Tembotrione/AE 0172747/PC Code 012801/Bayer CropScience/264
DACO 7.5.1/OPPTS 860.1480/OECD IIA 6.4.1, 6.4.2 and IIIA 8.2, 8.4.1, 8.4.2
Livestock Feeding Study – Poultry

Primary Evaluator	George F. Kramer, Ph.D., Senior Chemist Registration Action Branch (RAB1) Health Effects Division (HED) (7509P)	Date: 18-JUL-2007
Approved by	P.V. Shah, Ph.D., Branch Senior Scientist RAB1/HED (7509P)	Date: 18-JUL-2007

This DER was originally prepared under contract by Dynamac Corporation (2275 Research Boulevard, Suite 300; Rockville, MD 20850; submitted 11/30/2006). The DER has been reviewed by HED and revised to reflect current Office of Pesticide Programs (OPP) policies.

STUDY REPORT:

46695605 Mackie, S. (2005) AE 0172747 - Magnitude of the Residue in Laying Hens. Project Number: RAAEX041, 205/011/09, AE/004/A04/01. Unpublished study prepared by Bayer Corp. and Genesis Midwest Laboratories. 247 p.

The petitioner has submitted an evaluation template for the study (Bayer CropScience DER to Study RAAEX041), which was used to generate this DER; selected sections were copied without alteration or were modified to more specifically reflect the Agency's data evaluation requirements.

EXECUTIVE SUMMARY:

Bayer CropScience has submitted a poultry feeding study with tembotrione. Three treatment groups consisting of 12 laying hens each were dosed orally with gelatin capsules containing tembotrione at target dose rates of 0.2, 0.6, and 2.0 ppm in the diet for 29 consecutive days. Each treatment group consisted of three subgroups of four hens each; samples of eggs and tissues were composited by subgroup for analysis. Eggs were collected twice daily, and samples from study days 0, 1, 3, 7, 10, 14, 17, 21, 24, 26, and 28 were retained for analysis. The hens were sacrificed within 3-5 hours of the final dose on Day 29, and samples of liver (entire), skin (thigh and breast), fat (abdominal and subcutaneous), and muscle (thigh and breast) were collected from each bird.

Samples of eggs (combined yolks and whites; 2.0-ppm dose group only) and tissues were analyzed for residues of tembotrione using the proposed liquid chromatography/mass spectroscopy (LC/MS)/MS enforcement method, Method AE-004-A04-01. The validated limit of quantitation (LOQ) for tembotrione was 0.01 ppm in eggs and tissues, and the estimated limits of detection (LODs) ranged 0.0018-0.0031 ppm. The method is adequate for data collection based on acceptable concurrent recovery and method validation data. No storage stability data are required because all egg and tissue samples were stored frozen from collection to analysis and were analyzed within 23 days of collection.

Residues of tembotrione in eggs were below the LOQ (<0.01 ppm) in all samples from the 2.0-ppm dose group. In fat and muscle, residues of tembotrione were below the LOQ (<0.01 ppm) in all samples from the 0.2- and 0.6-ppm dose groups; maximum residues were 0.034 ppm in fat and 0.020 ppm in muscle from the 2.0-ppm dose group. In skin, residues of tembotrione were

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

MEMORANDUM

Date: 18-JUL-2007

Subject: PP#5F7009. Tembotrione: Section 3 Registration Request for Uses on Corn (Field, Pop, and Sweet). **Summary of Analytical Chemistry and Residue Data.**

DP#s:	325349, 325663, 331222, and 332977	Decision #s.:	362526 and 362531
PC Code:	012801	MRID #s.:	46695529-46695546, 46695601, 46695602, 46695604-46695614
40 CFR §180.	None		
Chemical Class:	Triketone Herbicide		

From: George F. Kramer, Ph.D., Senior Chemist
Registration Action Branch 1 (RAB1)
Health Effects Division (HED) (7509P)

Through: P.V. Shah, Ph.D., Acting Branch Chief
RAB1/HED (7509P)

To: **Eugene Wilson**/Joanne Miller, PM Team 23
Registration Division (RD; 7505P)

This document was originally prepared under contract by Dynamac Corporation (2275 Research Blvd, Suite 300; Rockville, MD 20850; submitted 12/04/2006). The document has been reviewed by HED and revised to reflect current Office of Pesticide Programs (OPP) policies.

Executive Summary

Tembotrione (company code AE 0172747) is a new postemergence herbicide developed by Bayer CropScience for the control of many annual grass and broadleaf weed species. Tembotrione is a member of the triketone chemical family. It is a carotenoid biosynthesis inhibitor, and its primary target site of action in plants is the enzyme 4-hydroxyphenylpyruvate dioxygenase (HPPD); inhibition of the enzyme results in the bleaching of weeds due to the blockage of phenylquinone biosynthesis in the plant tissue.

Bayer CropScience has submitted a Section 3 request to register the end-use product, AE 0172747 Herbicide, a suspension-concentrate (SC) formulation nominally containing 3.5 lb tembotrione ai per gallon (420 g ai/L) for use on field, pop, and sweet corn. This registration

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request represents the first food use for the herbicide. The end-use product is proposed for two foliar spray applications at 0.08 lb ai/A/application with a minimum retreatment interval (RTI) of 14 days, for a maximum seasonal rate of 0.16 lb ai/A. Applications may be made using ground equipment, and use of an adjuvant is required. A 45-day preharvest interval (PHI)/pregrazing interval is proposed for forage; no PHI has been proposed for grain or stover (application to corn that is more mature than growth stage V8 is prohibited). For enhanced weed control and application flexibility, the proposed label specifies that tembotrione can be tank-mixed with many other herbicides and insecticides approved for corn.

Concurrently, Bayer has proposed the establishment of permanent tolerances for residues of tembotrione (2-[2-chloro-4-(methylsulfonyl)-3-[(2,2,2-(trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione) and its metabolite AE 1417268 (metabolite M5; 2-[2-chloro-4-(methylsulfonyl)-3-[(2,2,2-(trifluoroethoxy)methyl]benzoyl]-4,6-dihydroxy-1,3-cyclohexanedione) in/on the following raw agricultural commodities (RACs):

Field Corn, grain	0.01 ppm
Field Corn, forage	0.6 ppm
Field Corn, stover	0.7 ppm
Sweet Corn, K + CWHR	0.03 ppm
Sweet Corn, forage	1.0 ppm
Sweet Corn, stover	1.5 ppm
Popcorn, grain	0.01 ppm
Popcorn, stover	0.20 ppm

In addition, Bayer has proposed the establishment of permanent tolerances for AE 1417268 (metabolite M5) in/on the following livestock commodities:

Cattle Liver	0.5 ppm
Cattle Kidney	0.07 ppm
Goat Liver	0.5 ppm
Goat Kidney	0.07 ppm
Hog Liver	0.5 ppm
Hog Kidney	0.07 ppm
Sheep Kidney	0.07 ppm
Sheep, meat by products	0.5 ppm
Horse Kidney	0.07 ppm
Horse, meat by products	0.5 ppm

The nature of the residue in corn, rotational crops, and livestock is adequately understood based on acceptable metabolism studies conducted on corn, rotational crops, lactating dairy cows, and laying hens.

In corn, tembotrione is metabolized by hydroxylation of the cyclohexyl moiety to form the monohydroxy (M10) and dihydroxy (M5) metabolites, followed by cleavage to the benzoic acid derivative M6. The formation of M6 directly from the parent herbicide could not be ruled out. The metabolite M2 is formed by the subsequent cleavage of the trifluoroethoxy ether bond of M6. The residues of concern for the tolerance expression and risk assessment for corn commodities are tembotrione and its metabolite M5 (Memo, L. Austin *et al.*, 7/18/07; D325935).

