UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

DEC 7 1995

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OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

Subject: 264-EUP-00/PP#5G4484. Proposed Temporary Tolerance Request For Isoxaflutole in/on Field Corn Grain. Evaluation of Analytical Method and Residue Data. D214199 & D214212. CBTS#'s 15430 & 15431.

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Rhone-Poulenc Ag Company has proposed temporary tolerances for the preemergent herbicide 5-cyclopropyl-4-isoxazolyl [2-(methylsulfonyl)-4-trifluoromethyl) phenyl] methanone (isoxaflutole, RPA 201772) and its metabolites, 1-(2-methylsulphonyl-4-trifluoromethylphenyl-2-cyano-3-cyclopropyl propane-1,3-dione (RPA 202248) and 2-methylsulphonyl-4-trifluoromethyl benzoic acid (RPA 203328) in/on the raw agricultural commodities as follows:

field corn, grain ---------- 0.1 ppm
field corn, fodder ---------- 0.2 ppm
field corn, forage ---------- 0.2 ppm

The registrant subsequently amended this tolerance request by deleting the requested tolerances for field corn fodder and forage.
The acceptable revised Section F requests a temporary tolerance for field corn, grain.

No documentation was submitted identifying isoxaflutole as the ANSI accepted name for the active ingredient 5-cyclopropyl-4-isoxazolyl [2-(methylsulfonyl)-4-trifluoromethyl) phenyl] methanone, but it will be used in this document for convenience. The chemical name used above is the uninverted chemical abstract name, and can be used in the temporary tolerance expression

if these tolerances are established.

This is the first tolerance request for this chemical.

The contractor, Dynamac Corporation (Contract No. 68-D4-0010), has summarized the submitted data and provided comments. The summary accurately reflects the submitted data, and the comments and conclusions reflect Agency policy.

The registrant identifies this chemical as one of a new class of benzoylisoxazoles which is taken up by the roots and effects the synthesis of quinone by inhibiting the enzyme 4-hydroxyphenyl-pyruvate dioxygenase. Because quinone is required for the biosynthesis of carotenoids, the susceptible grasses and weeds in corn are bleached.

Conclusions

1. The submitted product chemistry studies satisfies the data requirements for this temporary tolerance request. For the permanent tolerance request and once full commercial production has started, the registrant should submit the analysis of 5 batches of the technical grade active ingredient (GLN 62-1).

2a. For the purposes of this temporary tolerance request, the nature of the residue in plants is adequately understood. The major terminal residues of regulatory concern are the parent compound, isoxaflutole (RPA 201772), and its metabolites, 1-(2-methylsulfonyl-4-trifluoromethylphenyl)-2-cyano-3-cyclopropyl propane-1,3-dione (RPA 202248), and 2-methylsulfonyl-4-trifluoromethyl benzoic acid (RPA 203328).

2b. Once the deficiency in Conclusion 7b below is resolved, CBTS will verify the terminal residues of regulatory concern with the metabolism committee.

3a. No livestock metabolism studies were submitted in this petition. The nature of the residue in animals is not understood. However, because of the relatively low acreage (4,990 acres at 125 sites) involved in this requested EUP, and the restriction against feeding forage and fodder to livestock (see conclusion 4a), we will not withhold a favorable recommendation for this requested temporary tolerance.

3b. For a permanent tolerance request, ruminant and poultry metabolism studies will be necessary. Depending on the terminal residues and mass balance results, metabolism studies of separately C-14 labeled benzene and isoxazole rings may be necessary.

4a. The registrant has submitted a revised Section B restricting the use of isoxaflutole to field corn grown for grain only. The proposed use is acceptable for this temporary tolerance request. There is a restriction against feeding treated forage and fodder. This restriction is acceptable because of the low acreage (4,990 acres), multiple sites (125 trials in 15 states), a maximum plot size of 40 acres, a single low use rate (0.1875 lb a.i./A), one year EUP and low residues

expected.

4b. The restrictions against feeding treated forage and fodder to livestock and the use of isoxaflutole on field corn grown for grain only will not be acceptable for a permanent tolerance request. Tolerances for these commodities should be proposed in section F of the permanent tolerance petition.

5a. No feeding studies were submitted in this temporary tolerance request. These studies will not be necessary for the reasons stated in conclusion 4a above.

5b. For the permanent tolerance request and depending on the results of the metabolism studies, feeding studies in both ruminants and poultry may be necessary.

6a. A proposed enforcement method for corn grain, forage and fodder, and a second laboratory validation study has been submitted. These will be submitted to ACL for Agency validation. A successful Agency validation must be completed before a positive recommendation for a permanent tolerance is made.

6b. No proposed enforcement methodology was submitted for meat, milk, and eggs. Depending on the results of the metabolism and feeding studies as stated in conclusions 3b and 5b a proposed enforcement method for meat, milk and eggs may be needed. Any required proposed enforcement method must be validated successfully by the Agency before a positive recommendation for a permanent tolerance can be made. A second laboratory validation of the proposed enforcement method should also be provided.

6c. No radiovalidation of the proposed enforcement method was perform. For the permanent tolerance request, the petitioner should validate the proposed enforcement method using radiolabled samples from the corn and animal metabolism studies.

6d. For the permanent tolerance request, confirmatory methodology should be submitted for the proposed enforcement methods for isoxaflutole in corn and animal commodities.

7a. A storage stability study for radiolabeled samples has been submitted for the samples in acetonitrile. Stability as peak radioactivity was measured. Storage intervals were 0, 96, and 253 days. Isoxaflutole is stable in fodder, but there is breakdown to RPA 202248 in grain starting at 96 days of storage, and probable breakdown (about 12%) in forage at 253 days.

7b. No dates of sample extraction and analysis were submitted for the samples isolated in the plant metabolism study. For the permanent tolerance request, the registrant should submit the dates of sample extraction and analysis.

7c. No storage stability studies have been submitted for field trial residue samples. For this proposed temporary tolerance request, we will translate the results of the storage stability studies for the radiolabelled metabolites. For the proposed permanent tolerance and future submissions,

the registrant should submit a storage stability study for corn grain, forage, fodder, and processed commodities to support the submitted field residue data (a minimum of 15 months).

8a. With a restriction against feeding treated crop to livestock (see Conclusion 4a above), the submitted field residue studies are adequate to support the proposed temporary tolerance of 0.1 ppm in/on corn grain.

8b. The submitted field residue studies are not adequate to support permanent tolerance requests for isoxaflutole and its metabolites in corn grain, forage, and fodder. According to "EPA Guidance on Number and Location of Domestic Crop Field Trials for Establishment of Pesticide Residue Tolerances", June 1994, a minimum of 10 additional field trials, with analyses of 20 addition samples, will be needed for the permanent tolerance request. The field residue trials should be conducted with the 75% DF formulation at the maximum use rate and latest preemergence application time as proscribed in the proposed section B.

8c. Corn grain processing studies were submitted using both the wet and dry-milling methods. No concentration of residues was indicated from this proposed use in corn meal, grits, flour, starch, crude oil and refined oil. With submission of the storage stability studies noted in conclusion 7c above, the results of these studies would be satisfactory for any subsequent proposed permanent tolerance request.

8d. Results of an aspirated grain fraction study was also submitted. The proposed use pattern, and results of the metabolism and processing studies negated the requirement for a study. However the study does confirm the prediction that no tolerance on the aspirated grain fraction is necessary for this proposed use.

9. No confined or field rotational crop studies were submitted. The proposed label specifies rotational crops can be planted the season following use in corn. No studies will be necessary for this proposed use. For the permanent tolerance request, confined crop rotations will be necessary, and, depending on these results, field
rotational crop studies and proposed tolerances for inadvertent residues may be necessary.

10. There are no Codex, Canadian, or Mexican maximum residue limits for residues of isoxaflutole or its metabolites in corn commodities. A copy of the International Residue Limit Status sheet is attached.

Recommendation:

Tox considerations permitting, we can recommend for this requested temporary tolerance for field corn grain at 0.1 ppm.

For the permanent tolerance request the petitioner should provide the data requested in

conclusions 1, 3b, 4b, 5b, 6a, 6b, 6c, 6d, 7b, 7c, 8b, 8c, and 9. These deficiencies are summarized as follows:

Analysis of 5 batches of the technical grade active ingredient (GLN 62-1).

Ruminant and poultry metabolism studies. Metabolism studies using separately C-14 labeled benzene and isoxazole rings may be necessary.

Permanent tolerances proposed for treated corn forage (silage) and fodder.

Feeding studies in ruminants and poultry may be required.

A successful Agency validation must be completed for proposed enforcement methodology.

A proposed enforcement method and a second laboratory validation may be required for meat, milk, and eggs.

Validate all proposed enforcement methodology using radiolabeled samples from corn and animal metabolism studies.

Provide confirmatory methodology for the proposed enforcement methods for isoxaflutole in corn and animal commodities. Alternatively, show that current pesticides with established tolerances on corn, animal, milk and egg commodities do not interfere with the proposed enforcement methods.

Provide the dates of sample extraction and analysis for samples reported in the corn metabolism study.

Submit a storage stability study for corn grain, forage, fodder, and processed commodities to support the submitted field residue data (a minimum of 15 months) as well as future submissions.

Additional field residue trials should be conducted using the 75% DF formulation at the maximum use rate and latest preemergence application time as proscribed in the proposed section B.

Provide confined crop rotation studies, field rotation studies and proposed tolerances for inadvertent residues as necessary.

