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SCIENTIFIC DATA REVIEWS
EPA SERIES 361

3

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

Date: 8-October-2003

Subject: Trifloxystrobin. Summary of Wheat Metabolism Data. Conditional Data.

DP Barcode:	287242	Case No.:	063457
PC Code:	129112	Submission:	S619299
40 CFR 180.	555	MRID Nos.:	45721803, 45721804

From: Leung Cheng, PhD, Chemist
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Executive Summary

In connection with PP#9F05070 and 0F6121, HED recommended a conditional registration for the uses on wheat, field corn, pop corn, and rice in view of an earlier Metabolism Assessment Review Committee (MARC)'s decision that additional metabolism data on wheat would be required for a full Section 3 registration to support future uses on leafy vegetables and cereals or crops other than fruits, fruiting vegetables, cucurbit vegetables, and peanuts (D263040, L. Cheng, 5/8/2000; D267787, L. Cheng, 1/17/2002). Bayer AG (Bayer CropScience) has now submitted additional wheat metabolism studies to upgrade the supplementary wheat metabolism data.

The submitted wheat metabolism studies are adequate to fulfill the data requirements for plant metabolism. Thus, HED recommends a full Section 3 registration for the uses on wheat, field corn, pop corn and rice. In addition, since the theoretical maximum poultry dietary burden was estimated using feeds derived from field corn and rice, the currently time-limited tolerances in poultry eggs, fat, meat, and meat byproducts can now be converted to permanent tolerances with the submission of adequate wheat metabolism data (D267787, L. Cheng, 1/17/2002).

(2)

Background

MARC D257835 7/13/99

Previously, the HED MARC concluded that both trifloxystrobin and the free form of its acid metabolite CGA-321113 are of concern for both regulatory and risk assessment purposes for plant commodities, and also concluded that additional metabolism studies would be needed to support possible future uses on leafy vegetables, cereals or crops other than fruits, fruiting vegetables, cucurbit vegetables, and peanuts. The MARC also concluded that, in the interim, trifloxystrobin and the free form of its acid metabolite CGA-321113 are of concern in wheat for both regulatory and risk assessment purposes but that additional metabolism data on wheat would be required for a full Section 3 registration.

860.1300 Nature of the Residue - Plants

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Radiolabeled [^{14}C]trifloxystrobin, labeled in the tolyl (trifluoromethylphenyl) ring, was applied twice as foliar spray applications at approximately 250 g ai/ha (0.23 lb ai/A) per application to wheat plants (in an area of 1 m^2) at the BBCH33 stage (node 3 at least 2 cm above node 2) and stage 69 (end of flowering). An immmature wheat sample (hay fraction) was collected 3 days after the second treatment, and grain and straw (growth stage 89) were collected 35 days after the last application.

Total radioactive residues (TRR; expressed as trifloxystrobin equivalents) were 5.20 ppm in wheat hay, 6.13 ppm in wheat straw, and 0.120 ppm in wheat grain, respectively. The TRR of wheat hay, straw and grain were determined by summing the radioactivity in the combined aqueous acetonitrile extracts (measured by liquid scintillation counting, LSC) and in post-extraction solids (PES; measured by combustion and LSC).

The amounts of radioactivity extractable into the dichloromethane fraction were: 53% for hay, 48% for straw and 26% for grain; those remaining in the aqueous phase were: 39% for hay, 24% for straw, and 41% for grain. The amounts of unextractable activity left after either microwave treatment or diastase hydrolysis ranged from 2% for hay, 9% for straw, to 12% for grain. The major residue found in wheat grain, hay and straw was trifloxystrobin (26-44%) with small amounts of CGA-321113 (2-4%).

In another experiment, radiolabeled [^{14}C]trifloxystrobin, labeled in the glyoxyl ring, was applied twice as foliar spray applications at 250 g ai/ha to wheat plants (in an area of 1 m^2) at the BBCH33 stage (node 3 at least 2 cm above node 2) and stage 69 (end of flowering). An immmature wheat sample (hay fraction) was collected 3 days after the second treatment, and grain and straw (growth stage 89) were collected 35 days after the last application.

TRR were 5.98 ppm in wheat hay, 6.12 ppm in wheat straw, and 0.262 ppm in wheat grain, respectively. The TRR of wheat hay, straw and grain were determined by summing the

radioactivity in the combined aqueous acetonitrile extracts (measured by LSC) and in PES (measured by combustion and LSC).

The amounts of radioactivity extractable into the dichloromethane fraction were: 54% for hay, 50% for straw and 16% for grain; those remaining in the aqueous phase were: 40% for hay, 26% for straw, and 60% for grain. The amounts of unextractable activity left after either microwave treatment or diastase hydrolysis ranged from 1% for hay to 7% for grain and straw. The major residue found in wheat grain, hay and straw was trifloxystrobin (18-54%) with small amounts of CGA-321113 (1-4%).

The glyoxyl label study yielded some very polar metabolites (as opposed to the tolyl label), primarily phthalic acid derivatives, which were present in the aqueous phases of grain, hay and straw.

Chromatographic analyses were conducted on the dichloromethane, aqueous, and microwave phases of hay, straw and grain samples derived from both the tolyl and glyoxyl labels. The distribution of parent compound and metabolites containing the uncleaved molecule was very similar between the two carbon labels.

Based on the new metabolism studies, the petitioner has proposed that trifloxystrobin isomerizes to its E,Z, Z,E, and Z,Z isomers before undergoing hydrolysis to the corresponding acids such as CGA-321113. Hydroxylation of the imino-methyl group and on the tolyl ring also takes place. Portions of these hydroxylated metabolites are conjugated or the imino-hydroxymethyl metabolites are further oxidized to the carboxylic acids. However, all these metabolites were each found to be present at less than 10% TRR.

Conclusions. With the additional wheat metabolism studies, the qualitative nature of the residue in plants is adequately understood based on acceptable metabolism studies conducted on apples, cucumbers, and peanuts with trifloxystrobin. The additional wheat metabolism data support the decision made by the MARC regarding the residues of concern in wheat.