To fully understand the nature of the residue in plants, two additional metabolism studies on dissimilar food/feed crops will be required if the petitioner proposes additional food/feed uses in the future.

In rotational crops, the two residue components identified, M6 and M2, were also identified in the primary crop metabolism study. The metabolism of tembotrione in rotational crops appears to be consistent with the pathway observed in the corn metabolism studies. The submitted field rotational crop data indicate that residues of the parent and its metabolites (M2, M5, and M6) were each <0.010 ppm in/on all samples of various rotated crops at the plantback intervals (PBIs) tested. The residue of concern for rotational crops is tembotrione *per se* (Memo, L. Austin *et al.*, 7/18/07; D325935). Unless the petitioner requests PBIs shorter than 90 days, no additional data are required, and tolerances for inadvertent residues in/on rotational crops need not be established.

In livestock, tembotrione is not extensively metabolized. Only the parent was identified and confirmed in cow and poultry tissues following dosing of the test animals with tembotrione as the test substance. Only the metabolite M5 was identified in a supplementary study where cows were dosed with the major plant metabolite M5 as the test substance. The residues of concern for the tolerance expression and risk assessment for livestock commodities are tembotrione and its metabolite M5 (Memo, L. Austin *et al.*, 7/18/07; D325935).

Several liquid chromatography/mass spectroscopy (LC/MS)/MS residue analytical methods were submitted for the determination of residues of the tembotrione and its metabolites in/on corn and livestock commodities. Quantitation of tembotrione and its metabolites is done against a known amount of deuterated internal standard. Method AE/03/01 determines residues of tembotrione and its metabolites M6, M5, and M2 in/on corn commodities. Method 00967 determines residues of tembotrione and its metabolite M5 in meat, milk, and eggs. Method AE-003-A04-02 determines residues of tembotrione *per se* in beef tissues and milk. Method AE-004-A04-02 determines residues of tembotrione *per se* in poultry tissues (skin, muscle, and liver) and eggs (white and yolk). These methods were used as the data-collection methods in the analysis of samples for residues of concern from the various studies associated with the current petition. Each method has been adequately validated by the petitioner as well as by independent laboratories. Methods AE/03/01 and 00967 were also adequately radiovalidated using samples obtained from metabolism studies.

Methods AE/03/01 and 00967 may be suitable enforcement methods for corn and livestock commodities, respectively, provided these methods pass a petition method validation (PMV) by the Analytical Chemistry Laboratory/Biological and Economics Analysis Division (ACL/BEAD). In addition, the methods should be revised to incorporate information concerning residue confirmation as well as conversion of residues to parent equivalents.

The submitted magnitude of the residue data for the RACs of field corn, popcorn, and sweet corn are adequate. There are adequate storage stability data to validate the storage conditions and intervals of samples collected from the field trials.

An acceptable corn processing study is available. The corn study shows that following processing of field corn grain bearing quantifiable residues, total residues of tembotrione and its metabolites (as parent equivalents) concentrated slightly in meal (1.2x processing factor) but did

not concentrate in oil (0.02x), flour (0.80x), grits (1.0x), or starch (0.02x). A tolerance for corn meal need not be established as the recommended RAC tolerance will cover any expected residues in corn meal as a result of the proposed use. A processing study on rotated wheat was also submitted. The wheat study shows that total residues of tembotrione and its metabolites were below the method limit of quantitation (LOQ) of 0.010 ppm in/on rotated wheat grain following treatment of the primary crop at 5x. As residues in the RAC were <0.010 ppm, data on the processed commodities of wheat as a rotated crop are not required.

Adequate dairy cow and poultry feeding studies have been submitted; these studies are acceptable for determining tolerance levels for livestock commodities. Based on the submitted data, HED has concluded that the tolerances, expressed as tembotrione and its metabolite M5, are required for some for livestock commodities (meat byproducts).

Regulatory Recommendations and Residue Chemistry Deficiencies

Pending submission of a revised Section F (see requirements under Proposed Tolerances) and the submission of reference standards for tembotrione and its metabolite M5 (see requirements under Submittal of Analytical Reference Standards), there are no residue chemistry issues that would preclude granting a conditional registration for the requested uses of tembotrione on field corn, popcorn, and sweet corn. Registration should be made conditional pending the submission of additional information concerning the proposed enforcement methods (see requirements under Residue Analytical Methods) and completion of a successful PMV of the proposed enforcement methods for plant and livestock commodities by Agency chemists at ACL/BEAD.

The proposed uses and the submitted data support the following permanent tolerances for the combined residues of tembotrione and its metabolite M5 expressed as tembotrione equivalents, in/on the following corn commodities:

Corn, field, grain	0.03 ppm
Corn, field, forage	0.60 ppm
Corn, field, stover	0.45 ppm
Corn, sweet, kernel plus cob with husks removed	0.04 ppm
Corn, sweet, forage	1.0 ppm
Corn, sweet, stover	1.2 ppm
Corn, pop, grain	0.02 ppm
Corn, pop, stover	0.35 ppm

The proposed uses and the submitted data support the following tolerances for the combined residues of tembotrione and its metabolite M5, expressed as tembotrione equivalents in the following livestock commodities:

Cattle, liver	0.40 ppm
Cattle, meat byproducts, except liver	0.07 ppm
Goat, liver	0.40 ppm
Goat, meat byproducts, except liver	0.07 ppm
Horse, liver	0.40 ppm
Horse, meat byproducts, except liver	0.07 ppm
Sheep, liver	0.40 ppm

Sheep, meat byproducts, except liver ..... 0.07 ppm
Poultry, liver ..... 0.07 ppm

860.1340 Residue Analytical Methods

- To be acceptable as enforcement methods, LC/MS/MS Methods AE/03/01 for plant commodities and 00967 for livestock commodities should undergo successful PMVs by Agency chemists at ACL/BEAD.

- Both methods should be revised to include a calculation for the conversion of residues of the metabolite(s) to parent equivalents for quantitation.

- Separate confirmatory methods for Method AE/03/01 will not be requested provided that two ion transitions are monitored during MS/MS analysis for each analyte.

860.1650 Submittal of Analytical Reference Standards

- Analytical standards for tembotrione and its metabolite M5 are currently not available in the National Pesticide Standards Repository. Analytical reference standards of tembotrione and its metabolite (including the deuterated internal standards) should be supplied, and supplies replenished as requested by the Repository. The reference standards should be sent to the ACL, which is located at Fort Meade, to the attention of either Theresa Cole or Frederic Siegelman at the following address:

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

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

860.1550 Proposed Tolerances

The petitioner is requested to submit a revised Section F specifying the following:

- The tolerance expression for plant commodities should be revised to include the combined residues of tembotrione and M5, expressed as tembotrione equivalents.

- The tolerance expression for livestock commodities should be revised to include the combined residues of tembotrione and its metabolite M5, expressed as tembotrione equivalents.

- The revised tolerances and commodity definitions presented in Table 20 (summarized above).

A human-health risk assessment is forthcoming.

Background

Tembotrione is a herbicide active against a wide range of grasses and broadleaf weeds including cocklebur, crabgrass, mustard, nightshade, ragweed, Russian thistle, kochia, Johnson grass, velvetleaf, amaranth, lambs quarters, pigweed, barnyard grass and water hemp. Bayer CropScience is currently seeking the registration of this active ingredient for use on field corn, sweet corn, and popcorn. Tembotrione is in the triketone class of chemistry. Its mode of action is as an HPPD inhibitor which acts by competing with the enzyme 4-HPPD involved in carotenoid biosynthesis.

Details of the test compound nomenclature for tembotrione and its metabolites M6, M5, and M2 are presented in Table 1. The physicochemical properties of technical grade tembotrione are listed in Table 2. The chemical names and structures of tembotrione and its transformation products are presented in Appendix I.