Attachment 1: Review of Product Chemistry Data (Subdivision D), GLNs 61 tp 63
Attachment 2: Confidential Appendix
cc with attachments 1 and 2: P.Errico, PP#5G4484, RCAB [illegible] F.
cc without attachment 2: DRES, Circu
RDI: PErrico, 11/07/95: MMetzger, 11/27/95
7509C:CBTS:PErrico:pve:Rm 804L:CM#2:305-7329:11/29/95

(CBTS No. 15431 and 15430; DP Barcodes D214199 and D214212)

TEMPORARY TOLERANCE PETITION (PP#5G04484) AND EXPERIMENTAL USE PERMIT FOR USE OF ISOXAFLUTOLE ON FIELD CORN

August 29, 1995

Contract No. 68-D4-0010

Submitted to:
U.S. Environmental Protection Agency
Arlington, VA

Submitted by:
Dynamac Corporation
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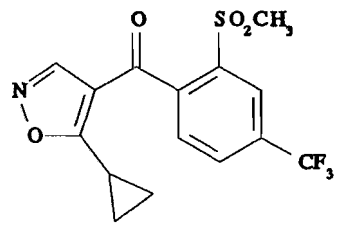
ISOXAFLUTOLE



TEMPORARY TOLERANCE PETITION (PP#5G04484) AND EXPERIMENTAL USE PERMIT FOR USE OF ISOXAFLUTOLE ON FIELD CORN

(CBTS NO. 15431; DP BARCODES D214199 AND D214212)

INTRODUCTION

Rhone-Poulenc Ag Company has submitted an application for an experimental use permit (EUP) and a petition for temporary tolerances for the herbicide isoxaflutole [(RPA 201772); Chemical Abstracts name: 5-cyclopropyl-4-isoxazolyl[2-(methylsulfonyl)-4-trifluoromethyl)phenyl]methanone; IUPAC name: 5-cyclopropyl-4-(2-methylsulfonyl-4-trifluoromethylbenzoyl) isoxazole] in/on field corn. The petitioner is proposing the establishment of temporary tolerances for the combined residues of isoxaflutole and its metabolites 1-(2-methylsulfonyl-4-trifluoromethylphenyl)-2-cyano-3-cyclopropyl propane-1,3-dione (RPA 202248) and 2-methylsulfonyl-4-trifluoromethyl benzoic acid (RPA 203328) as follows:

Corn, field, grain	0.1 ppm
Corn, field, fodder	0.2 ppm
Corn, field, forage	0.2 ppm

Isoxaflutole is a selective herbicide developed by Rhone-Poulenc for preplant and preemergence control of grasses and broadleaf weeds in corn and is a member of a new class of herbicides, the benzoylisoxazoles. The benzoylisoxazole herbicides inhibit 4-hydroxyphenylpyruvate dioxygenase thereby preventing the formation of a quinone required for carotenoid biosynthesis. The emerging or emerged weeds are bleached as the herbicide is taken up by the root system. The residual activity of isoxaflutole remains effective until corn has grown sufficiently to compete with late germinating weeds. No temporary or

permanent tolerances have been established for residues of isoxaflutole in/on any food, feed, or processed commodities.

Associated with this petition are 13 volumes of product and residue chemistry submissions which are evaluated in this document.

DETAILED CONSIDERATIONS

Product Chemistry (1993-1995; MRIDs 43573201-43573208)

The evaluation of product chemistry data associated with the EUP application is included in this document as Attachment I (including Confidential Appendix containing CBI). The review addressed the product chemistry data requirements for the isoxaflutole TGAI. Data submitted for the end-use product (1994; MRIDs 43573209-43573211) are not reviewed in this document.

Proposed Use

The 75% dry flowable (DF) formulation (RPA 201772 WDG brand; EPA File Symbol No. 264-EUP-00) is proposed for a single early preplant or preemergence broadcast application to field corn grown in either conventional, reduced tillage, or no-till crop management systems. The proposed application rates are dependent on application timing and soil type and are listed below:

	Rate (lb ai/A) By Soil Type	
Application Timing	Medium and Heavy Soils	Sandy Soils
Early preplant	0.1289-0.1875	0.0656-0.0938
Preemergence	0.0938-0.1172	0.0469-0.0586

Early preplant application may be made up to 30 days prior to planting. For effective weed control when the pesticide is applied early preplant, the label specifies that treated soil should not be moved out of the row; untreated soil should also not be moved to surface during planting. Application is to be made in a minimum of 10 gal/A using ground equipment and may be made alone or as a tank mix with other herbicides. Restrictions against the grazing of forage or feeding of fodder to livestock and the planting of rotational crops until the following season are proposed.

The residue field trials and processing study associated with this petition were conducted using a 50.8% wettable powder (WP) formulation (EXP30953B) instead of the 75% DF formulation proposed for use under the EUP. The Agency considers DF and WP formulations to be sufficiently similar to allow translation of residue data between them.

The proposed EUP program includes 125 trials in 15 different states (IL, IN, IA, KS, KY, MD, MI, MN, MO, NE, NY, OH, PA, SD, and WI) which together accounted for 90% of the 1991 U.S. field corn production (*1992 USDA Agricultural Statistics*). The maximum number of treated acres at each test site would be 40, with a total maximum of 4,990 treated acres each year. The proposed acreage represents 0.007% of the 1991 U.S. field corn acreage. Isoxaflutole (75% DF) would be applied as a single application, either preplant or preemergence, at up to 0.1875 lb ai/A. The maximum amount of isoxaflutole applied would be 935.625 lb ai, with no more than 170.625 lb ai to be applied in any one state. The proposed label also allows the tank mixing of formulations containing atrazine, metolachlor, acetochlor, alachlor and demethenamid. These active ingredients have established tolerances for field corn grain, fodder and forage.

Comments

The proposed use directions are adequate for purposes of this EUP and temporary tolerance petition. Due to the limited number of acres involved with this EUP, the proposed restrictions against the grazing of forage or feeding of fodder to livestock are acceptable.

The registrant has submitted an acceptable amended Section B restricting the proposed use to field corn grown for grain only. The use of this product on field corn grown for silage is prohibited.

For establishment of permanent tolerances, feeding and grazing restrictions on forage and fodder are not considered practical; the petitioner will need to submit a revised Section B to delete the restrictions against the grazing/feeding of field corn forage (silage) and fodder.

Qualitative Nature of the Residue in Plants

Field corn metabolism (1995; MRID 43573249)

Rhone-Poulenc submitted data depicting the metabolism of [phenyl-^{14}C]isoxaflutole in field corn. The study was initiated in 1993 and was conducted by Rhone-Poulenc (Research Triangle Park, NC). The test substance was prepared by mixing [phenyl-^{14}C]isoxaflutole (specific activity 18.35 mCi/mmol, radiochemical purity 98.7%) with [carbonyl-^{13}C]isoxaflutole and non-labeled isoxaflutole to a final specific activity of 37,600 dpm/μg. The test substance was applied to container-grown field corn as a single preplant incorporated application (PPI) or a single preemergence application (PRE); PPI applications were made immediately prior to planting, and PRE applications were made following planting. We note that on the proposed label, the petitioner specifies that preplant applications be surface applied, and states that weed control will be reduced if untreated soil is moved to the surface during planting. Eight containers were treated for each application method; four at the proposed maximum application rate and four at an exaggerated rate. An additional eight containers served as controls. Containers were constructed from 5-gallon polyethylene

buckets and were placed outside for the duration of the study. Application rates for the PPI mode of treatment were 0.187 lb ai/A (1x the maximum proposed application rate for preplant application) or 0.586 lb ai/A (3x; exaggerated rate). Application rates for the PRE mode of treatment were 0.203 lb ai/A (1.7x the maximum proposed application rate for preemergence application) or 0.960 lb ai/A (8.2x; exaggerated rate). Six seeds were planted in each container; at 21 days after planting, each container was thinned to two plants, one for harvest of forage and one for harvest of fodder and grain.

The petitioner reported that symptoms of phytotoxicity (bleaching and some necrosis) were initially observed in plants from both application types and treatment rates. However, no symptoms were visible 25 days after treatment, and harvest weights for treated plants were similar to those for untreated controls.

Field corn forage samples were collected 41 days posttreatment by defoliating one plant in each container. Plant stems were collected separately by cutting the plant approximately 2 inches above the soil surface. Field corn grain and fodder samples were collected at maturity, 122 and 138 days after treatment. Leaves and ears were collected from each plant 122 days posttreatment, and stems were collected 138 days posttreatment. Immediately after collection, all samples were transported on ice to freezer storage (~-20 C), where they were stored frozen for an unspecified period until analysis.

Total radioactive residues (TRR)

Forage leaf and stem samples were prepared by freezing the samples in liquid nitrogen and then grinding the samples in the presence of dry ice. Grain was removed from the cobs, frozen in liquid nitrogen, and ground in dry ice. Fodder leaves and ear husks were shredded and then ground in dry ice. Fodder stems were homogenized in liquid nitrogen and then ground in dry ice. The cobs were cut and ground in dry ice. Samples of fodder were then prepared by combining ground leaves, husks, stems, shanks, silks, and cobs. Following sample preparation, samples were analyzed in quadruplicate for total radioactive residues (TRR) by liquid scintillation spectroscopy (LSS) following combustion. The limit of quantitation was 0.008 ppm. The TRR in/on field corn forage, fodder, and grain is presented below in Table 1. Radioactive residues were nondetectable in control samples of field corn forage, fodder, and grain.

Table 1. Total radioactive residues (TRR) in/on field corn forage, fodder, and grain following a single PPI or PRE application of [phenyl-^{14}C]isoxaflutole.

Matrix	TRR, ppm [^{14}C]isoxaflutole equivalents [a]			
	PPI application		PRE application	
	0.187 lb ai/A (1x)	0.586 lb ai/A (3x)	0.203 lb ai/A (1.7x)	0.960 lb ai/A (8.2x)
Forage	0.198	0.800	0.228	0.491
Fodder	0.149	0.661	0.120	0.528
Grain	0.044	0.152	0.039	0.125

[a] Mean of four determinations.

Detectable radioactive residues were observed in all samples; residues were highest in samples from plants treated at exaggerated rates. Residue levels did not differ greatly between samples receiving the PPI application and samples receiving the PRE application.

Extraction and hydrolysis of residues

The petitioner provided descriptions and a flow chart of the fractionation scheme used in the study. At each step of the extraction procedure, radioactivity in the extract and in the unextracted residues was determined by LSS or combustion/LSS. Because samples of forage, fodder, and grain treated at 1x contained sufficient radioactivity for residue characterization and identification, the petitioner did not extract samples treated at exaggerated rates.

