.004-0.005 ppm).

An unknown metabolite, characterized as a conjugate of DBS-acid, was determined to be a significant residue in wheat forage and accounted for 28.2% TRR (0.008 ppm) at the 29-day PBI and 19.2% TRR (0.006 ppm) at the 121-day PBI. Unknown 2 was found in carrot tops (1.9-6.5% TRR, ≤0.003 ppm) and wheat straw (5.4-8.6% TRR, 0.008-0.068 ppm) at minor levels. Another unknown metabolite, characterized as two N-glucosides of hydroxylated DB-amine, was determined to be a minor residue in carrot tops (3.8-4.7% TRR, 0.002 ppm), wheat forage (5.9-6.5% TRR, 0.002 ppm), and wheat straw (4.2-5.7% TRR, 0.008-0.050 ppm). The remaining extractable residues were characterized as one or two unknowns in the aqueous phase present at <0.01 ppm in carrot tops and wheat forage and ≤0.02 ppm in wheat straw, and a single unknown in the organic phases present at <0.01 ppm in wheat straw.

Nonextractable residues were partially characterized as cellulose- and lignin-bound residues accounting for ~7-8% TRR in carrot tops (33- and 128-day PBIs), and 5-11% TRR in wheat straw (all PBIs); the uncharacterized nonextractable residues represented <0.05 ppm in these rotated crop matrices.

Study with [^{14}C-5-pyrimidinyl]orthosulfamuron (PY label) (46578966.der.doc)

Isagro S.p.A. submitted a confined rotational crop study with [^{14}C-5-pyrimidinyl]orthosulfamuron (PY label). The radiolabeled test substance was mixed with acetonitrile:water and applied micro-dropwise to sandy loam soil in plastic pots, maintained outdoors, at a nominal rate of 0.067 lb ai/A. Carrot (root vegetable), lettuce (leafy vegetable), and wheat (small grain) were planted in the treated soil as representative rotational crops at plantback intervals (PBIs) of approximately 30, 120, and 365 days. The in-life and analytical phases of the study were conducted at Isagro Ricerca (Novara, Italy).

Total radioactive residues (TRR) accumulated at ≥0.01 ppm in carrot top and wheat straw rotated crops planted 42/29, 127/121, or 376/365 days following treatment of the soil. TRR were below 0.01 ppm in carrot root, lettuce, wheat forage, and wheat grain rotated crop matrices at all plantback intervals (PBIs). Based on the carrot top and wheat straw TRR, TRR were highest at the ~120-day PBI. Residues were 0.0229 and 0.1090 ppm at the 42/29-day PBI, 0.0401 and 0.1224 ppm at the 127/121-day PBI, and 0.0299 and 0.0951 ppm at the 376/365-day PBI in carrot tops and wheat straw, respectively. In the other crop matrices with very low TRR, the TRR appear to decline with later PBIs.

Rotated crop matrices with TRR>0.005 ppm were subjected to residue characterization. The majority of the radioactivity (57-89% TRR) was extracted from the rotated crop matrices using ACN/ammonium bicarbonate. Extracts containing >0.01 ppm (carrot tops and wheat straw, all PBIs), were partitioned into DCM, ethyl acetate and aqueous soluble phases for metabolite analysis. The majority of the extractable residue in carrot tops was organosoluble, while the majority of the extractable residue in wheat straw was aqueous soluble. Nonextractable residues in the extracted crop matrices were <0.01 ppm in carrot tops, lettuce, wheat forage, and wheat grain, and <0.04 ppm in wheat straw; accountabilities ranged from 95% to 114%. The extraction procedures released sufficient residues from all PBIs. Metabolites (and the absence of the parent) were quantitated and identified by co-chromatography with the respective radiolabeled standard using normal and reverse phase TLC.