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MEMORANDUM

Date: *10/8/03*

Reviewers: Leung Cheng, PhD, Chemist
Registration Action Branch 3
Health Effects Division (7509C)

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Registration Action Branch 3
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DP Barcode: D287242

Citation: 45721804 Reiner, H. and R. Bongartz (2002) Metabolism of [glyoxyl-phenyl-UL-^{14}C]Trifloxystrobin in Spring Wheat. Bayer AG Report: MR-028/02. Unpublished study prepared by Bayer AG, FRG. 177 p.

Sponsor: Bayer AG

Executive Summary

Bayer AG (Bayer CropScience) has submitted a study investigating the metabolism of [^{14}C]trifloxystrobin in spring wheat (metabolism experiment), a new study to upgrade the current supplementary wheat metabolism data. Radiolabeled [^{14}C]trifloxystrobin, labeled in the glyoxyl ring, was applied twice as foliar spray applications at 250 g ai/ha (0.23 lb ai/A) per application to wheat plants (in an area of 1 m^2) at the BBCH33 stage (node 3 at least 2 cm above node 2) and stage 69 (end of flowering). An immmature wheat sample (hay fraction) was collected 3 days after the second treatment, and grain and straw (growth stage 89) were collected 35 days after the last application.

Total radioactive residues (TRR; expressed as trifloxystrobin equivalents) were 5.98 ppm in wheat hay, 6.12 ppm in wheat straw, and 0.262 ppm in wheat grain, respectively. The TRR of wheat hay, straw and grain were determined by summing the radioactivity in the combined aqueous acetonitrile extracts (measured by liquid scintillation counting, LSC) and in post-extraction solids (PES; measured by combustion and LSC).

The amounts of radioactivity extractable into the dichloromethane fraction were: 54% for hay, 50% for straw and 16% for grain; those remaining in the aqueous phase were: 40% for hay, 26% for straw, and 60% for grain. The amounts of unextractable activity left after either microwave treatment or diastase hydrolysis ranged from 1% for hay to 7% for grain and straw. The major residue found in wheat grain, hay and straw was trifloxystrobin (18-54%) with varying amounts of CGA-321113 (1-4%).

Based on the subject metabolism study, trifloxystrobin was isomerized to its E,Z, Z,E, and Z,Z isomers before undergoing hydrolysis to the corresponding acids. Hydroxylation of the imino-methyl group and also on the tolyl ring took place. Portions of these hydroxylated metabolites were conjugated or the imino-hydroxymethyl metabolites were further oxidized to the carboxylic acids.

This study yielded some very polar metabolites (as opposed to the tolyl label), primarily phthalic acid derivatives, which were present in the aqueous phases of grain, hay and straw.

Chromatographic analyses were conducted on the dichloromethane, aqueous, and microwave phases of hay, straw and grain samples derived from both the tolyl and glyoxyl labels. The distribution of parent compound and metabolites containing the uncleaved molecule was very similar between the two carbon labels.

[An additional experiment using wheat plants cultivated in a 0.5 m^2 container was similarly conducted, except that rain was prevented from hitting the plants by an automatically triggered overhead roof, to ensure higher activity for metabolite isolation and identification, if needed (supportive experiment).]

GLP Compliance

The study was conducted in compliance with the current OECD Principles of Good Laboratory Practice, and meets the requirement of US EPA's FIFRA Good Laboratory Practice (GLP; 40 CFR Part 160). Signed and dated Certification of GLP, Certificate of Authenticity, and Quality Assurance statement were provided.

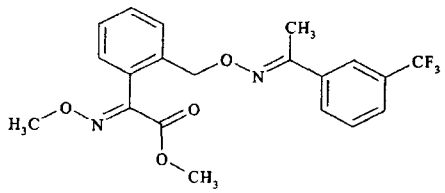
1. Materials and Methods

1.1. Substance

Active Ingredient

Common Name:	Trifloxystrobin
IUPAC Name:	Methoxyimino-{2-[1-(3-trifluoromethyl-phenyl)-ethylideneaminooxymethyl]-phenyl}-acetic acid methyl ester
CAS Name:	(E,E)-alpha-(methoxyimino)-2-[[[[1-[3-(trifluoromethyl)phenyl]ethylidene]amino]oxy]methyl]-benzeneacetic acid methyl ester
CAS Number:	141517-21-7
Company Name:	BO17211 or CGA-279202
Other Synonyms:	None provided

Location of Isotopic Label: Uniformally labeled in the glyoxyl ring
Radiochemical Purity: >99% (as determined by HPLC and TLC)
Specific Activity: 2.48 MBq/mg (67.0 µCi/mg, 27.4 mCi/mole)



Trifloxystrobin

1.2. Crop and Site

Type and Variety of Crop:	Spring wheat, Thasos variety
Growth Environment:	1 m^2 area (Hazelton, Munster, Germany) protected from birds with netting
Conditions:	fertilized and weed/disease controlled

1.3. Application

Type of Application: Foliar spray applications using a track sprayer
Application Matrix: The radiolabeled test substance was formulated as an EC125
Application Rate: 250 g ai/ha (0.23 lb ai/A)
Number of Applications: Two foliar applications

Timing of Applications: Plants at BBCH33 and BBCH69 growth stage
Pre-harvest Interval(s): 3 days for immature wheat plants (hay), and 35 days for mature wheat plants (grain and straw)

1.4. Harvest/Post-harvest Procedures

Hay was collected by cutting shortly above the soil surface. The hay sample was dried at room temperature for 4 days, cut in pieces and homogenized with liquid nitrogen. An aliquot of the sample was used for extraction.

Grain and straw were harvested (Aug 14, 2001) at maturity by cutting wheat plants shortly above the soil surface. The seeds were collected by hand and the remaining ears and chaffs were combined with the straw sample.

Straw was cut in pieces. Straw and grain were homogenized with liquid nitrogen. Aliquots of grain and straw were used for extraction.

Extraction of hay, straw and grain samples started within 2 weeks of sampling. These extracts (dichloromethane and aqueous phases) were anlayzed by HPLC in 1-2 weeks. The post-extraction solids were frozen until extraction and the extracts were analyzed without delay. Based on the study experimental termination date, samples of wheat forage, grain, and straw were stored for 12 months from harvest to analysis.