Samples of forage, fodder, and grain were mixed with hexane:ethyl acetate (EtOAc; 9:1, v:v) and filtered; grain samples were centrifuged prior to filtration. This procedure was repeated with acetonitrile (ACN), water (adjusted to pH 5.5 with 0.2 N HCl), and ACN:0.2 N HCl (1:1, v:v; acidic ACN). The water extract was adjusted to pH <2.5 using 2 N HCl and then both the water and acidic ACN extracts were separately partitioned three times with EtOAc. The organic phases were combined. All extracts containing residues greater than 10% of TRR or 0.01 ppm were concentrated under a stream of nitrogen and reserved for analysis by HPLC and/or TLC. The registrant reports that the parent compound, RPA 201772, is readily hydrolyzed at pH 6.5 and above, while it is relatively stable to hydrolysis at a lower pH.

Nonextractable residues remaining after ACN, water, and acidic ACN extraction which accounted for greater than 10% of TRR or 0.01 ppm were subjected to enzyme digestion. The nonextractable residues were digested with cellulase [0.5% solution (w:v) in 100 mM acetate buffer (pH 4.8)] at 37 C for 72 hours (forage) or 120 hours (fodder). The mixture was centrifuged, acidified to pH <2, and partitioned three times with EtOAc.

Characterization and identification of the residues

All extracts containing greater than 10% TRR or 0.01 ppm were analyzed by HPLC and TLC except for grain extracts which were only analyzed by HPLC due to small sample volumes. HPLC analyses were conducted using two systems. System 1 was equipped with a Hypercarb S graphitized column, a UV detector (210, 273, and 287 nm), and a radioisotope detector. The mobile phase consisted of ACN:water (1:1, v:v) containing ammonium acetate and tetrabutylammonium acetate. System 2 was equipped with an Altima C-18 column, a UV detector (210, 273, and 287 nm), and a radioisotope detector. The mobile phase consisted of a gradient of water (adjusted to pH 2.5 with 0.2 N HCl) and ACN changing from 80:20 (v:v) to 10:90 (v:v) over 17 minutes. The representative chromatograms provided indicate that all samples were analyzed using HPLC System 2. Metabolites were identified by co-chromatography with the following standards: isoxaflutole, RPA 202248, and RPA 203328. TLC analyses were conducted on silica-gel GF plates using a toluene:acetone:acetic acid (75:20:5, v:v:v) mobile phase; detection was by a phosphorimager plate scanner. TLC analyses were for qualitative purposes only. Metabolites tentatively identified by chromatographic analysis were confirmed by LC/MS analysis on a system equipped with an Altima C-18 column and an MS operating in the multiple reaction monitoring negative ion mode. Representative HPLC, TLC, and LC/MS chromatograms as well as raw data pertaining to dpm, TRR, %TRR, and ppm calculations were provided; however, no raw data pertaining to HPLC analyses (such as retention times, peak areas, or peak heights) were provided, and none of the peaks in the submitted HPLC chromatograms were labelled.

The petitioner stated that minor peaks other than RPA 203328 and RPA 202248 were observed in some HPLC chromatograms. However, none of these peaks comprised greater than 0.005 ppm.

The distribution and characterization/identification of residues in/on field corn forage, fodder, and grain is presented in Table 2. A summary of the characterized/identified residues is presented in Table 3.

The petitioner adequately characterized/identified the majority (~70-97% TRR; see Table 3) of the radioactive residues in/on field corn forage, fodder, and grain treated with [^{14}C]isoxaflutole either preplant incorporated at 1x the maximum proposed application rate or preemergence at 1.7x the maximum proposed preemergence application rate. The major metabolite was RPA 203328, comprising ~64-91% of TRR (0.029-0.185 ppm). The metabolite RPA 202248 was the only other metabolite identified (up to 7.5% TRR, 0.004 ppm). The parent was not identified in any matrix. The chemical names and molecular structures of these metabolites are depicted in Figure 1.

Table 2. Distribution of residues in/on field corn forage, fodder, and grain following a single PPI application of [phenyl-^{14}C]isoxaflutole at 1x or a single PRE application at 1.7x.

Fraction	% TRR	Ppm	Characterization/identification [a]
PPI Forage (TRR = 0.190 ppm) [b]			
Hexane:EtOAc	1.4	0.003	Not further analyzed (N/A).
ACN	45.3	0.090	HPLC analysis identified: RPA 202248 trace trace RPA 203328 43.2% TRR 0.082 ppm
Water	26.9	0.049	Acidified to pH <2 and partitioned with EtOAc.
EtOAc	22.8	0.042	Combined with EtOAc partition from acidic ACN extraction.
Aqueous	1.4	0.003	N/A.
Acidic ACN	14.5	0.026	Partitioned with EtOAc.
EtOAc	12.6	0.022	Combined with EtOAc partition from water extraction. HPLC analysis identified: RPA 202248 trace trace RPA 203328 28.4% TRR 0.054 ppm
Aqueous	0.6	0.001	N/A.
Nonextractable	12.5	0.023	Subjected to cellulase digestion.
Cellulase digest	5.1	0.010	Acidified to pH <2 and partitioned with EtOAc.
EtOAc	1.5	0.003	HPLC analysis identified: RPA 202248 0.5% TRR 0.001 ppm RPA 203328 1.1% TRR 0.002 ppm
Aqueous	7.6	0.014	N/A.
Solids	1.6	0.003	N/A.
PRE Forage (TRR = 0.204 ppm)			
Hexane:EtOAc	1.4	0.003	N/A.
ACN	68.9	0.144	HPLC analysis identified: RPA 202248 trace trace RPA 203328 67.2% TRR 0.137 ppm
Water	19.1	0.040	Acidified to pH <2 and partitioned with EtOAc.
EtOAc	16.4	0.035	Combined with EtOAc partition from acidic ACN extraction.
Aqueous	0.8	0.002	N/A.
Acidic ACN	5.8	0.012	Partitioned with EtOAc.

(continued; footnotes follow)

Table 2 *(continued)*.

Fraction	% TRR	Ppm	Characterization/identification [a]
EtOAc	4.5	0.010	Combined with EtOAc partition from water extraction. HPLC analysis identified: RPA 202248 trace trace RPA 203328 22.1% TRR 0.045 ppm
Aqueous	0.5	0.001	N/A.
Nonextractable	8.6	0.017	Subjected to cellulase digestion.
Cellulase digest	3.0	0.006	Acidified to pH <2 and partitioned with EtOAc.
EtOAc	1.8	0.004	HPLC analysis identified: RPA 202248 0.5% TRR 0.001 ppm RPA 203328 1.5% TRR 0.003 ppm
Aqueous	2.7	0.005	N/A.
Solids	1.3	0.003	N/A.
PPI Fodder (TRR = 0.160 ppm)			
Hexane:EtOAc	1.7	0.003	N/A.
ACN	17.6	0.028	HPLC analysis identified: RPA 202248 trace trace RPA 203328 17.5% TRR 0.028 ppm
Water	40.9	0.066	Acidified to pH <2 and partitioned with EtOAc.
EtOAc	35.9	0.058	Combined with EtOAc partition from acidic ACN extraction.
Aqueous	4.6	0.007	N/A.
Acidic ACN	13.1	0.021	Partitioned with EtOAc.
EtOAc	13.8	0.021	Combined with EtOAc partition from water extraction. HPLC analysis identified: RPA 203328 49.4% TRR 0.079 ppm
Aqueous	2.3	0.004	N/A.
Nonextractable	11.6	0.018	Subjected to cellulase digestion.
Cellulase digest	6.5	0.010	Acidified to pH <2 and partitioned with EtOAc.
EtOAc	2.7	0.004	HPLC analysis identified: RPA 202248 [c] trace trace RPA 203328 [c,d] 1.3% TRR 0.002 ppm
Aqueous	1.9	0.003	N/A.
Solids	9.7	0.015	N/A.
PRE Fodder (TRR = 0.113 ppm)			
Hexane:EtOAc	1.5	0.002	N/A.

(continued; footnotes follow)

Table 2 *(continued).*

Fraction	% TRR	Ppm	Characterization/identification [a]
ACN	20.2	0.023	HPLC analysis identified: RPA 203328 20.4% TRR 0.023 ppm
Water	40.9	0.045	Acidified to pH <2 and partitioned with EtOAc.
EtOAc	29.0	0.033	Combined with EtOAc partition from acidic ACN extraction.
Aqueous	6.8	0.007	N/A.
Acidic ACN	14.1	0.017	Partitioned with EtOAc.
EtOAc	11.6	0.013	Combined with EtOAc partition from water extraction. HPLC analysis identified: RPA 203328 40.7% TRR 0.046 ppm
Aqueous	2.0	0.002	N/A.
Nonextractable	14.2	0.017	Subjected to cellulase digestion.
Cellulase digest	6.5	0.007	Acidified to pH <2 and partitioned with EtOAc.
EtOAc	3.2	0.003	HPLC analysis identified: RPA 202248 [c] trace trace RPA 203328 [c,d] 2.7% TRR 0.003 ppm
Aqueous	2.0	0.002	N/A.
Solids	11.8	0.013	N/A.
PPI Grain (TRR = 0.053 ppm)			
Hexane:EtOAc	0.0	0.000	N/A.
ACN	60.7	0.032	Combined with EtOAc partitions from water and acidic ACN extracts.
Water	19.1	0.010	Acidified to pH <2 and partitioned with EtOAc.
EtOAc	17.5	0.009	Combined with ACN extract and EtOAc partition from acidic ACN extraction.
Aqueous	1.1	0.001	N/A.
Acidic ACN	6.9	0.004	Partitioned with EtOAc.
EtOAc	9.6	0.005	Combined with ACN extract and EtOAc partition from water extraction. HPLC analysis identified: RPA 202248 7.5% TRR 0.004 ppm RPA 203328 66.0% TRR 0.035 ppm
Aqueous	1.2	0.001	N/A.
Nonextractable	7.5	0.004	N/A.
PRE Grain (TRR = 0.043 ppm)			
Hexane:EtOAc	0.0	0.000	N/A.