Only carrot top and wheat straw extracts contained sufficient radioactivity for metabolite analysis; total identified residues ranged from 58% to 86% TRR. Parent orthosulfamuron was not identified in rotated carrot tops or wheat straw at any PBI. The major, and only, metabolite identified in rotated crop matrices was DOP urea. DOP urea accounted for 80.4%, 75.1%, and 86.3% TRR (0.018-0.030 ppm) in carrot tops from the 42-, 127-, and 376-day PBIs, respectively. DOP urea accounted for 75.1%, 63.1%, and 58.0% TRR (0.055-0.082 ppm) in wheat straw from the 29-, 121-, and 365-day PBIs, respectively. The remaining extractable residues in carrot tops were characterized as two unknowns in the ethyl acetate phase, each present at <0.01 ppm.

Nonextractable residues were further characterized as cellulose and lignin bound residues accounting for ~5-9% TRR in carrot tops (all PBIs), ~13-18% TRR in 29- and 121-day PBI wheat forage, ~8-13% TRR in wheat straw (all PBIs), and ~21-26% TRR in wheat grain (all PBIs). The uncharacterized nonextractable residues represented <0.03 ppm in these rotated crop matrices.

Conclusions. The nature of the residue in rotational crops is adequately understood. TRR ranged from 0.0007 to 0.8730 ppm in/on representative rotational crop commodities planted at various plantback intervals following treatment of soil with [^{14}C]orthosulfamuron at a 1x treatment rate. As with the rice metabolism study, the parent was identified as a minor component along with other metabolites. Residues of DBS acid and DOP urea were found in carrot tops, wheat forage, and wheat straw. Wheat forage and straw are animal feed items only, however. In carrot tops, the highest residue level for either DBS acid or DOP urea was only 0.0301 ppm (DOP urea at the 127-day PBI). Tolerances are not needed for rotational crops; therefore, the residues of concern in rotational crops are not being determined at the present time.

860.1900 Field Accumulation in Rotational Crops

Field rotational crop studies were not submitted and none are required at this time. Based on the results of the confined rotational crop studies, it is permissible to rotate to any crop after 30 days.

860.1550 Proposed Tolerances

The proposed tolerance expression is in terms of orthosulfamuron *per se*. The Agency has determined the tolerance expression based on review of the metabolism and confined rotational crop studies. No Codex maximum residue limits (MRLs) have been established for residues of orthosulfamuron on any crops at this time. A summary of the tolerance recommendations is presented in Table 8. The recommended tolerances were derived without the aid of the Tolerance/MRL Harmonization Spreadsheet because all samples treated at a 1x application rate bore residues below the LOQ of 0.05 ppm.

Table 8. Tolerance Summary for Orthosulfamuron.

Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments; *Correct Commodity Definition*
Rice, grain	0.05	0.05	
Rice, straw	0.05	0.05	

List of Attachments:

Attachment A: International Residue Limit Status Sheet
Attachment B Chemical Name and Structure Table
Attachment C: C. Stafford, Review of Proposed Tolerance Enforcement Method and ILV Study for Orthosulfamuron, 1/31/2007.

Attachment A: International Residue Limit Status Sheet

INTERNATIONAL RESIDUE LIMIT STATUS			
Chemical Name: 1-(4,6-dimethoxypyrimidin-2-yl)-3-[2-(dimethylcarbamoyl) phenyl sulphamoyl] urea	Common Name: Orthosulfamuron (IR5878)	X Proposed tolerance Reevaluated tolerance Other	Date: 5/5/06

Codex Status (Maximum Residue Limits)	U. S. Tolerances
X No Codex proposal step 6 or above Codex proposal step 6 or above for the crops requested	Petition Number: PP#5F6957 DP Barcode: D319264 Other Identifier: IR5878
Residue definition (step 8/CXL): N/A	Reviewer/Branch: C. Swartz/RAB3
	Residue definition: orthosulfamuron, 1-(4,6-dimethoxypyrimidin-2-yl)-3-[2-(dimethylcarbamoyl)phenyl sulphamoyl] urea