Table 1.4.1. Summary of Storage Conditions

Matrix	RAC or Extract	Storage Temperature (C)	Duration [1]
Wheat	Forage/hay	~-20	~12 months
	Grain		~11 months
	Straw		

[1] Based on study experimental termination date. Frozen storage stability data showed trifloxystrobin and CGA 321113 were stable in whole wheat plant, and wheat grain and straw for 24 months (D254213, PP#9F5070, L. Cheng, 4/6/00).

During the course of the study, aliquots of the stored homogenized grain samples were extracted twice (Jan 23, 2002 and Feb 22, 2002) following the initial extraction (Aug 21, 2001). HPLC analysis of the aqueous phases showed similar metabolic profile among the three extracts. The data are adequate to support the stability of the isomeric mixture of trifloxystrobin and the metabolites under the sample storage conditions.

1.5. Analytical Methods

Subsamples of homogenized wheat grain, hay and straw were extracted 4x with acetontrile:water (8:2 v:v) and suction filtered. The remaining pellet was further extracted (2x) with acetonitrile (ACN):1 N HCl (4:1, v:v) and centrifuged. The combined extracts were measured for TRR by

direct LSC (usually in triplicates). The TRR in the remaining nonextractable solids (PES 1) were determined by combustion/LSC. The TRR of wheat grain, hay and straw were determined by summing the radioactivity in the extracts and PES.

Aliquots of the combined extracts were concentrated, partitioned (3x) with dichloromethane, yielding an organic phase and an aqueous phase. The phases were concentrated, and each phase was subjected to radioactivity measurement and analyzed by HPLC.

A representative sample of hay and straw solids PES 1 were subjected microwave (150 C, 20 minutes) extraction with acetonitrile:water (1:1 v/v). The extracts were filtered and the radioactivity in the filtrate was measured by LSC. The post-extraction solids (PES 2) were dried, and aliquots were measured for radioactivity.

Aliquots of PES 1 were treated 2x with diastase in the presence of sodium azide in citrate-sodium hydroxide buffer (pH 6) at room temperature for 10 days. The suspension was filtered and the filtrates were combined before being measured for TRR.

An aliquot of the grain diastase extract mixed with toluene was hydrolyzed with concentrated HCl at 100 C for 3 hours. The hydrolysate was further extracted with toluene (3x). Alquots of both phases were measured for radioactivity and analyzed by TLC. Chromatography of the aqueous phase 2 was not possible due to the high matrix interference.

TLC analysis of the extracts was conducted using silica gel plates and a solvent system of chloroform:methanol:formic acid:water (75:20:4:21 v:v:v:v) or hexane:diethyl ether:tetrahydrofuran:formic acid:water (10:70:10:1:2 v:v:v:v:v). Radioactivity was detected and quantitated by radioanalytic imaging; nonlabeled standards were visualized under UV light (254nm). Reverse phase-HPLC analysis of the extractable residues was conducted using a radioactivity detector or UV detector set at 254 nm; solvent systems being combinations of water and acetic acid, with or without acetonitrile. Column recoveries ranged primarily from 95-104%. Limits of quantitation ranged from 0.01 ppm to 0.001 ppm. Residues were identified by TLC and HPLC co-chromatography with non-labeled reference standards of trifloxystrobin.

Metabolites isolated in the dichloromethane and water layers of straw and grain were investigated by HPLC/MS and HPLC/MS/MS. Metabolites were derivatized to the methyl esters with diazomethane (from N-methyl-N-nitroso-p-toluenesulfonamide and KOH) or to the acetates with acetic anhydride.

2. Results

Table 2.1. Total Radioactive Residues in Wheat Following Two Foliar Applications of Isotopically Labeled [trifluoromethyl-UL-phenyl-^{14}C] Trifloxystrobin.

Study	Crop Matrix	Application Rate	PHI (days)	TRR (ppm)

Metabolism experiment	Hay	262 g ai/ha +247 g ai/ha	3	5.98
	Straw		35	6.12
	Grain			0.262
Supportive experiment	Hay	259 g ai/ha +233 g ai/ha	3	30.39
	Straw		35	48.46
	Grain			0.563

Table 2.2.1 Extraction, Characterization, and Identification of Radioactive Residues in **Wheat Hay (TRR = 5.98 ppm)** Following Two Foliar Applications of **[Glyoxyl-UL-phenyl-^{14}C]Trifloxystrobin** at 250 g ai/ha.

Fraction ID	% TRR	ppm	Residue ID	%TRR	ppm
Dichloromethane	54.1	3.24	Trifloxystrobin	53.1*	3.18*
			CGA321113	1.3	0.08
			CGA373466	0.2	0.01
			NOA414412	0.7	0.04
			NOA443152	0.5	0.03
			BO172741		
			Unidentified peaks (each <0.02 ppm)	0.5	0.03
Aqueous	40	2.39	NOA413163	4.0	0.24
			FHW0115C	1.4	0.09
			FHW0115D	0.7	0.04
			NOA414412 conjugate 1	2.1	0.13
			NOA414412 conjugate 2	6.8	0.40
			NOA443152 conjugate 1	7.2	0.43
			NOA443152 conjugate 2	1.2	0.07
			BO172741 conjugate 1	3.7	0.22
			BO172741 conjugate 2	2.5	0.15
			SA04273	1.6	0.10
			Unidentified peaks (each <0.09 ppm)	9.1	0.54
PES-1 Microwave			Trifloxystrobin	**	**
			FHW0115C	#	#
			SA04271	0.1	0.01
			BO172631conjugate	0.1	0.00
			BO172323 conjugate	0.2	0.01
			Unidentified peaks (each <0.02 ppm)	1.5	0.09
PES-2			N/A	1.4	0.08

N/A = Not further analyzed.
* These values include all 4 isomers in both the dichloromethane and microwave fractions
** Amounts already included in the dichloromethane fraction for these metabolites
# Amounts already included in the aqueous fraction

Table 2.2.2 Extraction, Characterization, and Identification of Radioactive Residues in **Wheat Straw (TRR = 6.12 ppm)** Following Two Foliar Applications of **[Glyoxyl-UL-phenyl-^{14}C]Trifloxystrobin** at 250 g ai/ha.