Table 1. Test Compound Nomenclature for Tembotrione and its Metabolites M6, M5, and M2.

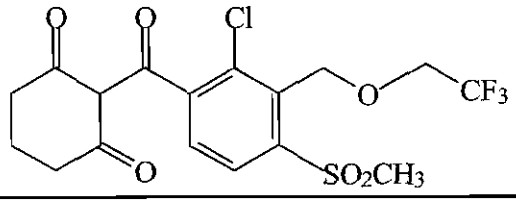
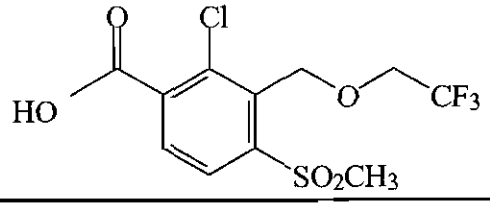
Compound: Tembotrione	Chemical Structure 
Proposed Common name	Tembotrione (Parent)
Company experimental name	AE 0172747
IUPAC name	2-{2-Chloro-4-mesyl-3-[(2,2,2-trifluorocthoxy)methyl]benzoyl}cyclohexane-1,3-dione
CAS name	2-[2-Chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione
CAS #	335104-84-2
End-use product/EP	AE 0172747 Herbicide, EPA Reg No. 264-xxx
Compound: AE 0456148	Chemical Structure 
Common name	Metabolite M6
Company experimental name	AE 0456148
IUPAC name	None provided
CAS name	2-chloro-4-mesyl-3-[(2,2,2-trifluroethoxy)methyl]benzoic acid
CAS #	None provided

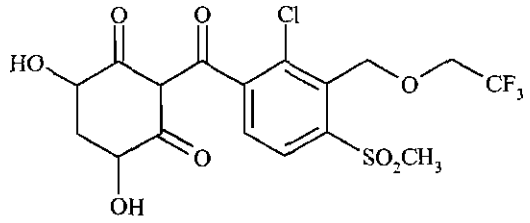
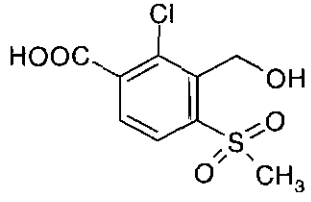
Table 1. Test Compound Nomenclature for Tembotrione and its Metabolites M6, M5, and M2.	
Compound: AE 1417268	Chemical Structure 
Common name	Metabolite M5
Company experimental name	AE 1417268
IUPAC name	None provided
CAS name	2-[2-chloro-4-(methylsulfonyl)-3-[2,2,2-trifluoroethoxy)methyl]benzoyl]-4,6-dihydroxycyclohexan-1,3-dione
CAS #	None provided
Compound: AE 1392936	Chemical Structure 
Common name	Metabolite M2
Company experimental name	AE 1392936
IUPAC name	None provided
CAS name	2-chloro-3-hydroxymethyl-4-mesylbenzoic acid
CAS #	None provided

Table 2. Physicochemical Properties of Technical Grade Tembotrione.		
Parameter	Value	Reference (MRID#)
Melting point	117 °C	46695402
pH @ 24 °C	3.63	
Density (g/mL @ 20 °C)	1.56	
Water solubility (mg/L @ 20 °C)	0.22 at pH 4 28.3 at pH 7 29.7 at pH 9	
Solvent solubility (g/L at 20 °C) DMSO Methylene Chloride Acetone Ethyl Acetate Toluene Hexane Ethanol	 >600 >600 300-600 180.2 75.7 47.6 8.2	
Vapor pressure (Torr, 20 °C)	8.25×10^{-11}	
Dissociation constant (pK_a)	3.2	
Octanol/water partition coefficient (P_{ow} @ 23 °C) (P_{ow} @ 24 °C) (P_{ow} @ 23 °C)	 0.0430 at pH 9.0 0.0807 at pH 7.0 144.9 at pH 2.0	

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Table 2. Physicochemical Properties of Technical Grade Tembotrione.		
Parameter	Value	Reference (MRID#)
UV/visible absorption spectrum (nm)	Primary: 205 Secondary: 284 Tertiary: 240	

860.1200 Directions for Use

The petitioner has submitted a draft label dated 11/5/06 for the 3.5 lb ai/gal SC formulation (AE 0172747 Herbicide; File Symbol 264-xxx). Information pertaining to the proposed end-use product is listed in Table 3. A summary of the proposed use pattern on corn (field, pop, and sweet) is detailed in Table 4. A list of other approved pesticides which may be tank-mixed with tembotrione is presented in Table 5. The proposed rotational crop restrictions are listed in Table 6.

Table 3. Summary of Proposed End-Use Product.						
Trade Name	Reg. No.	ai (% of formulation)	Formulation Type	Target Crops	Target Pests	Label Date
AE 0172747 Herbicide	264-xxx	34.5% (equivalent to 3.5 lb ai/gal)	SC	Field corn, silage corn, seed corn, sweet corn, and popcorn	Various annual broadleaf and grass weeds	Draft label submitted 11/5/06

Table 4. Summary of Proposed Directions for Use of Tembotrione (AE 0172747 Herbicide).					
Application Timing	Single Application Rate (lb ai/A)	Max. Number of Applications per Season	Retreatment Interval (days)	Max. Seasonal Application Rate (lb ai/A)	PHI (days)
Corn (Field, Silage, Seed, Sweet, and Pop)					
Postemergence Broadcast foliar spray	0.08	2	14	0.16	45 days for forage; none listed for grain and stover
Use Directions and Restrictions: Applications must be made to corn from emergence through the V8 stage of growth; application to corn that is more mature than growth stage V8 (i.e., more than 8 visible leaf collars) is prohibited. Applications are to be made in a minimum of 10 gal/A using ground equipment. Aerial application and/or application through any type of irrigation system are prohibited. Use of an external spray adjuvant is required, and the adjuvant type is dependent on the weed spectrum. A 45-day pregrazing interval is proposed for corn forage. AE 0172747 Herbicide may be tank mixed with other herbicides or insecticides; see Table 5 below.					

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Table 5. Tank Mix Partners.[1]	
Trade Name	*Use Directions and other Limitations*
Corn (Field, Silage, Seed, Sweet, and Pop)	
Atrazine	Application of AE 0172747 Herbicide at 0.08 lb ai/A in combination with atrazine at 0.05 lb ai/A will increase the speed of control, weed spectrum and consistency of control. *Do not use atrazine if corn is* >12 inches tall.
Option® Corn Herbicide (foramsulfuron)	AE 0172747 Herbicide at 0.08 lb ai/A may be tank mixed with foramsulfuron for additional grass control.
Liberty® Herbicide (glufosinate ammonium)	AE 0172747 Herbicide may be tank mixed with glufosinate *ammonium* at 32 fl. oz/A. Liberty® Herbicide can only be used on seed designated as LibertyLink®. Do not use MSO/ESO or COC adjuvants in this mixture; only add AMS at 3 lb/A or severe crop injury may occur.
Define™ SC (flufenacet)	AE 0172747 Herbicide at 0.08 lb ai/A may be tank mixed with flufenacet for additional grass residual activity on corn up to the 5-leaf stage.
Glyphosate	AE 0172747 Herbicide may be tank mixed with glyphosate for use on glyphosate-tolerant corn. AE 0172747 Herbicide will enhance broadleaf control, combat glyphosate-resistant weeds and reduce glyphosate-induced weed shifts. Do not use MSO/ESO or COC adjuvants in this mixture; only add AMS.
Ambush® Insecticide (permethrin)	To provide weed and insect control in corn, AE 0172747 Herbicide may be tank mixed with listed foliar insecticides.
Asana® XL Insecticide (esfenvalerate)	
Baythroid® Insecticide (cyfluthrin)	
Capture® Insecticide (bifenthrin)	
Decis® Insecticide (deltamethrin)	
Lorsban® Insecticide (chlorpyrifos)	
Mustang® Insecticide (zeta-cypermethrin)	
Pounce® 3.2EC Insecticide (permethrin)	
Sevin® XLR Insecticide (carbaryl)	
Warrior™ Insecticide (lambda-cyhalothrin)	

[1] All of the listed tank mix partners are registered for use on corn; tolerances or exemptions for tolerances on corn commodities are established.