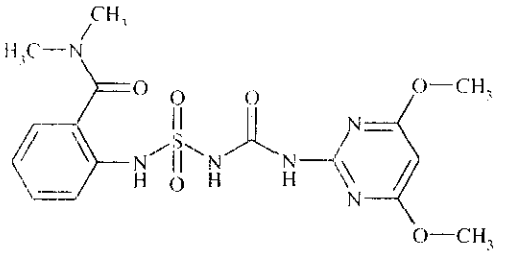
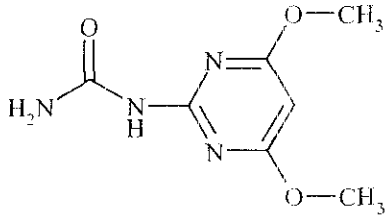
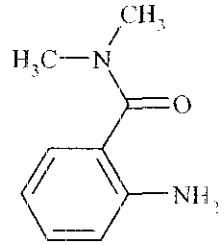
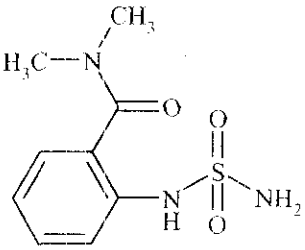
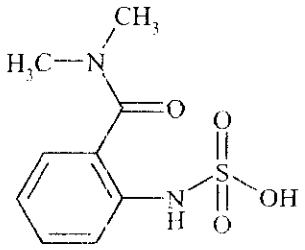
Crop (s)	MRL (mg/kg)	Crop(s)	Tolerance (ppm)
		Rice, grain	0.05
		Rice, straw	0.05

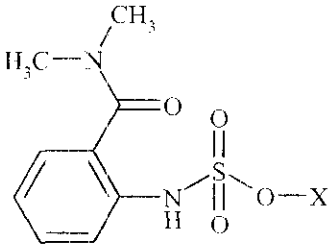
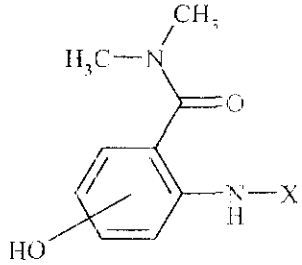
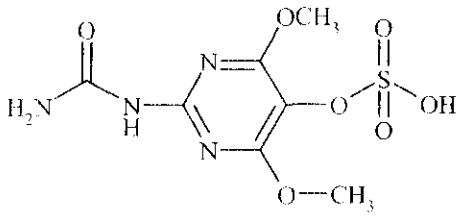
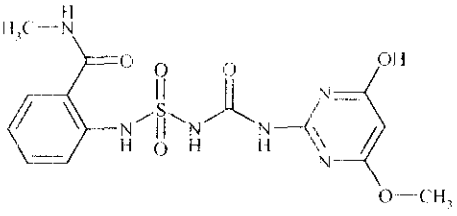
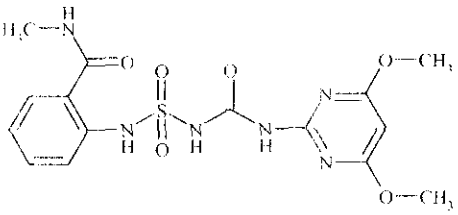
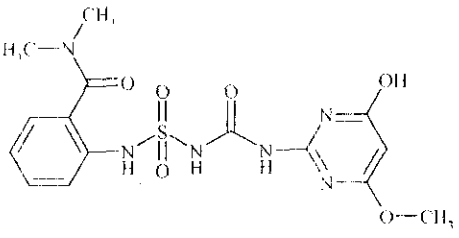
Limits for Canada	Limits for Mexico
X No Limits No Limits for the crops requested	X No Limits No Limits for the crops requested
Residue definition N/A	Residue definition: N/A