Fraction ID	% TRR	ppm	Residue ID	%TRR	ppm
Dichloromethane	50	3.06	Trifloxystrobin	29.3*	1.79*
			CGA321113	3.8	0.23
			CGA373466	2.0	0.12
			NOA414412	6.5#	0.40#
			NOA443152	5.9#	0.36#
			BO172741	3.5#	0.21#
			BO172631	0.7	0.04
			BO172323	0.5	0.03
			Unidentified peaks (each <0.04 ppm)	2.7	0.16
Aqueous	26.3	1.61	NOA414412	6.5##	0.40##
			NOA443152	5.9##	0.36##
			BO172741	3.5##	0.21##
			NOA413163	5.0	0.31
			NOA413161	1.4	0.08
			FHW0115C	3.0	0.18
			FHW0115D	1.2+	0.07+
			SA04271	1.5+	0.09+
			NOA414412 conjugate 1	0.3	0.02
			NOA414412 conjugate 2	0.5	0.03
			NOA443152 conjugate 1	2.0	0.12
			NOA443152 conjugate 2	0.3	0.02
			BO172741 conjugate 1	1.2	0.07
			SA04273	3.8	0.23
			Unidentified peaks (each <0.13 ppm)	7.6	0.46
PES-1	23.7	1.45			
Microwave	16.9	1.03	Z,E-isomer	**	**
			E,E-isomer	**	**
			FHW0115C	++	++
			FHW0115D	++	++
			BO172631conjugate	0.9	0.06
			BO172323 conjugate	0.9	0.05
			SA04273	++	++
			Unidentified peaks (each <0.16 ppm)	8.7	0.53
PES-2	6.8	0.42	N/A		

N/A = Not further analyzed
* These values include all 4 isomers in both the dichloromethane and microwave fractions
** Already included in the dichloromethane fraction values
# These values include the individual metabolites present in the aqueous fraction
Amounts already included in the dichloromethane fraction for these metabolites
+ These values include the individual metabolites present in the microwave fraction
++ Amounts already included in the aqueious fraction for these metabolites

Table 2.2.3 Extraction, Characterization, and Identification of Radioactive Residues in **Wheat Grain (TRR = 0.262 ppm)** Following Two Foliar Applications of **[Glyoxyl-UL-phenyl-^{14}C]Trifloxystrobin** at 250 g ai/ha.

Fraction ID	% TRR	ppm	Residue ID	%TRR	ppm
Dichloromethane	16.3	0.043	Trifloxystrobin	17.9*	0.047*
			CGA321113	1.7	0.005
			CGA373466	0.9	0.002
			NOA414412	2.4	0.006
			NOA443152	1.9	0.005
			Unidentified peaks (each <0.005 ppm)	2.4	0.006
Aqueous	60.2	0.158	Trifloxystrobin	**	**
			NOA413163	1.8	0.005
			NOA413161	0.3	0.001
			NOA443152 glucoside	3.4	0.009
			FHW0115C	3.6	0.009
			FHW0115D	3.1	0.008
			SA04271	9.6	0.025
			SA04275	1.5	0.004
			Unidentified peaks (each <0.019 ppm)	21.0	0.055
PES-1	23.5	0.061			
Diastase	17.0	0.044			
Ethyl acetate			Unidentified peaks (each <0.019 ppm)	14.0	0.037
Aqueous			Unknowns	3.0	0.008
PES-2	6.5	0.017			

N/A = Not further analyzed
* These values include all 4 isomers in both the dichloromethane and aqueous fractions
** Already included in the dichloromethane fraction values

Table 2.3. Summary of Characterization and Identification of Radioactive Residues in Wheat Following Two Foliar Applications of Isotopically Labeled Trifloxystrobin at 250 g ai/ha

Metabolite or Fraction	Wheat, Hay (TRR=5.98 ppm)		Wheat, Straw (TRR=6.12 ppm)		Wheat, Grain (TRR=0.262 ppm)	
	%TRR	ppm	%TRR	ppm	%TRR	ppm
Trifloxystrobin	53.1	3.18	29.3	1.79	17.9	0.047
CGA357261 Z,E-isomer	7.1	0.42	5.3	0.33	2.9	0.008
CGA279202 E,E-isomer	40.3	2.41	18.6	1.14	11.1	0.029
CGA357262 Z,Z-isomer	2.2	0.13	2.3	0.14	1.8	0.005
CGA331409 E,Z-isomer	3.6	0.21	3.1	0.19	2.1	0.005

CGA321113	1.3	0.08	3.8	0.23	1.7	0.005
CGA373466	0.2	0.01	2.0	0.12	0.9	0.002
NOA414412	0.7	0.04	6.5	0.40	2.4	0.006
NOA443152	0.5	0.03	5.9	0.36	1.9	0.005
BO172741 (isomer of NOA443152)			3.5	0.21		
NOA413163	4.0	0.24	5.0	0.31	1.8	0.005
NOA413161			1.4	0.08	0.3	0.001
BO172631			0.7	0.04		
BO172323			0.5	0.03		
BO17372						
NOA443152 glucoside					3.4	0.009
FHW0115C	1.4	0.09	3.0	0.18	3.6	0.009
FHW0115D	0.7	0.04	1.2	0.07	3.1	0.008
SA04271	0.1	0.01	1.5	0.09	9.6	0.025
SA04273	1.6	0.10	3.8	0.23	5.0	0.013
SA04275					1.5	0.004
NOA414412 conjugate 1	2.1	0.13	0.3	0.02		
NOA414412 conjugate 2	6.8	0.40	0.5	0.03		
NOA443152 conjugate 1	7.2	0.43	2.0	0.12		
NOA443152 conjugate 2	1.2	0.07	0.3	0.02		
BO172741 conjugate 1	3.7	0.22	1.2	0.07		
BO172741 conjugate 2	2.5	0.15				
BO172631 conjugate	0.1	0.00	0.9	0.06		
BO172323 conjugate	0.2	0.01	0.9	0.05		
Regions						
1,6 (@<0.02 ppm;organic phase)	0.5	0.03				
1,2,4,6,8-13,15,21,22 (@<0.09 ppm;aqueous phase)	9.1	0.54				
2-5,7,10-13 (@<0.02 ppm; microwave extract)	1.5	0.09				
Regions						
1-3,5,8,12,14,15 (@<0.04 ppm;organic phase)			2.7	0.16		
1-3,5,8,9,13,14,20,21,23(@<0.13 ppm;aq phase)			7.6	0.46		
4,5,9-13 (@<0.16 ppm;microwave extract)			8.7	0.53		
Regions						
1,6 (@<0.005 ppm; organic phase)					2.4	0.006
1-5,7,10,11,12 (@<0.019 ppm;aqueous phase 1)					21.0	0.055
1,2 (@<0.019 ppm;ethyl acetate phase)					14.0	0.037
Aqueous phase 2					3.0	0.008