Table 6. Proposed Rotational Crop Restrictions Listed on AE 0172747 Herbicide Label.

General: If a corn crop has been destroyed by hail or other means soon after an AE 0172747 Herbicide application, field corn, sweet corn, or popcorn may be replanted immediately after the application. Rotational intervals for all other crops following an AE 0172747 Herbicide application are presented in the chart below.

120 days	10 months	18 months
Small grains	Alfalfa	Cucurbits
	Canola	Dry beans
	Cotton	Sunflower
	Peas	Sugar beets
	Potatoes	All other crops
	Snap beans	
	Sorghum	
	Soybean	
	Tomato	

Conclusions: The submitted use directions for the 3.5 lb ai/gal SC formulations are adequate to allow evaluation of the residue data relative to the proposed use.

860.1300 Nature of the Residue - Plants

DER Reference List: 46695530.der.doc (Corn; PH label)
46695529.der.doc (Corn; CY label)

Corn (phenyl-label)

Bayer CropScience has submitted a study investigating the metabolism of [phenyl-U-^{14}C]tembotrione (PH label) in corn. The radiolabeled test substance was formulated as a 5% ai oil-based SC, containing the safener, isoxadifen-ethyl, for dilution in water. The formulated test substance was applied as a broadcast foliar application to container-grown corn (growth stage BBCH 12-14) at a rate equivalent to 0.103 lb ai/A (0.6X) or 0.181 lb ai/A (1.1X) in ~43 gal/A (400 L/ha). Plants were harvested at several intervals after application (days after treatment; DAT). The sampling intervals were: 0, 14, and 49 DAT (immature plants); 84 DAT (forage); and maturity, 124 DAT (stover and grain).

Total radioactive residues (TRR) in corn matrices were determined by summing the radioactivity in rinses (0- and 14-DAT immature plants) and extractable and nonextractable fractions. Following foliar application of PH-labeled tembotrione at 0.103 lb ai/A, TRR were 16.389, 1.516, and 0.013 ppm in immature plants harvested 0, 14, and 49 DAT, respectively, and TRR were 0.023 ppm in forage, 0.046 ppm in stover, and 0.011 ppm in grain. Following foliar application of PH-labeled tembotrione at 0.181 lb ai/A, TRR were 53.747, 3.785, and 0.053 ppm in immature corn plants harvested 0, 14, and 49 DAT, respectively, and TRR were 0.066 ppm in forage, 0.124 ppm in stover, and 0.029 ppm in grain.

Plants collected at 0 and 14 DAT were rinsed with acetonitrile (ACN)/water, which released 12-13% TRR and 4-5% TRR, respectively. Samples were homogenized and extracted with ACN/water (all samples) which released ~85-97% TRR in immature plants (0-49 DAT), 91-93% TRR in forage, 78-79% TRR in stover, and 82-88% TRR in grain. Nonextractable residues in immature plants (0-49 DAT), forage, and grain were <0.1-12.3% TRR. Nonextractable residues in stover were subjected to acid or base hydrolysis; acid hydrolysis released little radioactivity (2.2-2.5% TRR), but base hydrolysis released 13.0-13.4% TRR in stover. Nonextractable residues after exhaustive extractions were 7.6-8.6% TRR (0.004-0.009 ppm) in stover.

These procedures adequately extracted the majority of the residues from corn matrices. Because TRR were determined by summing extractable and nonextractable radioactivity, accountabilities were ~100%. Residues were identified and quantitated by high-performance liquid chromatography (HPLC) and confirmed by thin-layer chromatography (TLC). The petitioner reported significant loss of radioactivity (~18-19% TRR) on HPLC analysis of grain; no significant losses were observed for the other matrices. HPLC/MS, HPLC/MS/MS, and nuclear-magnetic resonance (NMR) analyses were also used for structure elucidation and identification/confirmation of metabolites. Adequate storage stability data were submitted to support the storage intervals and conditions of samples of immature plants and forage from the study. No additional storage stability data are required because all samples were stored frozen

for <6 months prior to initial analysis.

The identified metabolites and their relative distributions were similar for each matrix at both treatment levels. No residues of the parent, tembotrione, were found in 84-DAT forage, stover, or grain samples. Metabolite M6 was identified as the major residue in forage, stover, and grain, at 38.8-40.9% TRR (0.009 and 0.027 ppm) in forage, 33.1-39.6% TRR (0.015 and 0.049 ppm) in stover, and 47.1-59.5% TRR (0.005 and 0.017 ppm) in grain. Other identified residues included M2 at 10.2-10.3% TRR (0.002 and 0.007 ppm) in forage, and 11.6% TRR (0.005 and 0.014 ppm) in stover; and M5 at 9.3-9.8% TRR (0.002 and 0.006 ppm) in forage, and 5.5-6.2% TRR (0.003 and 0.007 ppm) in stover. Both of these metabolites were present at ≤1% TRR (<0.001 ppm) in grain. The unknowns in forage, stover, and grain accounted for ~10-40% TRR and were characterized by the polarity of the residue according to its behavior on HPLC analysis. None of the peaks or regions that were characterized exceeded a level of 14% TRR (0.008 ppm) in forage, 11.5% TRR (0.014 ppm) in stover, or 9.5% TRR (0.002 ppm) in grain.

The parent, tembotrione, was identified in immature corn plants, decreasing from ~27-43% TRR in 0-DAT samples to ≤0.6% TRR in 49-DAT samples. The metabolite M10 was also only identified in immature plants, decreasing from ~28-30% TRR in 0-DAT samples to ≤1.2% TRR in 49-DAT samples. Metabolite M5 was the major residue identified in 14-DAT plants at 64-66% TRR (0.999 and 2.438 ppm), and was also a significant residue in 0-DAT plants (12-24% TRR) and 49-DAT plants (11-14% TRR). Metabolite M6 (the major residue in forage and mature matrices) increased in immature plants with later sampling intervals (≤7% TRR at 0 DAT to 60-65% TRR at 49 DAT). Residues of M2 also increased in immature plants with later sampling intervals (<0.1% TRR at 0 DAT to <8% TRR at 49 DAT).

Based on the PH-labeled corn metabolism study, tembotrione is metabolized in corn by hydroxylation of the cyclohexyl moiety to form the monohydroxy (M10) and dihydroxy (M5) metabolites, followed by cleavage to the benzoic acid derivative (M6). Formation of this metabolite, M6, directly from the parent herbicide could not be ruled out. The metabolite M2 is formed by the subsequent cleavage of the trifluoroethoxy ether bond of M6.

Corn (Cyclohexyl label)

Bayer CropScience has submitted a study investigating the metabolism of [cyclohexyl-U-^{14}C]tembotrione (CY label) in corn. The radiolabeled test substance was formulated as a 5% ai oil-based SC containing the safener, isoxadifen-ethyl, for dilution in water. The formulated test substance was applied as a broadcast foliar application to container-grown corn (growth stage BBCH 14-15) at a rate equivalent to 0.153 lb ai/A (1.1X) in ~43 gal/A (400 L/ha). Whole plants were harvested at several intervals after application. The sampling intervals were: 0, 14, 29, and 49 DAT (immature plants); 89 DAT (forage); and at maturity, 113 DAT (stover and grain).