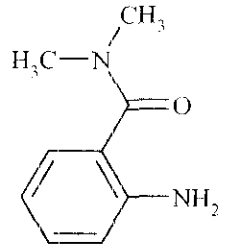
Crop(s)	MRL (mg/kg)	Crop(s)	MRL (mg/kg)

Notes/Special Instructions: S. Funk, 05/07/2006

Attachment B: Chemical Name and Structures of Metabolites Identified in the Rice Metabolism, Goat Metabolism, and Confined Accumulation Studies

Identification of Compounds from the Rice Metabolism, Goat Metabolism, and Confined Rotational Crop Studies (MRIDs 46578961, 46578962, 46578963, 46578966, and 46578988)		
Common name/code [Matrix]	Chemical name	Chemical structure
Orthosulfamuron [Rice grain and straw] [Rotated wheat straw] [Goat milk, kidney, and liver]	2-[[[[(4,6-dimethoxy-2-pyrimidinyl)-amino]carbonyl]amino]sulfonyl]amino]-N,N-dimethylbenzamide	
DOP urea [Rice grain and straw] [Rotated carrot tops and wheat straw] [Goat liver]	N-(4,6-dimethoxypyrimidin-2-yl)urea	
DB amine [Rice grain and straw] [Rotated wheat straw]	2-amino-N,N-dimethylbenzamide	
DBS amide [Rice grain and straw] [Rotated wheat forage and straw] [Goat milk, kidney, and liver]	2-sulfamoylamino-N, N-dimethylbenzamide	
DBS acid [Rice grain and straw] [Rotated carrot tops and wheat forage and straw] [Goat milk, kidney, and liver]	2-sulfoamino-N,N-dimethylbenzamide	

Identification of Compounds from the Rice Metabolism, Goat Metabolism, and Confined Rotational Crop Studies (MRIDs 46578961, 46578962, 46578963, 46578966, and 46578988)		
Common name/code [Matrix]	Chemical name	Chemical structure
DBS-acid conjugate [Rotated carrot tops and wheat forage and straw]		
Hydroxy-DBS-amine conjugates [Rotated carrot tops and wheat forage and straw]		
Pyr-O-Sulf DOP urea [Goat milk, kidney, and liver]	(4,6-dimethoxy-5-sulfate pyrimidin-2-yl)urea	
N-desm-O-desm IR5878 [Goat milk, kidney, and liver	1-(4-methoxy-6-hydroxypyrimidin-2-yl)-3-[2-(methylcarbamoyl) phenylsulfamoyl]urea	
N-desm IR5878 [Goat milk, kidney, and liver]	1-(4,6-dimethoxypyrimidin-2-yl)-3-[2-(methylcarbamoyl)phenylsulfamoyl]urea	
O-desm IR5878 [Goat milk, kidney, and liver]	1-(4-methoxy-6-hydroxypyrimidin-2-yl)-3-[2-(dimethylcarbamoyl) phenylsulfamoyl]urea	

Identification of Compounds from the Rice Metabolism, Goat Metabolism, and Confined Rotational Crop Studies (MRIDs 46578961, 46578962, 46578963, 46578966, and 46578988)		
Common name/code [Matrix]	Chemical name	Chemical structure
N-desm DB amine [Goat milk, kidney, and liver]	2-amino-N-methylbenzamide	

Attachment C: Review of Proposed Tolerance Enforcement Method and ILV Study

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C., 20460
Analytical Chemistry Branch
701 Mapes Road
Ft. Meade, Maryland 20755-5350

OFFICE OF
PREVENTION, PESTICIDES AND TOXIC
SUBSTANCES

January 31, 2007

MEMORANDUM

SUBJECT: PP#5F6957. Review of Proposed Tolerance Enforcement Method and ILV Study for Orthosulfamuron. PC Code 108209. DP Barcode # D332290. ACB Project # B07-7.