PES-2	1.4	0.08	6.8	0.42	6.5	0.017
Total Identified (TI)	85.9	5.13	70.4	4.31	48.2	0.126
Total Characterized (TC) [1]	12.7	0.76	22.8	1.39	45.3	0.119
Total Extractable (TE) [2]	98.6	5.89	93.2	5.70	93.5	0.245
% Mass Balance [3]	100		100		100	

[1] TC = Sum of all unidentified, extractable residues
[2] TE = Sum of TI and TC; TE is reported as the extractable fraction because of low TRR levels achieved with characterization/identification of the metabolites.
[3] % Mass Balance = TE %TRR + PES-2 %TRR

Trifloxystrobin Reviews
MRID# 45721803, 45721804

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Pages 15 through 16 are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

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3. Discussion

3.1. Methods

Radiolabeled [^{14}C]trifloxystrobin, labeled in the glyoxyl-UL-phenyl ring, was applied as two foliar spray applications at a total of 500 g ai/ha (0.45 lb ai/A) to wheat plants. The first application was made at the BBCH33 growth stage (node 3 at least 2 cm above node 2) and the second was made at the end of flowering (growth stage 69). An immature wheat sample (hay) was collected 3 days after the second treatment, and grain and straw were harvested at maturity (35 days after the second treatment). The TRR were determined by combustion/LSC.

Metabolites were identified by TLC, HPLC, and/or LC/MS analysis (CGA357262, CGA331409, CGA357261, CGA321113, CGA373466, NOA443152 or FHW0115A, NOA414412, NOA413161, NOA413163, SA04271, SA04272 or FHW0115D, SA04274 or FHW0115C) . These methods adequately identified (isomers of trifloxystrobin showed different mass fragmentation patterns) or characterized the metabolites in the various fractions of wheat hay, straw and grain.

3.2. Results

The amounts of radioactivity extractable into the dichloromethane fraction were 54% for hay, 50% for straw and 16% for grain; those remaining in the aqueous phase were 40% for hay, 26% for straw, and 60% for grain. The amounts of unextractable activity left after either microwave treatment or diastase hydrolysis ranged from 1% for hay, 7% for straw, to 7% for grain.

Trifloxystrobin and its 3 isomers were the major residues present in hay (53%), straw (29%) and grain (18%). The results indicate that trifloxystrobin was isomerized to its E,Z, Z,E, and Z,Z isomers before undergoing hydrolysis to the corresponding acids. Hydroxylation of the imino-methyl group and also on the tolyl ring took place. Substantial portions of these hydroxylated metabolites were conjugated to sugars or the imino-hydroxymethyl metabolites were further oxidized to the carboxylic acids. However, all these metabolites were present at less than 10% TRR. The recoveries of the radioactivity in the wheat hay, straw and grain were high, although these matrices were not measured for total radioactivity before sample extraction.

This study yielded some very polar metabolites (as opposed to the tolyl label), primarily phthalic acid derivatives, which were present in the aqueous phases of grain, hay and straw.

Chromatographic analyses were conducted on the dichloromethane, aqueous, and microwave phases of hay, straw and grain samples derived from both the tolyl and glyoxyl labels. The distribution of parent compound and metabolites containing the uncleaved molecule was very similar between the two carbon labels.

4. Deficiencies

None.

5. References

45721803.DER

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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

Date: *10/8/03*

Reviewers: Leung Cheng, PhD, Chemist
Registration Action Branch 3
Health Effects Division (7509C)

Stephen Dapson, PhD, Branch Senior Scientist
Registration Action Branch 3
Health Effects Division (7509C)

DP Barcode: D287242

Citation: 45721803 Reiner, H. and R. Bongartz (2002) Metabolism of [trifluoromethyl-phenyl-UL-^{14}C]Trifloxystrobin in Spring Wheat. Bayer AG Report: MR-027/02. Unpublished study prepared by Bayer AG, FRG. 200 p.

Sponsor: Bayer AG

Executive Summary

Bayer AG (Bayer CropScience) has submitted a study investigating the metabolism of [^{14}C]trifloxystrobin in spring wheat (metabolism experiment), a new study to upgrade the current supplementary wheat metabolism data. Radiolabeled [^{14}C]trifloxystrobin, labeled in the tolyl (trifluoromethylphenyl) ring, was applied twice as foliar spray applications at 250 g ai/ha (0.23 lb ai/A) per application to wheat plants (in an area of 1 m^2) at the BBCH33 stage (node 3 at least 2 cm above node 2) and stage 69 (end of flowering). An immmature wheat sample (hay fraction) was collected 3 days after the second treatment, and grain and straw (growth stage 89) were collected 35 days after the last application.

Total radioactive residues (TRR; expressed as trifloxystrobin equivalents) were 5.20 ppm in wheat hay, 6.13 ppm in wheat straw, and 0.120 ppm in wheat grain, respectively. The TRR of wheat hay, straw and grain were determined by summing the radioactivity in the combined aqueous acetonitrile extracts (measured by liquid scintillation counting, LSC) and in post-extraction solids (PES; measured by combustion and LSC).

The amounts of radioactivity extractable into the dichloromethane fraction were: 53% for hay, 48% for straw and 26% for grain; those remaining in the aqueous phase were: 39% for hay, 24% for straw, and 41% for grain. The amounts of unextractable activity left after either microwave treatment or diastase hydrolysis ranged from 2% for hay, 9% for straw, to 12% for grain. The major residue found in wheat grain, hay and straw was trifloxystrobin (26-44%) with varying amounts of CGA-321113 (2-4%).