(continued; footnotes follow)

Table 2 *(continued).*

Fraction	% TRR	Ppm	Characterization/identification [a]
ACN	59.0	0.025	Combined with EtOAc partitions from water and acidic ACN extracts.
Water	17.5	0.007	Acidified to pH <2 and partitioned with EtOAc.
EtOAc	12.9	0.005	Combined with ACN extract and EtOAc partition from acidic ACN extraction.
Aqueous	1.3	<0.001	N/A.
Acidic ACN	6.7	0.003	Partitioned with EtOAc.
EtOAc	4.2	0.002	Combined with ACN extract and EtOAc partition from water extraction. HPLC analysis identified: RPA 202248 trace trace RPA 203328 67.4% TRR 0.029 ppm
Aqueous	0.6	<0.001	N/A.
Nonextractable	10.4	0.004	N/A.

[a] Extracts were analyzed by HPLC, and metabolite identifications were confirmed by LC/MS, unless otherwise indicated. The presence of RPA 203328 in each extract, except those of grain samples, was confirmed by TLC unless otherwise indicated.

[b] The petitioner re-determined TRR prior to residue extraction; these re-determined TRR differed slightly from the values reported in Table 1.

[c] This metabolite was not detected in LC/MS analysis of this extract.

[d] This metabolite was not detected in TLC analysis of this extract.

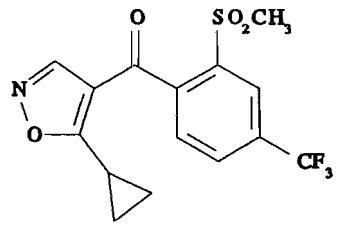
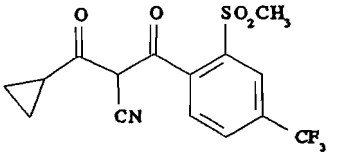
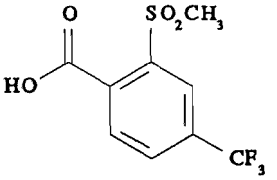
Table 3. Summary of radioactive residues characterized/identified in/on field corn forage, fodder, and grain following a single PPI application of [^{14}C]isoxaflutole at 1x or a single PRE application at 1.7x.

Metabolite/ Fraction	Forage				Fodder				Grain			
	PPI		PRE		PPI		PRE		PPI		PRE	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
Identified												
Isoxaflutole	ND [a]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
RPA 202248	0.5	0.001	0.5	0.001	Trace	Trace	Trace	Trace	7.5	0.004	Trace	Trace
RPA 203328	72.6	0.138	90.7	0.185	68.1	0.109	63.7	0.072	66.0	0.035	67.4	0.029
Total Identified	**73.2**	**0.139**	**91.2**	**0.186**	**68.1**	**0.109**	**63.7**	**0.072**	**73.6**	**0.039**	**67.4**	**0.029**
Characterized												
Hexane:EtOAc	1.4	0.003	1.4	0.003	1.7	0.003	1.5	0.002	0.0	0.000	0.0	0.000
Aqueous [b]	8.9	0.017	4.1	0.008	8.2	0.013	10.4	0.012	2.3	0.001	1.8	0.001
Total Characterized/ Identified	**83.7**	**0.159**	**96.6**	**0.197**	**78.10**	**0.125**	**76.1**	**0.086**	**75.5**	**0.040**	**69.8**	**0.030**
Nonextractable	1.6	0.003	1.3	0.003	9.7	0.015	11.8	0.013	7.5	0.004	10.4	0.004

[a] ND = Not detected.

[b] Combined aqueous extracts remaining after EtOAc partitions.

Figure 1. Chemical structures of isoxaflutole and its metabolites in field corn (MRID 43573249).

Common Name Chemical Name	Structure	Substrate
Isoxaflutole; RPA 201772 5-cyclopropyl-4-(2-methylsulfonyl-4-fluoromethyl)benzoyl isoxazole		
RPA 202248 1-(2-methylsulfonyl-4-trifluoromethylphenyl)-2-cyano-3-cyclopropyl propane-1,3-dione		Field corn forage, fodder [a], and grain
RPA 203328 2-methylsulfonyl-4-trifluoromethyl benzoic acid		Field corn forage, fodder, and grain

[a] Detected in trace quantities.

Storage stability

Samples and extracts were stored frozen at -20 C prior to analysis. The petitioner only provided dates of sample treatment and harvest. Because no dates of sample combustion, extraction, or analysis were provided, sample storage intervals could not be determined.

The petitioner provided data to demonstrate the storage stability of isoxaflutole and RPA 202248. Samples of processed forage, fodder, and grain were fortified with [^{14}C]isoxaflutole dosing solution, which also contained RPA 202248, stored frozen at -20 C, and extracted and analyzed using the procedures described above for the metabolism study after 0, 96, and 253 days of storage. The results of the storage stability study are presented in Table 4.

Table 4. Storage stability of fortified residues of [^{14}C]isoxaflutole and RPA 202248 in/on field corn forage, fodder, and grain.

Matrix	Storage interval, days	Percent of total peak area		
		Isoxaflutole	RPA 202248	RPA 203328
Dosing solution	0 (prior to fortification)	78.4	21.6	0.0
Forage	0	79.6	20.4	0.0
	96	74.4	25.6	0.0
	253	65.2	34.1	0.8
Fodder	0	77.5	22.6	0.0
	96	69.1	30.9	0.0
	253	78.4	21.6	0.0
Grain	0	72.7	27.3	0.0
	96	51.3	48.7	0.0
	253	58.0	42.0	0.0
Dosing solution	253	72.8	27.2	0.0

To demonstrate stability in extracts, the petitioner re-analyzed the extracts of the 0-day samples after 96 days of storage; the extracts were found to be stable in ACN for 96 days of storage. The submitted storage stability data indicate that isoxaflutole is generally stable in field corn fodder, but there is breakdown to RPA 202248 in grain starting at 96 days and some breakdown (about 12%) in forage at 253 days.

For the purposes of this temporary tolerance petition and EUP, no additional storage stability data are required to support the field corn metabolism study. For establishment of permanent tolerances, the petitioner must submit the dates of sample extraction and analysis so that storage intervals can be determined. In addition, the petitioner must submit data demonstrating the stability of RPA 203328 in field corn matrices over the longest interval that samples were stored.

Radiovalidation of the proposed enforcement method

Radiovalidation of the proposed enforcement method using samples from the submitted plant metabolism studies was not conducted. This is not required for the purposes of this EUP and temporary tolerance petition; however, radiovalidation data of field incurred residues are required for establishment of permanent tolerances.

Radiovalidation of submitted proposed enforcement methodology for animal, milk and egg commodities will also be needed for the permanent tolerance request. Radiolabeled samples from the animal metabolism studies should be used.

Justification of the ^{14}C label position (1995; MRID 43573250)

The petitioner submitted a discussion of their rationale for conducting the metabolism study with isoxaflutole labelled in the phenyl ring. The petitioner stated that they conducted numerous preliminary metabolism studies, with plants, soil, and animals, in which isoxaflutole was labelled in the phenyl ring, in the isoxazole ring, or at the carbonyl carbon. These preliminary studies were not conducted under GLPs. Based on these studies, the petitioner observed that RPA 203328 is the major metabolite, that the isoxazole ring is highly unstable and hydrolyzes rapidly to form RPA 202248, and that the cyclopropyl moiety metabolizes/degrades to cyclopropane carboxylic acid. The petitioner notes that the opening of the isoxazole ring to form RPA 202248 was observed in plants, soil, and rats, and that the half-life for isoxaflutole in both clay and sandy soils is less than 24 hours. The petitioner believes that metabolism/degradation of RPA 202248 may occur via two pathways. In the first, RPA 203328 and an a-cyanomethyl cyclopropylketone would be formed from reaction of RPA 202248 with a strong nucleophile. In alkaline conditions, the cyclopropyl ketone would break down to cyclopropane carboxylic acid. In acidic conditions, the cyclopropyl ketone would undergo ring opening to form the amide. In the second pathway, RPA 202248 would break down to a-cyanoacetophenone and cyclopropane carboxylic acid via attack by a weaker nucleophile (such as cysteine or glutathione). The petitioner stated that both pathways were observed in plants during 7-day kinetic studies. The petitioner also stated that when plant studies were conducted with the ^{14}C-label in the isoxazole ring, $^{14}CO_2$ was released, indicating loss of the cyano group.

The petitioner noted that cyclopropane carboxylic acid was observed as a reaction product in preliminary hydrolysis and plant metabolism studies, and that it has been shown to be a metabolite/degradate of several pesticides containing a cyclopropyl moiety, including synthetic pyrethroids. The petitioner cited several published papers (which were attached to the submission) that demonstrated that cyclopropane carboxylic acid is integrated into biomolecules, conjugated to form polar compounds, or broken down via ring opening.

The petitioner concluded that the metabolism of isoxaflutole results in the formation of RPA 203328 and cyclopropane carboxylic acid, and that no additional information would be obtained from a study in which the molecule was labelled in the isoxazole ring or the cyclopropyl ring, due to the short half-life of the isoxazole ring and the metabolism/degradation of the cyclopropyl ring into compounds of little toxicological significance.

Comments

The qualitative nature of the residues in/on field corn forage, fodder, and grain is adequately understood for purposes of this EUP and temporary tolerance petition. The petitioner's discussion regarding use of isoxaflutole labelled in the phenyl ring as the test substance (as opposed to isoxaflutole labelled in the isoxazole and/or cyclopropyl ring(s)) is acceptable for purposes of this EUP and temporary tolerance petition only. In the metabolism study, in

which field corn was treated with a single preplant incorporated (PPI) application of [phenyl-^{14}C]isoxaflutole at 0.187 lb ai/A (1x) or a single preemergence (PRE) application at 0.203 lb ai/A (1.7x), a significant portion (~70-97%) of the total radioactive residues (TRR) in/on field corn commodities was sufficiently characterized and identified. The major identified metabolite was RPA 203328, comprising ~73% and 91% of TRR (0.138 and 0.185 ppm) in forage, ~68% and 64% of TRR (0.109 and 0.072 ppm) in fodder, and ~66% and 67% of TRR (0.035 and 0.029 ppm) in grain from PPI and PRE applications, respectively. The metabolite RPA 202248 was the only other metabolite identified (up to 7.5% TRR, 0.004 ppm). The parent was not identified in any matrix.