FROM: Charles Stafford, Team Leader
Analytical Chemistry Branch
Biological and Economic Analysis Branch (7503P)

THRU: Frederic L. Siegelman, Chief
Analytical Chemistry Branch
Biological and Economic Analysis Branch (7503P)

TO: Douglas Dotson, Chemist
Registration Action Branch 2 (RAB 2)
Health Effects Division (HED) (7509P)

INTRODUCTION

The Analytical Chemistry Branch (ACB) was requested by HED/RAB 2 to review the food tolerance enforcement method and independent lab validation (ILV) data submitted by ISAGRO USA to support tolerances for the herbicide orthosulfamuron on rice. ACB has reviewed the proposed enforcement method data without a laboratory validation.

ANALYTICAL METHOD(S) AND DOCUMENTATION

MRID #: 47030001- Study Title: Independent Laboratory Validation of the Dr. Specht Laboratories Method for the Determination of IR5878 in Rice. Author: William E. Pruitt. Study Completion Date: January 12, 2007. Performing Laboratory: EN-CAS Analytical Laboratories, Winston-Salem, NC. Sponsor: Mel Graben, ISAGRO USA, Morrisville, NC. Project #: EN-CAS Study 406-0044.

RECOMMENDATIONS

1. The ACB recommends that based on our review of the proposed enforcement method (found as Appendix II in MRID# 47030001) without ACB laboratory validation, the method appears to meet the OPPTS 860.1340 Residue Chemistry Test Guidelines for an acceptable tolerance enforcement method.

2. The ACB recommends that an Agency laboratory validation is not necessary for the following reasons:

a. The method appears well-written and includes detailed instructions.
b. The method appears quick and easy.
c. The recovery data show acceptable recoveries for rice commodities.
d. The method is both quantitative and specific, requiring no independent confirmatory method.

3. The ACB recommends that the Independent Laboratory Validation (ILV) data is acceptable.

4. The ACB recommends that the petitioner be required to submit an analytical reference standard of orthosulfamuron to the EPA National Pesticide Standard Repository as a condition of registration.

COMMENTS

1. Analytical Method Comments:

a. The method estimates LOD = 0.01 ppm and LOQ = 0.05 ppm. Validation of each commodity (rice grain, rice straw and rice green plant) was based on fortification at two levels, the LOQ and 10x LOQ. Average recoveries were within 70 – 120%.

b. Analysis is done by LC/MS/MS. Two multiple reaction monitoring (MRM) ion transitions are monitored during analysis. One MRM transition is used for quantitation, while the second serves as a confirmatory transition. A separate, confirmatory method is not necessary.

2. Independent Laboratory Validation Study Comments:

a. The analytical method was developed by Dr. Specht & Partner Chemische Laboratorien GMBH, Hamburg, Germany and the ILV was performed at EN-CAS Analytical Laboratories, Winston-Salem, NC. The ILV report states that there was no contact between the ILV lab and the sponsor during the method validation. The requirement for ILV lab independence appears to be satisfied.

b. The independent laboratory successfully validated the method in rice grain and rice straw at 0.05 and 0.10 ppm, which correspond to the method's stated LOQ and 2x LOQ. The ILV requirement for method validation at the LOQ and 2x LOQ is satisfied.

c. The independent laboratory achieved acceptable recoveries between 70-120% on the first sample set.

d. The independent laboratory followed the original method as written, with one minor modification. The ILV lab calculated recoveries based on the linear regression equation of the calibration curve, while the original method used a single point calibration. This modification should not appreciably affect results and can be considered an acceptable minor change.

3. An analytical reference standard for orthosulfamuron has not been received by the EPA National Pesticide Standard Repository for distribution to State and Federal regulatory labs.

13544

R142118

Chemical: Orthosulfamuron

PC Code:
108209
HED File Code: 11500 Petition Files Chemistry
Memo Date: 2/14/2007
File ID: DPD332290
Accession #: 000-00-0119

HED Records Reference Center
4/24/2007