Based on the subject metabolism study, the petitioner has proposed that trifloxystrobin undergoes ester hydrolysis in wheat to form the acid metabolite. Hydroxylation of the imino-methyl group and also on the tolyl ring took place. Portions of these hydroxylated metabolites were conjugated or the imino-hydroxymethyl metabolites were further oxidized to the carboxylic acid. However, all these metabolites were each present at less than 10% TRR.

[An additional experiment using wheat plants cultivated in an 0.5 m^2 container was similarly conducted, except that rain was prevented from hitting the plants by an automatically triggered overhead roof, to ensure higher activity for metabolite isolation and identification, if needed (supportive experiment).]

GLP Compliance

The study was conducted in compliance with the current OECD Principles of Good Laboratory Practice, and meets the requirement of US EPA's FIFRA Good Laboratory Practice (GLP; 40 CFR Part 160). Signed and dated Certification of GLP, Certificate of Authenticity, and Quality Assurance statement were provided.

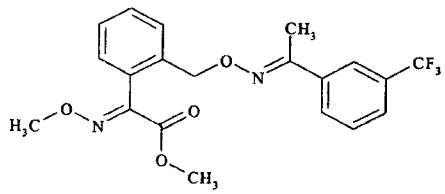
1. Materials and Methods

1.1. Substance

Active Ingredient

Common Name:	Trifloxystrobin
IUPAC Name:	Methoxyimino-{2-[1-(3-trifluoromethyl-phenyl)-ethylideneaminooxymethyl]-phenyl}-acetic acid methyl ester
CAS Name:	(E,E)-alpha-(methoxyimino)-2-[[[[1-[3-(trifluoromethyl)phenyl]ethylidene]amino]oxy]methyl]-benzeneacetic acid methyl ester
CAS Number:	141517-21-7
Company Name:	BO17211 or CGA-279202
Other Synonyms:	None provided

Location of Isotopic Label: Uniformally labeled in the tolyl ring
Radiochemical Purity: >98% (as determined by HPLC and TLC)
Specific Activity: 3.72 MBq/mg (100.6 µCi/mg, 41.1 mCi/mole)



Trifloxystrobin

1.2. Crop and Site

Type and Variety of Crop:	Spring wheat, *var.* Thasos
Growth Environment:	1 m^2 area (Hazelton, Munster, Germany) with netting
Conditions:	fertilized and weed/disease controlled

1.3. Application

Type of Application: Foliar spray applications using a track sprayer
Application Matrix: The radiolabeled test substance was formulated as an EC125
Application Rate: ~250 g ai/ha (0.23 lb ai/A)
Number of Applications: Two foliar applications
Timing of Applications: Plants at BBCH33 and BBCH69 growth stage

Pre-harvest Interval(s): 3 days for immature wheat plants (hay), and 35 days for mature wheat plants (grain and straw)

1.4. Harvest/Post-harvest Procedures

Hay was collected by cutting shortly above the soil surface. The hay sample was dried at room temperature for 4 days, cut in pieces and homogenized with liquid nitrogen. An aliquot of the sample was used for extraction.

Grain and straw were harvested at maturity by cutting wheat plants shortly above the soil surface. The seeds were collected by hand and the remaining ears and chaffs were combined with the straw sample.

Straw was cut in pieces. Straw and grain were homogenized with liquid nitrogen. Aliquots of grain and straw were used for extraction.

Actual extraction and analysis dates were not provided for the wheat metabolism study; however, based on the study experimental termination date, samples of wheat forage, grain, and straw were stored for <6 months from harvest to analysis. Therefore, supporting storage stability data are not required.

Table 1.4.1. Summary of Storage Conditions

Matrix	RAC or Extract	Storage Temperature (C)	Duration [1]
Wheat	Forage/hay	~-20	161 days (5.3 months)
	Grain		100 days (3.3 months)
	Straw		

[1] Based on study experimental termination date.

1.5. Analytical Methods

Subsamples of homogenized wheat grain, hay and straw were extracted 4x with acetontrile:water (8:2 v:v) and suction filtered. The remaining pellet was further extracted (2x) with acetonitrile (ACN):1 N HCl (4:1, v:v) and centrifuged. The combined extracts were measured for TRR by direct LSC (usually in triplicates). The TRR in the remaining nonextractable solids (PES 1) were determined by combustion/LSC. The TRR of wheat grain, hay and straw were determined by summing the radioactivity in the extracts and PES.

Aliquots of the combined extracts were concentrated, partitioned (3x) with dichloromethane, yielding an organic phase and an aqueous phase. The phases were concentrated, and each phase was subjected to radioactivity measurement and analyzed by HPLC.

A representative sample of hay and straw solids PES 1 were subjected microwave (150 C, 20 minutes) extraction with acetonitrile:water (1:1 v/v). The extracts were filtered and the

radioactivity in the filtrate was measured by LSC. The post-extraction solids (PES 2) were dried, and aliquots were measured for radioactivity.

Aliquots of PES 1 were treated 2x with diastase in the presence of sodium azide in citrate-sodium hydroxide buffer (pH 6) at room temperature for 10 days. The suspension was filtered and the filtrates were combined before being measured for TRR.

An aliquot of the grain diastase extract mixed with toluene was hydrolyzed with concentrated HCl at 100 C for 3 hours. The hydrolysate was further extracted with toluene (3x). Alquots of both phases were measured for radioactivity and analyzed by TLC. Chromatography of the aqueous phase 2 was not possible due to the high matrix interference.

TLC analysis of the extracts was conducted using silica gel plates and a solvent system of chloroform:methanol:formic acid:water (75:20:4:21 v:v:v:v) or hexane:diethyl ether:tetrahydrofuran:formic acid:water (10:70:10:1:2 v:v:v:v:v). Radioactivity was detected and quantitated by radioanalytic imaging; nonlabeled standards were visualized under UV light (254nm). Reverse phase-HPLC analysis of the extractable residues was conducted using a radioactivity detector or UV detector set at 254 nm; solvent systems being combinations of water and acetic acid, with or without acetonitrile. Column recoveries ranged primarily from 95-104%. Limits of quantitation ranged from 0.01 ppm to 0.001 ppm. Residues were identified by TLC and HPLC co-chromatography with non-labeled reference standards of trifloxystrobin

Metabolites isolated in the dichloromethane and water layers of straw and grain were investigated by HPLC/MS and HPLC/MS/MS.