TRR in corn matrices except grain were determined by summing the radioactivity in the rinses (0- and 14-DAT immature plants) and extractable and nonextractable fractions; TRR in grain were determined by combustion/LSC. Following application of CY-labeled tembotrione, TRR were 13.721, 0.715, 0.120, and 0.019 ppm in immature plants harvested 0, 14, 29, and 49 DAT, respectively, and TRR were 0.035 ppm in forage, 0.025 ppm in stover, and 0.003 ppm in grain. Grain samples were not extracted or further analyzed because of low radioactivity.

Plants collected at 0 and 14 DAT were rinsed with ACN/water before homogenization, which released ~24% and 8% TRR, respectively. Solvent extraction with ACN/water (all samples) released ~75-87% TRR in immature whole plants (0-49 DAT), 67% TRR in forage, and 62% TRR in stover. Nonextractable residues in immature plants (0-49 DAT) ranged from 1.2% TRR (0.159 ppm) in 0-DAT plants to 20.9% TRR (0.004 ppm) in 49-DAT plants. Nonextractable residues in forage and stover, were subjected to acid or base hydrolysis; acid hydrolysis released little radioactivity (5.6-6.5% TRR), but base hydrolysis released 21- 22% TRR in forage and stover. Nonextractable residues after exhaustive extractions were 9.7% and 10.2% TRR (0.003 ppm) in forage and stover, respectively.

These procedures adequately extracted the majority of the residues from corn matrices. Because TRR were determined by summing extractable and nonextractable radioactivity, accountabilities were 100% in all matrices except forage (98.4%) and stover (94.0%), where additional hydrolysis procedures were performed. Residues were identified and quantitated by HPLC and confirmed by TLC. HPLC/MS, HPLC/MS/MS, and NMR analyses were also used for structure elucidation and identification/confirmation of metabolites. Adequate storage stability data were submitted to support the storage intervals and conditions of samples of immature plants and forage from the study. No additional storage stability data are required because all samples were stored for <6 months prior to initial analysis.

The parent, tembotrione, was only identified in early immature plants, decreasing from ~30% TRR in 0-DAT samples to <1% TRR in 29-DAT samples; tembotrione was not found in 49-DAT immature plants, forage or stover. Metabolite M5 was identified as the major residue in all corn matrices: 41.7% TRR (5.723 ppm) in 0-DAT immature plants; 62.7% TRR (0.449 ppm) in 14-DAT immature plants; 60.0% TRR (0.072 ppm) in 29-DAT immature plants; 44.1% TRR (0.008 ppm) in 49-DAT immature plants; 33.9% TRR (0.012 ppm) in forage; and 24.9% TRR (0.006 ppm) in stover. The metabolite M10 was also identified as a major residue in 0-DAT immature plants at 20% TRR and as a minor residue in 14-DAT immature plants at <1% TRR. The remaining solvent-extractable residues, accounting for ~7-37% TRR, were characterized by the polarity of the residue according to its behavior on HPLC. None of the peaks or regions that were characterized as very polar, polar, or medium polar exceeded 9.9% TRR (0.003 ppm) in forage or 14.1% TRR (0.003 ppm) in stover.

Based on the corn metabolism study with CY-labeled tembotrione, tembotrione is metabolized in corn by the hydroxylation of the cyclohexyl moiety to form the monohydroxy metabolite (M10) and dihydroxy metabolite (M5). The cyclohexyl portion of the molecule appeared to be metabolized very rapidly and was apparently incorporated or bound to natural compounds, if not mineralized.

Conclusions: The submitted metabolism data for corn, using test substances radiolabeled in the phenyl and cyclohexyl rings, are adequate to elucidate the nature of the residue in the subject crop. Tembotrione is metabolized in corn by hydroxylation of the cyclohexyl moiety to form the monohydroxy (M10) and dihydroxy (M5) metabolites, followed by cleavage to the benzoic acid derivative M6 (figure 1). The formation of M6 directly from the parent herbicide could not be ruled out. The metabolite M2 is formed by the subsequent cleavage of the trifluoroethoxy ether bond of M6. The residues of concern for the tolerance expression and risk assessment for corn commodities are tembotrione and its metabolite M5 (Memo, L. Austin *et al.*, 7/18/07; D325935). To fully understand the nature of the residue in plants, two additional metabolism studies on

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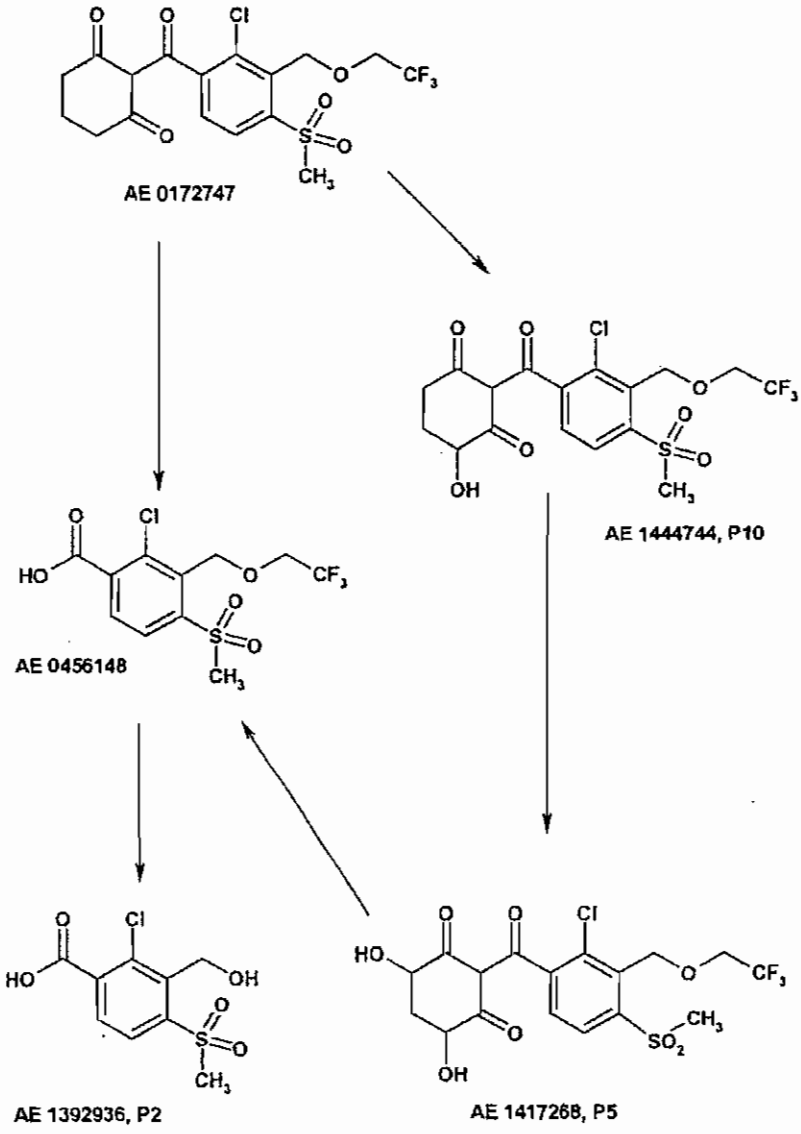
dissimilar food/feed crops will be required if the petitioner applies for additional food/feed uses in the future.