For establishment of permanent tolerances, the qualitative nature of the residue in field corn will be considered to be adequately understood provided that supporting storage stability data as well as radiovalidation data are submitted. The petitioner must submit the dates of sample extraction and analysis so that storage intervals can be determined. In addition, the petitioner must submit data demonstrating the stability of RPA 203328, the major metabolite found in field corn matrices, over the longest interval that samples from this corn metabolism study were stored. Because isoxaflutole is translocated and metabolized in field corn commodities, the petitioner is required to conduct radiovalidation of the proposed enforcement method using samples from the corn metabolism study. CBTS reserves the right to re-examine in the future the issue concerning the appropriate radiolabelling of the test substance.

Qualitative Nature of the Residue In Animals

No animal metabolism studies were included in this petition. Animal metabolism data will not be required for purposes of this EUP and temporary tolerance petition due the label restrictions against the feeding of treated forage and fodder to livestock and the limited number of acres involved.

Acceptable nature of the residue studies in ruminants and poultry will be required for the establishment of permanent tolerances. If there are significant isoxaflutole metabolites identified in corn which are not identified in animals, then CBTS may also require metabolism studies using these metabolites.

Residue Analytical Methods

Residue data collection - field corn (1995; MRIDs 43573253 and 43588003)

Samples of field corn commodities from the field trial and processing studies submitted with this petition were analyzed at Hazleton Wisconsin, Inc. (Madison, WI) using a modification of the GC/MSD method entitled "Analytical Method for the Determination of Residues of RPA 201772, RPA 202248, and RPA 203328 in Maize Grain and Fodder." The method involves hydrolysis of residues of isoxaflutole to RPA 202248, conversion of RPA 202248 residues to RPA 203328, and then derivatization of RPA 203328 to a methyl ester for GC

analysis. Briefly, field corn commodity samples are ground in dry ice. Residues are extracted by homogenizing ground samples three times with methanol. Crude and refined oil samples are mixed with hexane prior to methanol extraction. A 2% sodium hydroxide solution is added to the combined extracts to hydrolyze isoxaflutole to RPA 202248; the mixture is left at room temperature for at least one hour. The methanol is removed by rotary evaporation, and the extract is salinized with a saturated sodium chloride solution and sequentially washed with dichloromethane (twice) and petroleum ether. The aqueous extract is acidified with concentrated hydrochloric acid to ~pH 1.0, partitioned into dichloromethane, and drained through anhydrous sodium sulfate. The partitioning is repeated two more times. The dichloromethane phase is then evaporated to dryness and hydrolyzed with 1 M methanolic sodium hydroxide solution at 100 C for one hour to convert RPA 202248 residues to RPA 203328. Water is added, and the pH is lowered to ~1.0 using concentrated hydrochloric acid. The hydrolysate is partitioned into dichloromethane, and the dichloromethane phase is evaporated to dryness. The residue is re-dissolved in dichloromethane and derivatized to the methyl ester RPA 204497 with a diazomethane solution at 30 C for one hour. Acetic acid is added to destroy any excess diazomethane, and the derivatized extract is brought to volume with dichloromethane and analyzed by GC/MSD in the selective ion mode. Residues are reported as ppm isoxaflutole equivalents using the molecular weight conversion factor of 1.273. The limit of quantitation is 0.01 ppm.

The petitioner submitted method validation and concurrent method recovery analyses to determine the suitability of this method for data collection purposes. Untreated control samples of field corn (forage, silage, fodder, and grain) and its processed commodities (flour, starch, and crude oil) were separately fortified with isoxaflutole, RPA 202248, and RPA 203328 at 0.01 and 0.05 ppm and analyzed by GC/MSD. These data are presented in Table 5. Raw data, sample calculations, and representative chromatograms were submitted. This proposed enforcement method will be submitted to the Analytical Chemistry Laboratory for method validation.

Table 5. Method validation and concurrent method recovery of isoxaflutole equivalents from samples of untreated field corn and its processed fractions fortified with each analyte and analyzed by GC/MSD.

Matrix Analyte	Method validation		Concurrent method recovery	
	Fortification level, ppm [a]	Percent recovery (Number of samples) [b]	Fortification level, ppm [c]	Percent recovery (Number of samples)
Forage				
Isoxaflutole	0.01, 0.05	74.3-119 (13)	0.01	96.3-118 (8)
RPA 202248	0.01, 0.05	70.8-106 (11)	0.0375	118 (2); 124
RPA 203328	0.01, 0.05	86.6-120 (12)	0.075	115-120 (3)
Silage				
Isoxaflutole	0.01, 0.05	71.3-99.3 (12)	0.01	91.2-120 (8)
RPA 202248	0.01, 0.05	73.3-103 (12)		
RPA 203328	0.01, 0.05	79.0-117 (12)		
Fodder				
Isoxaflutole	0.01, 0.05	81.5-104 (11); 125	0.01	90.8-120 (8)
RPA 202248	0.01, 0.05	71.4-104 (12)		
RPA 203328	0.01, 0.05	83.2-108 (13)		
Grain				
Isoxaflutole	0.01, 0.05	79.8-101 (12)	0.01	77.5-105 (9)
RPA 202248	0.01, 0.05	79.9-95.7 (12)		
RPA 203328	0.01, 0.05	61.8-69.2 (11); 74.1 [d]		
Flour				
Isoxaflutole	0.01, 0.05	64.0; 75.6-89.6 (11)	0.01	105
RPA 202248	0.01, 0.05	71-93.5 (12)		
RPA 203328	0.01, 0.05	61.4-69.5 (5); 77.5-92.7 (7)		
Starch				
Isoxaflutole	0.01, 0.05	76.7-96.2 (12)	0.01	103
RPA 202248	0.01, 0.05	76.3-101 (12)		
RPA 203328	0.01, 0.05	59.3-68.0 (6); 71.8-83.6 (6)		
Crude oil				
Isoxaflutole	0.01, 0.05	59.1-69.8 (3); 71.3-79.0 (9)	0.01	72.7, 81.5
RPA 202248	0.01, 0.05	52.8-68.2 (8); 70.6-81.8 (7) [d]		

(continued; footnotes follow)

Matrix Analyte	Method validation		Concurrent method recovery	
	Fortification level, ppm [a]	Percent recovery (Number of samples) [b]	Fortification level, ppm [c]	Percent recovery (Number of samples)
RPA 203328	0.01, 0.05	63.5-68.9 (5); 71.8-86.3 (7)		

(continued; footnotes follow)

Table 5 *(continued)*.

Matrix Analyte	Method validation		Concurrent method recovery	
	Fortification level, ppm [a]	Percent recovery (Number of samples) [b]	Fortification level, ppm [c]	Percent recovery (Number of samples)
Grain dust				
Isoxaflutole RPA 202248 RPA 203328	--	--	0.01	93.8
Grits				
Isoxaflutole RPA 202248 RPA 203328	--	--	0.01	103
Meal				
Isoxaflutole RPA 202248 RPA 203328	--	--	0.01	98.5
Refined oil				
Isoxaflutole RPA 202248 RPA 203328	--	--	0.01	92.4, 92.7

[a] Method validation consisted of individual fortification of untreated control samples with isoxaflutole, RPA 202248, and RPA 203328.

[b] Recovery values outside the 70-120% range are listed separately.

[c] Concurrent method recovery consisted of the fortification of untreated control samples with a mixture of isoxaflutole, RPA 202248, and RPA 203328 containing each at the listed fortification level.

[d] Average recovery for this analyte from this matrix was <70%.

Independent laboratory validation (ILV) of proposed enforcement method - (1995; MRID 43573251)

Rhone-Poulenc submitted data pertaining to independent laboratory validation of the proposed enforcement method for the determination of residues of isoxaflutole and its metabolites RPA 202248 and RPA 203328 in/on field corn forage, fodder, and grain. The method used was entitled "Analytical Method for Determination of Residues of RPA 201772, RPA 202248, and RPA 203328 in Corn Forage, Silage, Grain, and Fodder," and it is essentially identical to the method used for residue data collection. The validation was conducted by ABC Laboratories (Pan-Ag Division, Madera, CA), and field corn grain was chosen as the representative matrix for validation. Some minor modifications to the method were made by the laboratory; most changes involved substitution of equipment, such as use of a 125-mL separatory funnel instead of a 60-mL separatory funnel, or use of a stream of nitrogen with a 40 C water bath

to evaporate samples instead of use of a TurboVap evaporator. In addition, a slight change was made in the method of preparation of the diazomethane used in the methylation step.

The laboratory ran separate trials for each of the analytes. Each trial consisted of a reagent blank, two samples of untreated field corn grain, and two samples each of untreated corn grain fortified at 0.05, 0.1, and 0.5 ppm; these levels correspond to 0.5x, 1x, and 5x the proposed tolerance level for field corn grain, respectively. In the case of isoxaflutole and RPA 203328, inadvertent errors were made during the analysis of samples; therefore, a second trial was run for each of these analytes. Only the results of the second trials are reported here for isoxaflutole and RPA 203328. The laboratory stated that analysis of a set of nine samples required approximately 20 hours. Representative chromatograms were submitted.

Recoveries of isoxaflutole, RPA 202248, and RPA 203328 from fortified field corn grain samples are presented in Table 6. Apparent residues of isoxaflutole, RPA 202248, and RPA 203328 were nondetectable (<0.01 ppm) in/on two samples each of unfortified field corn grain, and were nondetectable in the reagent blanks.

Table 6. Recoveries of isoxaflutole, RPA 202248, and RPA 203328 from fortified field corn grain samples analyzed using the proposed enforcement method (MRID 43573251).

Fortification level, ppm	Number of samples	Percent recovery		
		Isoxaflutole	RPA 202248	RPA 203328
0.05	2	86.3, 87.7	74.7, 89.5	65.5, 75.0
0.1	2	83.5, 88.6	88.0, 92.8	73.5, 78.7
0.5	2	82.6, 82.9	80.2, 88.0	80.5, 81.3

The submitted data are adequate to satisfy the requirements for independent laboratory validation (as per PR Notice 88-5) of the proposed enforcement method.

FDA multiresidue methods

Data pertaining to the recovery of isoxaflutole and its metabolites RPA 202248 and RPA 203328 using FDA multiresidue methods were submitted (1995; MRID 43573252). These multiresidue screening data will be forwarded to FDA.