2. Results

Table 2.1. Total Radioactive Residues in Wheat Following Two Foliar Applications of Isotopically Labeled [trifluoromethyl-UL-phenyl-^{14}C] Trifloxystrobin.

Study	Crop Matrix	Application Rate	PHI (days)	TRR (ppm)
Metabolism experiment	Hay	263 g ai/ha +249 g ai/ha	3	5.20
	Straw		35	6.13
	Grain			0.120
Supportive experiment	Hay	261 g ai/ha +231 g ai/ha	3	24.45
	Straw		35	44.73
	Grain			0.556

Table 2.2.1 Extraction, Characterization, and Identification of Radioactive Residues in **Wheat Hay (TRR = 5.20 ppm)** Following Two Foliar Applications of **[Trifluoromethyl-UL-phenyl-^{14}C]Trifloxystrobin** at 250 g ai/ha.

Fraction ID	% TRR	ppm	Residue ID	%TRR	ppm
Dichloromethane	53	2.75	Trifloxystrobin	43.5*	2.26*
			CGA321113	1.6	0.08
			CGA373466	0.3	0.02
			NOA414412	2.1	0.11
			NOA443152	1.8	0.09
			BO172741	0.9	0.04
			Unidentified peaks (each <0.07 ppm)	4.3	0.22
Aqueous	39.3	2.04	NOA413163	3.7	0.19
			NOA413161	nd	nd
			NOA414412 conjugate 1	3.5	0.18
			NOA414412 conjugate 2	5.3	0.28
			NOA443152 conjugate 1	8.1	0.42
			NOA443152 conjugate 2	0.9	0.05
			BO172741 conjugate 1	4.5	0.23
			BO172741 conjugate 2	3.7	0.19
			Unidentified peaks (each <0.09 ppm)	9.7	0.50
PES-1	7.7	0.40			
Microwave	5.6	0.29	Z,E-isomer	**	**
			E,E-isomer	**	**
			BO172631conjugate	0.3	0.02
			BO172323 conjugate	0.6	0.03
PES-2	2.1	0.11	N/A		

N/A = Not further analyzed.
* These values include all 4 isomers in both the dichloromethane and microwave fractions
** Amounts already included in the dichloromethane fraction for these metabolites

Table 2.2.2 Extraction, Characterization, and Identification of Radioactive Residues in **Wheat Straw (TRR = 6.13 ppm)** Following Two Foliar Applications of **[Trifluoromethyl-UL-phenyl-^{14}C]Trifloxystrobin** at 250 g ai/ha.

Fraction ID	% TRR	ppm	Residue ID	%TRR	ppm
Dichloromethane	47.8	2.93	Trifloxystrobin	25.5*	1.56*
			CGA321113	4.2	0.26
			CGA373466	1.8	0.11
			NOA414412	7.0#	0.43#
			NOA443152	6.5#	0.40#
			BO172741	4.1#	0.25#
			BO172631	1.0	0.06
			BO172323	0.9	0.05
			Unidentified peaks (each <0.04 ppm)	4.3	0.26
Aqueous	24.1	1.48	NOA414412	##	##
			NOA443152	##	##
			BO172741	##	##
			BO17372	0.9	0.06
			NOA413163	5.8	0.35
			NOA413161	1.8	0.11
			NOA414412 conjugate 1	0.5	0.03
			NOA414412 conjugate 2	0.7	0.04
			NOA443152 conjugate 1	2.2	0.14
			NOA443152 conjugate 2	0.7	0.04
			BO172741 conjugate 1	1.1	0.07
			Unidentified peaks (each <0.07 ppm)	6.0	0.37
PES-1	28.1	1.72			
Microwave	19.1	1.17	Z,E-isomer	**	**
			E,E-isomer	**	**
			BO172631conjugate	1.3	0.08
			BO172323 conjugate	1.1	0.07
			Unidentified peaks (each <0.23 ppm)	13.5	0.83
PES-2	9.0	0.55	N/A		

N/A = Not further analyzed
* These values include all 4 isomers in both the dichloromethane and microwave fractions
** Already included in the dichloromethane fraction values
# These values include the individual metabolites found in the aqueous fraction
Amounts already included in the dichloromethane fraction for these metabolites

Table 2.2.3 Extraction, Characterization, and Identification of Radioactive Residues in **Wheat Grain (TRR = 0.120 ppm)** Following Two Foliar Applications of **[Trifluoromethyl-UL-phenyl-^{14}C]Trifloxystrobin** at 250 g ai/ha.

Fraction ID	% TRR	ppm	Residue ID	%TRR	ppm
Dichloromethane	26.2	0.032	Trifloxystrobin	39.7	0.048
			CGA321113	2.6	0.003
			CGA373466	1.2	0.001
			NOA414412	5.2	0.006
			NOA443152	4.6	0.006
			BO172741	1.5	0.002
Aqueous*	40.7	0.049	NOA413163	2.9	0.004
			NOA413161	0.3	0.001
			NOA443152 glucoside	3.4	0.004
			Unidentified peaks (each <0.003 ppm)	5.5	0.007
PES-1	33.1	0.040			
Diastase	21.4	0.026			
Toluene			Unidentified peaks (each <0.007 ppm)	10.5	0.013
Aqueous			Unknowns	10.9	0.013
PES-2	11.7	0.014			

N/A = Not further analyzed

* Also contained the 4 isomers of trifloxystrobin, the amount of which was already included in the dichloromethane fraction for trifloxystrobin

Table 2.3. Summary of Characterization and Identification of Radioactive Residues in Wheat Following Two Foliar Applications of Isotopically Labeled Trifloxystrobin at 250 g ai/ha