FIGURE 1. Proposed Metabolic Profile of Tembotrione in Corn



860.1300 Nature of the Residue - Livestock

DER Reference List
46695532.der.doc (Cow; PH label)
46695531.der.doc(Cow; CY label)
46695535.der.doc (Cow; M5 study)
46695534.der.doc (Hen; PH label)
46695533.der.doc (Hen; CY label)

Cow (PH label)

Bayer CropScience has submitted a study investigating the metabolism of [phenyl-U-^{14}C]tembotrione in lactating cows. The test substance was administered orally to two cows, one at 1 ppm and one at 10 ppm in the diet. The actual doses, based on feed consumption during the experiment, were 0.82 (0.69X the calculated dietary burden, see Table 8A) and 8.01 (6.8X) ppm. The cows were dosed two times daily for 7 consecutive days. Milk was collected twice daily throughout the study, and tissues (muscle, fat, liver, and kidney) were collected at sacrifice, ~23 hours after the final dose.

TRR following dosing at 0.82 ppm were <LOQ in milk, muscle (fore and hindquarter), and omental fat, 0.031 ppm in renal fat, 0.433 ppm in kidney, and 1.696 ppm in liver. TRR following dosing at 8.01 ppm were <LOQ in milk, muscle (fore and hindquarter), and fat (renal and omental), 0.550 ppm in kidney, and 2.128 ppm in liver. At both dose levels, radioactivity was highest in liver, and radioactivity in milk was below the LOQ at all time points. The majority of the radioactivity (~73-111% of the administered dose) was excreted.

Metabolic profiling was conducted on kidney and liver from the high-dose (8.01 ppm) cow. Solvent extraction with hexane, ethyl acetate, ACN, and acidified ACN released ~87-103% of the TRR in kidney and liver. Polar organic solvents extracted more residues than nonpolar solvents; hexane dissolved little residue, ethyl acetate dissolved more, but ACN was the most efficient solvent. Nonextractable residues following solvent extraction were 6.3% TRR (0.034 ppm) in kidney. Nonextractable residues in liver were subjected to protease hydrolysis, which released an additional 3.4% TRR. Nonextractable residues after exhaustive extractions were 0.7% TRR (<0.02 ppm) in liver.

The extraction procedures were adequate; and the accountabilities were ~93 and 107% in kidney and liver, respectively. Residues were identified and quantitated by HPLC and confirmed by LC/MS. Acceptable storage stability data from a cow metabolism study with cyclohexyl-labeled tembotrione (46695531.der.doc) are available to support the storage intervals and conditions of samples of liver from the current study. No additional storage stability data are required because it appears that all samples were stored frozen for <6 months prior to analysis.

The major and only residue identified was the parent, tembotrione. Tembotrione was identified at 70.1% TRR (0.386 ppm) in kidney, and 96.8% TRR (2.061 ppm) in liver. Two unknowns, accounting for 2.9% TRR (0.016 ppm) in kidney and 1.7% TRR (0.035 ppm) in liver were detected but were not further investigated.

Based on the cow metabolism study with PH-labeled tembotrione, tembotrione is not extensively metabolized in ruminants, with the major component in tissues being parent compound. Although the dosing levels differed by 10x, the differences in TRR in kidney and liver from the

different dosing levels did not approach this order of magnitude (i.e., there was a lack of residue-level dose dependence). These results suggest that accumulation of tembotrione in tissues was approaching saturation at the low-dose level and that comparable levels of residues would eventually be reached following any dose level, provided the duration of dosing was sufficiently prolonged.

Cow (CY label)

Bayer CropScience has submitted a study investigating the metabolism of [cyclohexyl-U-^{14}C]tembotrione in lactating cows. The test substance was administered orally to two cows, one at 1 ppm and one at 10 ppm in the diet. The actual doses, based on feed consumption during the study, were 0.98 (0.83X) and 9.67 (8.2X) ppm. The cows were dosed two times daily for 7 consecutive days. Milk was collected twice daily throughout the study, and tissues (muscle, fat, liver, and kidney) were collected at sacrifice, 23.3 hours after the final dose.

TRR following dosing at 1 ppm were <LOQ-0.002 ppm in milk, <LOQ in muscle (fore and hindquarter) and omental fat, 0.011 ppm in renal fat, 0.550 ppm in kidney, and 2.730 ppm in liver. TRR following dosing at 10 ppm were 0.008-0.018 ppm in milk, <LOQ in forequarter muscle, 0.011 ppm in hindquarter muscle, 0.094 ppm in renal fat, 0.076 ppm in omental fat, 0.829 ppm in kidney, and 3.082 ppm in liver. Radioactivity was highest in liver and appeared to plateau in milk following 3 days of dosing. The majority of the radioactivity (~76-87% of the administered dose) was excreted.

Metabolic profiling was conducted on milk and tissues from the high-dose (10 ppm) cow. Solvent extraction with hexane, ethyl acetate, ACN, and acidified ACN released ~41-47% of the TRR in milk (Day 5) and hindquarter muscle, and ~90-94% TRR in fat, kidney, and liver. Nonextractable residues following solvent extraction were 58.4% TRR (0.010 ppm) in milk, 25.8% TRR (0.003 ppm) in muscle, 5.4% TRR (0.005 ppm) in fat, and 1.5% TRR (0.012 ppm) in kidney. Nonextractable residues in liver were subjected to protease digestion, which released an additional 2.3% TRR. A separate sample of kidney was subjected to protease digestion without prior solvent extraction, which released ~97% TRR. Nonextractable residues after exhaustive extractions were 0.7% and 1.8% TRR (≤0.02 ppm) in liver and kidney, respectively.

The extraction procedures were adequate; and the accountabilities were 82-106%. Residues were identified and quantitated by HPLC and confirmed by LC/MS. Adequate storage stability data were submitted to support the storage intervals and conditions of samples of liver from the study. No additional storage stability data are required because it appears that all samples were stored frozen for <6 months prior to initial analysis.

The major and only residue identified in milk and all tissues was the parent, tembotrione. Tembotrione was identified at 21.2% TRR (0.003 ppm) in milk, 45.4% TRR (0.005 ppm) in muscle, 82.5% TRR (0.070 ppm) in fat, 92.3% TRR (0.765 ppm) in kidney, and 92.8% TRR (2.859 ppm) in liver. A second metabolite, accounting for 3.4% TRR (0.106 ppm) in liver, was characterized by LC/MS, but no structure was elucidated. An unknown in milk, accounting for 13.8% TRR (0.002 ppm) and with a retention time similar to that of the liver unknown, was not further investigated.

Based on the CY-labeled cow metabolism study, tembotrione is not extensively metabolized in ruminants, with the major component in all tissues being parent compound.

Cow (M5 study)

Bayer CropScience has submitted a study investigating the metabolism of [cyclohexyl-U-^{14}C]M5, a plant metabolite of the herbicide tembotrione, in lactating cows. The test substance was administered orally to a single cow at 10 ppm in the diet. The actual average dose, based on feed consumption during the experiment, was 11.8 ppm (10X). The cow was dosed two times daily for 5 consecutive days. Milk was collected twice daily throughout the study, and tissues (muscle, fat, liver, and kidney) were collected at sacrifice, ~24 hours after the final dose.

TRR following dosing at 11.8 ppm were 0.003-0.012 ppm in milk, <LOQ in muscle and fat (renal and omental), 0.176 ppm in kidney, and 0.611 ppm in liver. TRR were highest in liver, and the highest residues in milk were observed just prior to final dosing. The majority of the radioactivity (~74% of the administered dose) was excreted.

Metabolic profiling was conducted on kidney, liver, and milk (sample designated Day 6 a.m.). Solvent extraction with hexane, ethyl acetate, ACN, and acidified ACN released ~87-88% of the TRR in kidney and liver, and solvent extraction with ACN and methanol released ~36% TRR in milk. Nonextractable residues following solvent extraction were 11.1% TRR (0.020 ppm) in kidney and 64.1% TRR (0.008 ppm) in milk. Nonextractable residues in liver were subjected to methanol extraction and subsequent protease hydrolysis, which released an additional 6.2% and 6.5% TRR, respectively. Nonextractable residues in liver after exhaustive extractions were 2.9% TRR (<0.02 ppm).