Comments

The petitioner has proposed a GC/MSD common moiety method for tolerance enforcement. The method involves hydrolysis of residues of isoxaflutole to RPA 202248, conversion of RPA 202248 residues to RPA 203328, and then derivatization of RPA 203328 to a methyl ester for GC analysis. This GC/MSD method will determine all isoxaflutole residues of concern, as proposed by the petitioner in the tolerance expression. An identical GC/MSD method was used in the analysis of samples collected from magnitude of the residue studies; acceptable concurrent recoveries were obtained for all analytes.

An independent laboratory validation of this method was performed by ABC Laboratories (Pan-Ag Division, Madera, CA) using field corn grain as the matrix. Acceptable recoveries were obtained for all analytes. CBTS will forward this method to ACL (Beltsville) for petition method validation (PMV). Data pertaining to the recovery of isoxaflutole and its metabolites using FDA multiresidue methods were also submitted (1995; MRID 43573252); these multiresidue screening data will be forwarded to FDA.

With a label restriction prohibiting the use of isoxaflutole on corn grown for silage, or feeding treated fodder to livestock, low residues of parent and metabolites on corn grain, and the low acreage involved in this temporary tolerance request, no temporary tolerances or proposed enforcement methods are required for animal commodities for purposes of this EUP and temporary tolerance petition. If animal metabolism/feeding studies demonstrate a potential for transfer of residues to meat, meat byproducts, milk, or eggs, then the petitioner will be required to propose permanent tolerances for these animal commodities and to develop the appropriate analytical enforcement methodology. Any required enforcement methods for meat, meat byproducts, milk, and eggs will need successful independent laboratory validation and petition method validation before being judged acceptable by CBTS.

Confirmatory methodology for corn and, as needed, animal, milk, and egg commodities should be submitted for the permanent tolerance request.

Storage Stability Data

No storage stability data were submitted with this petition. Rhone-Poulenc indicated that a storage stability study utilizing samples from the field corn field residue and processing studies is planned.

Samples of field corn commodities from the submitted field residue study were placed into frozen storage (temperature unspecified) within 3.5 hours of harvest where they remained for <1-124 days until shipment via freezer truck to Rhone-Poulenc (Research Triangle Park, NC). At Rhone-Poulenc, all samples were homogenized in dry ice and then shipped frozen (either overnight on dry ice or by freezer truck) to Hazelton Wisconsin, Inc. (Madison, WI) for analysis. At the laboratory, samples were stored frozen (-20 to -10 C) prior to analysis.

Total storage intervals between harvest and analysis were 400-458 days (~13-15 months) for forage, 346-406 days (~11-13 months) for silage, 318-379 days (~10-12 months) for fodder, and 300-358 days (~10-12 months) for grain.

Field corn grain samples from the submitted processing study were transferred to frozen storage (temperature unspecified) within 2.5 hours of harvest and shipped on the day of sampling to Rhone-Poulenc, where they were stored frozen for 302 days. Samples were then shipped via freezer truck to the Engineering Biosciences Research Center of Texas A&M University (Bryan, TX) for processing. Field corn grain samples were stored frozen at the processing facility for 21 days prior to processing. The processed fractions were stored frozen (temperature unspecified) and shipped frozen (overnight on dry ice) to Rhone-Poulenc and then to the analytical laboratory (Hazelton). At the analytical laboratory, samples were stored frozen (-20 to -10 C) prior to analysis. The interval between harvest and processing was 323 days (~11 months), and the interval between generation of the processed fraction and residue analysis was 65-79 days (~2-3 months); for unprocessed field corn grain, the interval between harvest and residue analysis was 444 days (~15 months).

Comments

No storage stability data are required for purposes of this EUP and temporary tolerance petition. For establishment of permanent tolerances, storage stability data will be required to validate the storage intervals and conditions of: (i) samples from the current field corn field trial and processing studies; and (ii) samples from all future magnitude of the residue studies. To support the available field trial and processing data, the petitioner should investigate the frozen storage stability of isoxaflutole and its metabolites RPA 202248 and RPA 203328 in/on field corn forage, fodder, and grain for a maximum interval of 15 months, and in processed field corn commodities for a maximum interval of 3 months.

Magnitude of the Residue in Plants

Field corn

Rhone-Poulenc has submitted residue data (1995; MRID 43588003) from ten field trials conducted in IL(2), IN(2), IA(1), MN(2), MO(1), NE(1), and OH(1) depicting residues of isoxaflutole and its metabolites RPA 202248 and RPA 203328 in/on field corn commodities. Eleven field trials were originally scheduled; however, one field trial in SD was terminated prior to harvest due to weather-related crop loss. Each test site consisted of one untreated and two treated plots.

Field corn was treated with a single preemergence broadcast application of isoxaflutole (50.8% WP formulation) at 0.134 (0.124-0.139) or 0.223 (0.217-0.239) lb ai/A (0.7x or 1.2x the maximum proposed application rate on the label; 1.1x or 1.9x the maximum proposed application rate for this type of application) in 10.2-21.1 gal/A of water using a CO_2 backpack

sprayer, a tractor mounted sprayer, or a bicycle sprayer. Three treated samples and one untreated sample were harvested per trial. Forage samples were harvested 55-60 days after treatment. Corn silage samples were harvested at the dent stage of growth, 99-126 days after treatment. Corn grain and fodder samples were collected at crop maturity, 123-161 days after treatment.

Samples of field corn forage, silage, fodder, and grain were analyzed for residues of isoxaflutole equivalents using the previously described GC/MSD common moiety method. Sample calculations and representative chromatograms were submitted. Apparent combined residues of isoxaflutole, RPA 202248, and RPA 203328 were nondetectable (<0.01 ppm) in/on 10 samples each of untreated field corn forage, silage, fodder, and grain. The results of the field trials are presented in Table 7. Following a single preemergence application of isoxaflutole at 0.134 or 0.223 lb ai/A, the combined residues of isoxaflutole and its metabolites RPA 202248 and RPA 203328 were <0.01-0.18 ppm in/on 60 samples of field corn forage harvested 55-60 days after application, <0.01-0.083 ppm in/on 60 samples of field corn silage harvested 91-126 days after application, and <0.01-0.053 ppm and <0.01-0.057 ppm, respectively, in/on 60 samples each of field corn fodder and field corn grain harvested 123-161 days after application.

Table 7. Residues of isoxaflutole equivalents in/on field corn harvested 55-161 days after a single preemergence broadcast application of isoxaflutole (50.8% WP formulation) at 0.134 or 0.223 lb ai/A (0.7x-1.2x).

Field corn matrix	Application rate, lb ai/A	Location	PTI, days	Residues, ppm isoxaflutole equivalents [a]
Forage	0.134	IL-1	56	0.015, 0.018, 0.018
		IL-2	56	0.026, 0.026, 0.032
		IN-1	55	0.027, 0.027, 0.041
		IN-2	58	<0.010, 0.016, 0.033
		IA	60	<0.010 (3)
		MN-1	55	0.016, 0.016, 0.019
		MN-2	55	0.040, 0.054, 0.059
		MO	58	0.020, 0.024, 0.024
		NE	60	0.045, 0.060, 0.066
		OH	58	0.016, 0.016, 0.020
	0.223	IL-1	56	0.082, 0.094, 0.095
		IL-2	56	0.047, 0.054, 0.066
		IN-1	55	0.035, 0.038, 0.041
		IN-2	58	0.016, 0.022, 0.023
		IA	60	<0.010 (3)
		MN-1	55	0.020, 0.022, 0.023
		MN-2	55	0.060, 0.069, 0.070
		MO	58	0.039, 0.049, 0.051
		NE	60	0.13, 0.14, 0.18
		OH	58	0.023, 0.024, 0.031
Silage	0.134	IL-1	109	0.020, 0.020, 0.026
		IL-2	99	0.018, 0.020, 0.023
		IN-1	114	0.059, 0.062, 0.078
		IN-2	91	<0.010 (3)
		IA	126	<0.010 (3)
		MN-1	123	<0.010 (3)
		MN-2	118	0.015, 0.016, 0.016
		MO	100	0.023, 0.023, 0.031
		NE	126	0.020, 0.032, 0.034
		OH	103	<0.010, 0.010, 0.012
	0.223	IL-1	109	0.034, 0.060, 0.083

(continued; footnotes follow)

Table 7 *(continued).*

Field corn matrix	Application rate, lb ai/A	Location	PTI, days	Residues, ppm isoxaflutole equivalents [a]
		IL-2	99	0.059, 0.061, 0.062
		IN-1	114	0.043, 0.053, 0.071

(continued; footnotes follow)

Table 7 *(continued)*.

Field corn matrix	Application rate, lb ai/A	Location	PTI, days	Residues, ppm isoxaflutole equivalents [a]
Silage (continued)	0.223	IN-2	91	0.013, 0.015, 0.038
		IA	126	<0.010 (3)
		MN-1	123	<0.010 (3)
		MN-2	118	<0.010, 0.010, 0.014
		MO	100	0.032, 0.034, 0.056
		NE	126	0.044, 0.061, 0.082
		OH	103	0.024, 0.026, 0.030
Fodder	0.134	IL-1	139	<0.010 (3)
		IL-2	135	<0.010, <0.010, 0.011
		IN-1	142	0.012, 0.014, 0.029
		IN-2	123	<0.010 (3)
		IA	148	<0.010 (3)
		MN-1	161	<0.010 (3)
		MN-2	161	<0.010, <0.010, 0.012
		MO	140	<0.010 (3)
		NE	151	<0.010, 0.012, 0.013
		OH	149	<0.010 (3)
	0.223	IL-1	139	<0.010 (3)
		IL-2	135	0.018, 0.024, 0.028
		IN-1	142	0.027, 0.030, 0.053
		IN-2	123	0.020, 0.021, 0.023
		IA	148	<0.010 (3)
		MN-1	161	<0.010 (3)
		MN-2	161	0.010, 0.010, 0.011
		MO	140	<0.010 (3)
		NE	151	0.026, 0.037, 0.047
		OH	149	<0.010 (3)
Grain	0.134	IL-1	139	<0.010 (3)
		IL-2	135	<0.010 (3)
		IN-1	142	0.012, 0.029, 0.031
		IN-2	123	<0.010 (3)
		IA	148	<0.010 (3)
		MN-1	161	<0.010 (3)
		MN-2	161	<0.010 (3)

(continued; footnotes follow)

Table 7 *(continued).* 34

Field corn matrix	Application rate, lb ai/A	Location	PTI, days	Residues, ppm isoxaflutole equivalents [a]
Grain (continued)	0.134	MO	140	<0.010 (3)
		NE	151	<0.010, 0.012, 0.014
		OH	149	<0.010 (3)
	0.223	IL-1	139	<0.010, 0.010, 0.013
		IL-2	135	0.014, 0.016, 0.017
		IN-1	142	0.049, 0.051, 0.057
		IN-2	123	<0.010 (3)
		IA	148	<0.010 (3)
		MN-1	161	<0.010 (3)
		MN-2	161	<0.010 (3)
		MO	140	<0.010 (3)
		NE	151	<0.010, <0.010, 0.013
		OH	149	<0.010 (3)

[a] Each residue value represents a single sample unless otherwise indicated in parentheses.