Metabolite or Fraction	Wheat, Hay (TRR=5.20 ppm)		Wheat, Straw (TRR=6.13 ppm)		Wheat, Grain (TRR=0.120 ppm)	
	%TRR	ppm	%TRR	ppm	%TRR	ppm
Trifloxystrobin	(43.5)	(2.26)	(25.5)	(1.56)	(39.9)	(0.048)
CGA357261 Z,E-isomer	6.7	0.35	5.3	0.32	8.0	0.010
CGA279202 E,E-isomer	31.1	1.61	14.3	0.88	19.6	0.024
CGA357262 Z,Z-isomer	2.0	0.11	2.4	0.14	6.3	0.008
CGA331409 E,Z-isomer	3.8	0.20	3.6	0.22	5.8	0.007
CGA321113	1.6	0.08	4.2	0.26	2.6	0.003
CGA373466	0.3	0.02	1.8	0.11	1.2	0.001
NOA414412	2.1	0.11	7.0	0.43	5.2	0.006
NOA443152	1.8	0.09	6.5	0.40	4.6	0.006
BO172741 (isomer of NOA443152)	0.9	0.04	4.1	0.25	1.5	0.002
NOA413163	3.7	0.19	5.8	0.35	2.9	0.004
NOA413161	nd	nd	1.8	0.11	0.3	<0.001
BO172631			1.0	0.06		
BO172323			0.9	0.05		
BO17372			0.9	0.06		
NOA443152 glucoside					3.4	0.004
NOA414412 conjugate 1	3.5	0.18	0.5	0.03		
NOA414412 conjugate 2	5.3	0.28	0.7	0.04		
NOA443152 conjugate 1	8.1	0.42	2.2	0.14		
NOA443152 conjugate 2	0.9	0.05	0.7	0.04		
BO172741 conjugate 1	4.5	0.23	1.1	0.07		
BO172741 conjugate 2	3.7	0.19				
BO172631 conjugate	0.3	0.02	1.3	0.08		
BO172323 conjugate	0.6	0.03	1.1	0.07		
Regions						
1,2,4,6,10 (@<0.07 ppm;organic phase)	4.3	0.22				
1-5,7,12,14,15 (@<0.09 ppm;aqueous phase)	9.7	0.50				
3-6 (@<0.09 ppm; microwave extract)	3.2	0.17				
Regions						
1-8,10,11,14,18,20,21 (@<0.04 ppm;organic phase)			4.3	0.26		
1-10,13,15,21(@<0.07 ppm;aqueous phase)			6.0	0.37		
1-3,5,7-12 (@<0.23 ppm;microwave extract)			13.5	0.83		
Regions						
1-3 (@<0.003 ppm;aqueous phase 1)					5.5	0.007
1-4 (@<0.007 ppm;toluene phase)					10.5	0.013
Aqueous phase 2					10.9	0.013

PES-2	2.1	0.11	9.0	0.55	11.7	0.014
Total Identified (TI)	80.7	4.19	67.1	4.11	61.4	0.074
Total Characterized (TC) [1]	17.2	0.89	23.9	1.46	26.9	0.032
Total Extractable (TE) [2]	97.9	5.09	91	5.58	88.3	0.106
% Mass Balance [3]	100		100		100	

[1] TC = Sum of all unidentified, extractable residues
[2] TE = Sum of TI and TC; TE is reported as the extractable fraction because of low TRR levels achieved with characterization/identification of the metabolites.
[3] % Mass Balance = TE %TRR + PES-2 %TRR

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Pages _____ through _____ are not included in this copy.

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_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

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✓ FIFRA registration data.

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_____ Proprietary information pertaining to the chemical composition of an inert ingredient provided by the source of the ingredient.

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3. Discussion

3.1. Methods

Radiolabeled [^{14}C]trifloxystrobin, labeled in the trifluoromethylphenyl ring, was applied as two foliar spray applications at a total of 512 g ai/ha (0.46 lb ai/A) to wheat plants. The first application was made at the BBCH33 growth stage (node 3 at least 2 cm above node 2) and the second was made at the end of flowering (growth stage 69). An immature wheat sample (hay) was collected 3 days after the second treatment, and grain and straw were harvested at maturity (35 days after the second treatment). The TRR were determined by combustion/LSC.

Metabolites from straw were isolated and purified by HPLC. The isomers of trifloxystrobin were identified by HPLC based on unlabeled reference compounds with known E/Z structure. Metabolite BO17262 was identified by LC/MS and co-chromatography with the reference compound (hydroxymethyl carboxylic acid, NOA443152). Metabolite BO17222 was identified as the major monocarboxylic acid CGA321113 by LC/MS and cochromatography; BO17241 identified as CGA373466 as a minor monocarboxylic acid. Metabolites BO17231 and BO17133 were identified as NOA441412 (hydroxylated carboxylic acid) and BO172741 (hydroxymethyl carboxylic acid). These methods adequately identified (isomers of trifloxystrobin showed different mass fragmentation patterns) or characterized the metabolites in the various fractions of wheat hay, straw and grain.

3.2. Results

The amounts of radioactivity extractable into the dichloromethane fraction were 53% for hay, 48% for straw and 26% for grain; those remaining in the aqueous phase were 39% for hay, 24% for straw, and 41% for grain. The amounts of unextractable activity left after either microwave treatment or diastase hydrolysis ranged from 2% for hay, 9% for straw, to 12% for grain.

Trifloxystrobin and its 3 isomers were the major residues present in hay (44%), straw (26%) and grain (40%). The results indicate that trifloxystrobin was isomerized to its E,Z, Z,E, and Z,Z isomers before undergoing hydrolysis to the corresponding acids. Hydroxylation of the imino-methyl group and also on the tolyl ring took place. Portions of these hydroxylated metabolites were conjugated or the imino-hydroxymethyl metabolites were further oxidized to the carboxylic acid. However, all these metabolites were each present at less than 10% TRR. The recoveries of the radioactivity in the wheat hay, straw and grain were high, although these matrices were not measured before sample extraction.

4. Deficiencies

None.

5. References

B1

13544

038365

Chemical:	**Benzeneacetic acid,.alpha.-(methoxyimino**
PC Code:	**129112**
HED File Code	**11000 Chemistry Reviews**
Memo Date:	**01/17/2002**
File ID:	**DPD267787**
Accession Number:	**412-02-0281**

HED Records Reference Center
05/10/2002