The extraction procedures were adequate; and the accountabilities were 100-103%. Residues were identified and quantitated by HPLC equipped with a flow-through radiodetector and confirmed by LC/MS. Supporting storage stability data are not required because samples were analyzed within <6 months of collection.

The major and only residue identified in tissues was the unchanged metabolite, M5. M5 was identified at 81.4% TRR (0.143 ppm) in kidney and 76.1% TRR (0.466 ppm) in liver. Two minor metabolites were observed in kidney (both ≤4.2% TRR) and liver (both ≤8% TRR), but were not further investigated.

Based on the cow metabolism study with CY-labeled metabolite M5, the metabolite undergoes minimal metabolism in ruminants, with the major component in tissues and excreta being the unchanged M5.

Hen (PH label)

The metabolism of [phenyl-U-^{14}C]tembotrione in laying hens was investigated. The test substance was administered orally to groups of five hens at 1 ppm and 10 ppm in the diet. The actual doses, based on the average feed consumption during the experiment, were 1.31 and 11.33 ppm (~54x and 470x the dietary burden for tembotrione; see Table 8A). The hens were dosed once daily for 14 consecutive days. Eggs were collected twice daily throughout the study, and

tissues (muscle, fat, liver, and skin with attached fat) were collected at sacrifice, within ~24 hours of the final dose.

TRR following dosing at 1.31 ppm in the diet were <LOQ to 0.0003 ppm in egg whites, <LOQ-0.013 ppm in egg yolks, 0.011 ppm in muscle, 0.005 ppm in fat, 1.556 ppm in liver, and 0.065 ppm in skin with attached fat. TRR in hen matrices following dosing at 11.33 ppm were 0.001-0.003 ppm in egg whites, 0.001-0.106 ppm in egg yolks, 0.061 ppm in muscle, 0.043 ppm in fat, 2.099 ppm in liver, and 0.371 ppm in skin with attached fat. At both dose levels, radioactivity was highest in liver. Radioactivity in egg whites was low at all time points, while radioactivity in egg yolks appeared to plateau after ~7 days of dosing (both dosing levels). The majority of the radioactivity (~89-92% of the administered dose) was excreted.

Metabolic profiling was conducted on tissues and egg yolk (Day 8) from the high dose (11.33 ppm) hens. A second subsample of liver was also extracted using the same procedures to further investigate a metabolite. Solvent extraction with hexane, ethyl acetate, ACN and acidified ACN released ~82-104% of the TRR in muscle, fat, skin and egg yolk, and 54% and 95% TRR in the first and second liver subsamples, respectively. Hexane extracted only minor residues in all matrices except fat (3.7% TRR), ethyl acetate extracted the majority of residues in fat, skin, and egg yolk, and ACN extracted the majority of residues for liver. Nonextractable residues following solvent extraction were 2.1-5.7% TRR (0.002-0.008 ppm) in muscle, fat, skin and egg yolk. Nonextractable residues in liver (both subsamples) were subjected to protease hydrolysis which released an additional 35% and 4% TRR from the first and second subsamples, respectively. Nonextractable residues of the first extraction sample were also subjected to acid hydrolysis which released an additional 1.5% TRR. Nonextractable residues in liver after exhaustive extractions were 2.6% TRR (0.055 ppm) and 0.4% TRR (0.008 ppm) in first and second subsamples, respectively.

The extraction procedures were adequate; and the accountabilities were 89-107%. Residues were identified and quantitated by HPLC, and confirmed by LC/MS. Acceptable storage stability data, submitted in support of a hen metabolism study with cyclohexyl-labeled tembotrione (46695533.der.doc), are available to support the storage intervals and conditions of samples of liver from the current study. No additional storage stability data are required because all samples were stored frozen for <6 months prior to analysis.

The major and only residue identified was the parent, tembotrione. Tembotrione was identified at 74.6% TRR (0.046 ppm) in muscle, 62.6% TRR (0.027 ppm) in fat, 82.6% TRR (1.730 ppm) in liver (first extraction), 97.1% TRR (2.037 ppm) in liver (second extraction), 81.7% TRR (0.303 ppm) in skin with attached fat, and 72.9% TRR (0.077 ppm) in egg yolk. The identity of the parent was confirmed by LC/MS analysis of the ethyl acetate extract (ACN/water phase) of skin and liver, the combined ACN extract of liver, and the ethyl acetate phase following protease hydrolysis of liver. Unknowns accounted for to 0.7-5.3% TRR in egg yolk and tissues; no single unknown was present in any matrix at >2.6% TRR (0.043 ppm).

Based on the hen metabolism study with PH-labeled tembotrione, the petitioner concluded that tembotrione was not extensively metabolized by hens, with the major component in all tissues being parent compound. The petitioner stated that the similarity in the residue concentrations in liver at the two dose levels suggested that accumulation of tembotrione in liver was close to

saturation at the low dose level. The 10-fold increase in the dose level produced an increase of 5.7-8.9x in the radioactivity in all other matrices, and only a 1.3x increase in liver.

Hen (CY label)

Bayer CropScience has submitted a study investigating the metabolism of [cyclohexyl-U-^{14}C]tembotrione in laying hens. The test substance was administered orally to groups of five hens at 1 ppm and 10 ppm in the diet. The actual doses, based on the average feed consumption during the experiment, were 1.14 (48X) and 12.34 (510X) ppm. The hens were dosed once daily for 14 consecutive days. Eggs were collected twice daily throughout the study, and tissues (muscle, fat, liver, and skin with attached fat) were collected at sacrifice, ~24 hours after the final dose.

TRR following dosing at 1.14 ppm in the diet were 0.001 ppm in egg whites, <0.001-0.018 ppm in egg yolks, 0.011 ppm in muscle, 0.004 ppm in fat, 1.688 ppm in liver, and 0.053 ppm in skin with attached fat. TRR following dosing at 12.34 ppm were 0.002-0.017 ppm in egg whites, <LOQ to 0.196 ppm in egg yolks, 0.063 ppm in muscle, 0.030 ppm in fat, 1.712 ppm in liver, and 0.404 ppm in skin with attached fat. At both dose levels, TRR were highest in liver. TRR plateaued after 3 days of dosing in egg whites and after 6 days of dosing in egg yolk. The majority of the radioactivity (~92-96% of the administered dose) was excreted.

Metabolic profiling was conducted on tissues and egg whites and yolk (Day 13) from the high-dose (12.34 ppm) hens. Solvent extraction with hexane, ethyl acetate, ACN, and acidified ACN released ~80-94% of the TRR in muscle, fat, liver, skin and egg yolk; and 41% TRR in egg whites. Hexane extracted only minor residues in all matrices except fat, where ~24% TRR were extracted. Nonextractable residues following solvent extraction were 1.9-8.1% TRR (0.002-0.008 ppm) in muscle, fat, and skin; nonextractable residues in egg whites were 51.4% TRR (0.005 ppm). Nonextractable residues in liver and egg yolk were subjected to protease hydrolysis which released an additional 5-6% TRR, and a separate subsample of skin was subjected to protease hydrolysis without previous solvent extraction which released ~90% of the TRR. Nonextractable residues after exhaustive extractions were 1.7% TRR (0.029 ppm) in liver, 12.2% TRR (0.018 ppm) in egg yolk, and 1.8% TRR (0.007 ppm) in skin.

The extraction procedures were adequate; and the accountabilities were 91-102%. Residues were identified and quantitated by HPLC equipped with a flow-through radiodetector and confirmed by LC/MS. Adequate storage stability data were submitted to support the liver storage intervals and conditions. No additional storage stability data are required because it appears that all samples were stored for <6 months prior to initial analysis.