Residue data for the aspirated grain fractions of field corn are presented in the "Magnitude of the Residue - Processed Food/Feed" section of this review.

Comments

The submitted field residue data are adequate for purposes of this EUP and temporary tolerance petition. Ten field trials were conducted in the states of IL(16%), IN(7%), IA(19%), MN(10%), MO(3%), NE(13%), and OH(4%), which together accounted for 72% of the U.S. field corn production (*1992 USDA Agricultural Statistics*). These trials were conducted using a 50.8% wettable powder (WP) formulation (EXP30953B) instead of the 75% DF formulation proposed for use under the EUP; the Agency considers DF and WP formulations to be sufficiently similar to allow translation of residue data between them.

The available data indicate that the combined residues of isoxaflutole and its metabolites RPA 202248 and RPA 203328 will not exceed the proposed 0.1-ppm tolerance in/on field corn grain or the proposed 0.2-ppm tolerance in/on field corn forage and fodder following a single preemergence broadcast application of isoxaflutole (50.8% WP formulation) at 0.134 or 0.223 lb ai/A (0.7x or 1.2x the maximum proposed application rate). Due to the grazing/feeding restrictions on the proposed label, tolerances for field corn forage and fodder are not necessary for this EUP and temporary tolerance petition. The petitioner must submit a revised Section F to delete the tolerance proposals for forage and fodder.

Prior to Section 3 registration, permanent tolerances will need to be proposed for the field corn commodities forage and fodder. Additional field trial data will be needed to support these required proposals. According to "EPA Guidance on Number and Location of Domestic Crop Fields Trials for Establishment of Pesticide Residue Tolerances", issued June 1994 (E. Saito and E. Zager), a minimum of 20 field trials are required for the establishment of tolerances on individual crops. The registrant has already conducted 10 field trials in conjunction with this EUP. To fulfill the remainder of requirements, a minimum of 10 additional field trials will be required. These trials should utilize the 75% DF formulation at the maximum proposed rate and should be divided into five trials reflecting preplant application and five trials reflecting preemergence application. The trials should be conducted in Regions 1 (one trial), 2 (one trial), and 5 (eight trials). Two independently composited samples of grain, forage, and fodder should be collected and analyzed from each site.

Magnitude of the Residue - Processed Food/Feed (1995; MRID 43573253)

Rhone-Poulenc has submitted data depicting the concentration of residues of isoxaflutole and its metabolites RPA 202248 and RPA 203328 in field corn processed commodities.

In two tests conducted in IN and NE in 1993, field corn grain was harvested 166-180 days following a single preemergence broadcast application of the 50.8% WP formulation at 0.223-1.116 lb ai/A (1.2-6x the proposed maximum application rate) using ground equipment. Three replicate treated grain samples and one untreated control sample were harvested from plots treated at 0.67 lb ai/A (3.6x the proposed maximum application rate). This was the highest application rate that exhibited no phytotoxicity. Although grain was harvested from both IN and NE tests sites, only field corn grain samples from the NE test site were used for processing.

At the Engineering Biosciences Research Center of Texas A&M University (Bryan, TX), aspirated grain fractions were collected, and samples of field corn were processed into germ, hulls, coarse gluten-starch, gluten, starch, presscake, crude oil, refined oil, and soapstock using a small-scale wet milling commercial procedure, and into germ, hulls, grits, flour, meal, presscake, crude oil, refined oil, and soapstock using a small-scale dry milling commercial procedure. The registrant submitted adequate material balance information and descriptions of the field corn processing procedures.

Aspirated grain fraction collection procedures simulated commercial techniques. Briefly, grain was dried by forced air to ~12% moisture, then circulated through a dust-generating apparatus consisting of a bucket elevator, two drag conveyors, and two holding bins for 120 minutes. During this interval, dust was collected at specific points using hoses connected to a dust collector. The grain was then transferred to a holding bin, and all equipment and surfaces were vacuumed. The grain was transferred from the holding bin to a stainless steel Kice aspiration unit adjusted to collect light impurities. The grain dust fractions from the

dust collector and the vacuum cleaners were combined and classified by screening through 2540-, 2030-, 1180-, 850-, and 425-μm mesh screens. All screened fractions were then composited. The light impurities collected from the aspiration unit were not analyzed.

Another portion of the grain sample was cleaned by aspiration and mechanical screening. The aspirated fractions were not analyzed since grain dust was generated by an alternate laboratory procedure. The cleaned grain was then wet-milled as follows: grain was steeped in water and sulfurous acid, the steepwater was drained, and the wet grain was disc-milled to separate the germ from hulls and endosperm. The germ fractions were washed with water to remove starch, oven-dried, and frozen for oil extraction. The fraction remaining after germ was separated was ground and washed with water to separate the hulls. The remaining fraction was screened, washed with water, refrigerated, and centrifuged to separate the starch from the gluten.

Another portion of cleaned grain was dry milled as follows: grain was steeped in water, cracked by an impact mill, dried by forced air, cooled and put through a shaker screen. Material collected on the screens was aspirated to separate hulls/germ from grits/detached germ. To separate germ from hulls, the hulls/germ material was remilled and re-aspirated. The grits/detached germ material was gravity-separated into germ and large grits. The germ was oven-dried and frozen for oil extraction. The large grits fraction was screened to isolate medium grits, small grits, coarse meal, meal, and flour.

Both the wet- and dry-milled germ fractions were moistened, heated, flaked, and processed in an expeller to produce crude oil and presscake. The crude oil was filtered. The residual oil in the presscake was extracted with hot hexane three times. The hexane/oil fractions were combined and heated to remove hexane. Crude oil fractions were combined, and a portion was combined with NaOH and heated in a refining machine, then refrigerated; the refined oil was decanted and filtered. The remaining fraction was soapstock.

Residues in/on treated and untreated field corn and its processed commodities were determined using the previously described GC/MSD common moiety method. The results of the field corn processing study are presented in Table 8. Apparent combined residues of isoxaflutole and its metabolites RPA 202248, and RPA 203328 were nondetectable (<0.01 ppm) in/on one untreated sample each of whole grain, grain dust, grits, meal, flour, starch, wet-milled crude oil, wet-milled refined oil, dry-milled crude oil, and dry-milled refined oil.

Table 8. Combined residues of isoxaflutole and its metabolites RPA 202248, and RPA 203328 in/on commodities processed from field corn grain treated with a single preemergence broadcast application of the 50.8% WP formulation at 0.67 lb ai/A (3.7x).

Field corn commodity	Residues, ppm isoxaflutole equivalents [a]	Concentration/reduction factor [b]
Whole grain	0.037, 0.038, 0.041 [0.039]	--
Grain dust dry milling	0.023, 0.025, 0.029 [0.026]	0.7x
Grits dry milling	0.035, 0.037, 0.039 [0.037]	0.9x
Meal dry milling	0.035, 0.037, 0.038 [0.037]	0.9x
Flour dry milling	0.026, 0.028, 0.031 [0.028]	0.7x
Starch wet milling	<0.01, <0.01, <0.01 [<0.01]	<0.3x
Crude oil dry milling	<0.01, <0.01, <0.01 [<0.01]	<0.3x
Crude oil wet milling	<0.01, <0.01, <0.01 [<0.01]	<0.3x
Refined oil dry milling	<0.01, <0.01, <0.01 [<0.01]	<0.3x
Refined oil wet milling	<0.01, <0.01, <0.01 [<0.01]	<0.3x

[a] Bracketed values represent the average of all samples.

[b] Calculated by dividing average residues found in processed fraction by the average residues found in whole grain.

Comments

Adequate data pertaining to aspirated grain fractions of corn were collected in connection with the field corn processing study. No concentration of combined residues of isoxaflutole and its metabolites RPA 202248, and RPA 203328 was observed in aspirated grain fractions collected from field corn grain samples bearing detectable residues (average combined residues were 0.039 ppm) following a single preemergence broadcast application of the 50.8% WP formulation at 3.7x. Based on these data, no tolerance for aspirated grain fractions is required at this time.

The submitted processing data are adequate for purposes of this EUP and temporary tolerance petition. Detectable residues of isoxaflutole and its metabolites RPA 202248, and RPA 203328 were found in/on field corn grain treated with a single preemergence broadcast

application of the 50.8% WP formulation at 3.7x; the average combined residues were 0.039 ppm. When these field corn grain samples bearing detectable residues were processed according to simulated commercial procedures, no concentration of combined residues was observed in grits, meal, flour, starch, dry- and wet-milled crude oil, and dry- and wet-milled refined oil. Based on these data, no food/feed additive tolerances are required for the processed commodities of field corn.

These processing data can also be used to support the permanent tolerance petition, provided that the petitioner submits adequate storage stability data for isoxaflutole and its metabolites RPA 202248, and RPA 203328 in corn processed fractions.

Magnitude of the Residue in Meat, Milk, Poultry, and Eggs

No studies pertaining to magnitude of the residue in eggs, milk, and meat were submitted with this petition. Livestock feeding studies will not be required for purposes of this EUP and temporary tolerance petition due to the label restrictions against the feeding of treated forage and fodder to livestock, the limited number of acres involved, restrictions against use in corn grown for silage, and low residues in field corn grain.

Acceptable ruminant and poultry feeding studies may be required for the establishment of permanent tolerances. If the required ruminant and poultry metabolism studies indicate reasonable expectation that isoxaflutole residues of concern could transfer to animal commodities, then livestock feeding studies will be required.

Confined/Field Rotational Crops

No confined or field rotational crop studies were submitted with this petition. The proposed label specifies that rotational crops may not be planted until the following season. For the purposes of this EUP, no rotational crop studies are required. However, for establishment of permanent tolerances, the petitioner must submit a confined rotational crop study. The results of this study will be used to determine the appropriate crop rotation restrictions and/or the need for limited rotational crop field trials.

Codex Harmonization

There are no established or proposed Codex limits for residues of isoxaflutole in/on field corn. Therefore, no compatibility issues exist with regard to the proposed field corn tolerances and Codex MRLs.

Attachments

I. Review of Product Chemistry Data for Isoxaflutole.
II. Review of Product Chemistry Data for Isoxaflutole - Confidential Appendix.
III. International Residue Limit Status Sheet.

MASTER RECORD IDENTIFICATION NUMBERS

References (used):

43573201 Truchon, A. (1994) RPA 201772: Product Identity and Composition: Lab Project Number: 94-03. Unpublished study prepared by Rhone-Poulenc Industrialisation. 98 p.

43573202 Cousin, J. (1994) Technical RPA 201772: Analysis and Certification of Product Ingredients: Lab Project Number: 93-128: R&D/CRLD/AN/9416425. Unpublished study prepared by Rhone-Poulenc Secteur Agro. 162 p.

43573203 Cousin, J. (1993) RPA 201772 Active Ingredient: Physical and Chemical Characteristics: Part A: Physical Characteristics: Lab Project Number: 93-129: R&D/CRLD/AN/9316753. Unpublished study prepared by Rhone-Poulenc Secteur Agro. 20 p.

43573204 Cousin, J. (1993) RPA 201772 Active Ingredient: Physical and Chemical Characteristics: Part B: pH and Dissociation Constant: Lab Project Number: 93-129: R&D/CRLD/AN/9316835. Unpublished study prepared by Rhone-Poulenc Secteur Agro. 24 p.

43573205 Cousin, J. (1993) RPA 201772 Active Ingredient: Physical and Chemical Characteristics: Part C: Solubilities: Lab Project Number: 93-129: R&D/CRLD/AN/9316923. Unpublished study prepared by Rhone-Poulenc Secteur Agro. 54 p.

43573206 Cousin, J. (1995) RPA 201772 Active Ingredient: Physical and Chemical Characteristics: Part D: Octanol/Water Partition Coefficient: Final Report: Amendment Number 1: Lab Project Number: 93-129, PART D: R&D/CRLD/AN. 9415236: R&D/CRLD/AN/9515091. Unpublished study prepared by Rhone-Poulenc Secteur Agro. 18 p.

43573207 Cousin, J. (1993) RPA 201772 Active Ingredient: Physical and Chemical Characteristics: Part E: Stability: Lab Project Number: 93-129: R&D/CRLD/AN/9316985. Unpublished study prepared by Rhone-Poulenc Secteur Agro. 40 p.

43573208 Cousin, J. (1994) RPA 201772 Active Ingredient: Physical and Chemical Characteristics: Part F: Vapour Pressure: Lab Project Number: 93-129: R&D/CRLD/AN/9415227. Unpublished study prepared by Rhone-Poulenc Secteur Agro. 51 p.

43573249 Hampton, R.; Pettaway, J. (1995) (Carbon 14)-RPA 201772: Metabolic Fate and Distribution in Corn (Zea mays L.): Lab Project Number: EC-93-243. Unpublished study prepared by Rhone-Poulenc Ag Co. and A&L Great Lakes Labs. 230 p.

43573250 Hampton, R.; Cappy, J. (1995) Rationale for Site of (Carbon 14)-Labelling of Isoxaflutole (RPA 201772). Unpublished study prepared by Rhone-Poulenc Ag Co. 79 p.

43573251 Schuster, L. (1995) PR Notice 88-5 Enforcement Method Confirmation for RPA 201772 and Its Metabolites RPA 202248 and RPA 203328 in Corn Grain: Lab Project Number: 94454: EC-94-292. Unpublished study prepared by ABC Labs, Pan-Ag Division. 109 p.

43573253 Cappy, J. (1995) EXP 30953B/Field Corn/Magnitude of Residue in Processing Fractions: Final Report: Lab Project Number: US93703R: 94-0154. Unpublished study prepared by Rhone-Poulenc Ag Co. 528 p.

43588003 Cappy, J. (1995) EXP 30953B/Field Corn/Magnitude of Residue: Final Study Report: Lab Project Number: 44661: US93702R: 93-0147. Unpublished study prepared by Rhone Poulenc Ag Co. 613 p.

References (not used):

[The following references were not reviewed since they contain data pertaining to the isoxaflutole end-use product.]

43573209 Helfant, L. (1994) EXP 31130A: Product Identity and Composition: Lab Project Number: 94-009: 44540: PC-94-009. Unpublished study prepared by Rhone-Poulenc Ag Co. 49 p.

43573210 Helfant, L.; Wheeler, G.; King, S. (1994) EXP 31130A: Product Chemistry: Series 62-Analysis and Certification of Ingredients: Lab Project Number: PC-94-008: 44534. Unpublished study prepared by Rhone-Poulenc Ag Co. 62 p.

43573211 Helfant, L. (1994) EXP 31130A: Product Chemistry: Series 63-Physical and Chemical Characteristics: Lab Project Number: PC-94-010: 44541. Unpublished study prepared by Rhone-Poulenc Ag Co. 22 p.

[The following reference pertaining to multi-residue method testing of isoxaflutole and its metabolites will be forwarded to FDA for review.]

43573252 Thiem, D. (1994) RPA201772: PAM I Multiresidue Protocol Testing for RPA201772, RPA202248, and RPA203328: Final Report: Lab Project Number: EC-94-266: 1218. Unpublished study prepared by Colorado Analytical Research & Development Corp. 422 p.

Attachment I

REVIEW OF PRODUCT CHEMISTRY (SUBDIVISION D), GLNs 61 TO 63

Chemical Name (IUPAC, ANSI, etc.)	Isoxaflutole methanone, (5-cyclopropyl-4-isoxazolyl)[2-(methylsulfonyl)-4-(trifluoromethyl)phenyl]
Chemical Number (CAS; PC Code)	CAS No. 141112-29-0 Shaughnessy No. 123000
Registration No.	none
Type of Product (T, FI, MP, EP)	98% TGAI
CB No.	15431 (PP#5G04484)
DP Barcode	D214199 and D214212
Reviewer	
Approvals	
Section/Team	
Branch Senior Scientist	
Branch Chief	

Rhone-Poulenc Ag Company has submitted product chemistry data concerning the 98% isoxaflutole TGAI and 75% WDG formulation (no EPA Reg. No. assigned) in support of a petition for a temporary tolerance on field corn. Only product chemistry data pertaining to the TGAI are addressed under this petition; data for the end-use product (1994; MRIDs 43573209-43573211) are not reviewed herein.

Table 1: Manufacturing and Impurity Data for the Rhone-Poulenc 98% TGAI.

GLN	MRID	Status [1]	Details and/or Deficiency
61-1: Product Identity & Disclosure of Ingredients	43573201	N/A	see Confidential Appendix
61-2: Starting Materials & Manufacturing Process	43573201	A	see Confidential Appendix
61-3: Discussion of Impurities	43573201	A	see Confidential Appendix
62-1: Preliminary Analysis	43573202	A	see Confidential Appendix. A preliminary analysis study must be submitted reflecting analysis of five batches representative of the final full-scale manufacturing process once commercial production begins.
62-2: Certification of Limits	43573202	N/A	see Confidential Appendix
62-3: Analytical Methods	43573202	N/A	isoxaflutole per se: HPLC Method R-771-09-94(E) impurities: see Confidential Appendix

[1] A = Acceptable; N = Unacceptable (see Deficiency); N/A = Not Applicable.

Table 2: Physical and Chemical Properties for Rhone-Poulenc 98% TGAI.			
GLN	MRID	Status[1]	Result[2] or Deficiency
63-2: Color	43573203	A	yellow
63-3: Physical State	43573203	A	granular powder
63-4: Odor	43573203	A	slight acetic acid-like odor
63-5: Melting Point	43573203	A	135-136 ± 1 C (decomposes at 160 C)
63-6: Boiling Point	43573203	N/A	solid at room temperature
63-7: Density, Bulk Density, or Specific Gravity	43573203	A	1.419 20 C/20 C (specific gravity) 1.416 g/mL at 20 C (density)
63-8: Solubility	43573205	A	0.00062 g/100 mL in water (pH 5.5) 0.00068 g/100 mL in pH 5 buffer 29.3 g/100 mL in acetone 23.3 g/100 mL in acetonitrile 14.2 g/100 mL in ethyl acetate 34.6 g/100 mL in dichloromethane 0.010 g/100 mL in hexane 3.12 g/100 mL in toluene 1.38 g/100 mL in methanol 0.076 g/100 mL in 1-octanol
63-9: Vapor Pressure	43573208	A	1.0×10^{-6} Pa at 25 C
63-10: Dissociation Constant	43573204	N/A	not determined: solubility in 3% acetonitrile or methanol was too low for potentiometric determination.
63-11: Octanol/Water Partition Coefficient	43573206	A	P = 219 (log P = 2.34) at 20 C
63-12: pH	43573204	A	4.6 at 25 C (1% w:v aqueous suspension containing 2% acetonitrile, v:v)
63-13: Stability	43573207	A	Stable for 14 days at elevated temperatures (54 C) and under simulated sunlight; stable in the presence of iron, tin, and aluminum powders at 30-150 C; degradation occurred in the presence of ferric chloride at 40-90 C.

[1] A = Acceptable; N = Unacceptable (see Deficiency); N/A = Not applicable.
[2] For example, "brown" for 63-1; "155° C" for 63-4.

Attachment: Confidential Attachment