The major and only residue identified was the parent, tembotrione, identified at 90.5% TRR (0.057 ppm) in muscle, 23.3% TRR (0.007 ppm) in fat, 89.8% TRR (1.536 ppm) in liver, 90.1% TRR (0.364 ppm) in skin with attached fat, 79.7% TRR (0.114 ppm) in egg yolk, and 18.2% TRR (0.002 ppm) in egg whites. Up to three unknowns were observed in muscle, liver, and egg white. In muscle and egg white, no single unknown was present at >0.001 ppm. In liver, one unknown, present at 3.6% TRR (0.061 ppm), was further investigated by LC/MS and was tentatively identified as a hydroxy product of the ammonium-adducted parent compound; the position of hydroxylation could not be determined. The two remaining liver unknowns were each present at ≤2.3% TRR (≤0.040 ppm) and were not further investigated.

Based on the results of the CY-labeled hen metabolism study, tembotrione was not extensively metabolized in hens, with the major component in all tissues being parent compound. Only one other minor residue was tentatively identified in liver, the hydroxy metabolite of the parent compound, and a structure was not proposed.

Conclusions: The submitted cow and poultry metabolism data, using the parent compound radiolabeled in the phenyl and cyclohexyl rings, and the cow metabolism data using cyclohexyl-labeled M5 are adequate to satisfy data requirements. The livestock metabolism studies indicate that tembotrione and its M5 metabolite are not extensively metabolized. Only the parent was identified and confirmed in cow and poultry tissues, and only metabolite M5 was identified in the supplementary study. The residues of concern for the tolerance expression and risk assessment for livestock commodities are tembotrione and its metabolite M5 (Memo, L. Austin *et al.*, 7/18/07; D325935).

860.1340 Residue Analytical Methods

Plant method

DER Reference List	46695537.der.doc (Includes MRIDs 46695540, 46695542, and 46695544); LC/MS/MS Method AE/03/01

LC/MS/MS Method AE/03/01

Bayer CropScience has submitted descriptions and validation data for LC/MS/MS Method AE/03/01 (also referred to as Method 201059 in one study report). The method determines residues of tembotrione (parent) and its metabolites M6, M5, and M2 in/on plant commodities. Method AE/03/01 was the data-collection method used for determination of residues of the parent and its metabolites (M6, M5, and M2) in/on plant samples collected from supporting studies (storage stability, crop field trials, processing, and limited field rotational trials) associated with PP#5F7009. It is also the proposed enforcement method.

Using Method AE/03/01, residues of tembotrione and its metabolites M2, M5, and M6 are extracted from crop matrices with ACN:water (1:1, v:v) using accelerated solvent extraction. Internal standards of the deuterated analytes are added to the extract. For analysis of parent, M5, and M6, an aliquot of the extract is concentrated via Turbo-Vap. For analysis of M2, an aliquot of the extract is loaded onto a strong-anion-exchange (SAX) solid-phase extraction (SPE) cartridge and eluted with oxalic acid. The SPE eluate is concentrated. The concentrates are reconstituted in 0.1% formic acid and filtered for LC/MS/MS analysis. Quantitation of tembotrione and its metabolites is done against a known amount of deuterated internal standard. Identification is confirmed by comparing the ion ratio of the analyte to that of the analytical standard. The LOQ, determined as the lowest fortification level with adequate recovery, is 0.010 ppm for each analyte. The calculated LODs for the parent and its metabolites were each $\leq$0.004 ppm in corn matrices.

The initial validation of Method AE/03/01, performed by the petitioner, was conducted using control samples of: field corn forage, fodder, and grain (early and mature grains); sweet corn grain (early and mature grains); sugarcane; and turnip roots. Two fortification levels of 0.01 and

0.05 ppm were used for each combination of matrix and analyte. The method recoveries were, overall, adequate and within the acceptable range of 70-120% with the exception of turnip root samples fortified with M5 which yielded average recoveries of 124% and 130% at the respective fortification levels of 0.01 and 0.05 ppm, and field corn forage fortified with M5 at 0.05 ppm which yielded an average recovery of 129%.

The method was also successfully validated by an independent laboratory using corn grain and forage at fortification levels of 0.01 ppm (LOQ), 0.05 ppm, and 0.50 ppm. The fortification levels used in method validations as well as from concurrent analysis of samples from various studies are adequate to bracket expected residue levels. Finally, Method AE/03/01 was adequately validated using weathered samples of corn stover obtained from a previous corn metabolism study.

The method has been shown to be specific for the target analytes. The method used LC/MS/MS for detection and quantitation of the analytes. The study report for MRID 46695537 stated that Revision AE/03/01-01, once signed and issued, will supersede Method AE/03/01; however, no descriptions of the revisions were included except a statement that the revision is essentially the same as the original method and further provides a second ion transition which may be used for confirmation purposes.

Livestock methods

DER Reference List	46695545.der.doc (Includes MRID 46940601); LC/MS/MS Method 00967 46695536.der.doc (Includes MRIDs 46695538 and 46695543); LC/MS/MS Method AE-003-A04-02 46695539.der.doc (Includes MRID 46695541); LC/MS/MS Method AE-004-A04-02

LC/MS/MS Method No. 00967

Method No. 00967 determines residues of tembotrione and its dihydroxy metabolite M5 in meat, milk, and eggs. Method No. 00967 was the data-collection method used for the analysis of M5 residues in samples taken from the cattle feeding study. It is also one of the proposed livestock enforcement methods.

Using Method No. 00967, residues of tembotrione and M5 are extracted from poultry eggs, bovine meat, kidney and liver with a mixture of ACN:water (8:2, v:v). For milk, the extraction is performed with ACN. After centrifugation and a second extraction with subsequent centrifugation, the supernatant of the extract is partitioned twice with hexane. The hexane phase is discarded, and the ACN fraction is removed *in vacuo*. Methanol and acetic acid are added resulting in a final mixture of methanol:0.2% acetic acid (1:1, v:v). Quantification of tembotrione and M5 is performed with LC/MS/MS. The LC/MS/MS method includes measurement of a second MS transition for both analytes to serve as the confirmatory method. The validated LOQs for each analyte are 0.002 ppm in whole milk and 0.010 ppm in other matrices. The estimated LODs for each analyte were 0.005 ppm in whole milk and 0.002 ppm for beef meat, kidney and liver, and poultry egg.

The initial validation of Method No. 00967, performed by the petitioner, was conducted using control samples of chicken eggs, whole milk, and beef meat, liver, and kidney. The results

demonstrated adequate method recoveries of tembotrione and M5 from all tested matrices. The fortification levels for both analytes in all matrices were at the LOQ and 10x LOQ. For milk, the fortification levels were 0.002 ppm and 0.02 ppm. For eggs and beef meat, liver, and kidney, the fortification levels were 0.01 ppm and 0.10 ppm. Recoveries of tembotrione and M5, respectively, ranged: 92-105% and 91-108% in chicken eggs; 86-108% and 88-110% in beef meat; 86-113% and 85-114% in beef liver; 90-117% and 88-109% in beef kidney; and 93-100% and 79-99% in whole milk. The petitioner also conducted method validation analysis at the second ion transition for all matrices with overall recoveries in the range of 76-114% for tembotrione and 81-113% for M5.

The method was also successfully validated by an independent laboratory using the same matrices and fortification levels cited above. Method recoveries ranged 70-115% for tembotrione and 63-101% for M5 for all matrices.

LC/MS/MS Method AE-003-A04-02

Method AE-003-A04-02 determines residues of tembotrione *per se* in beef tissues and milk and was the data-collection method used for determination of tembotrione residues in samples collected from the cattle feeding study. It is also the same as one of the proposed livestock enforcement methods associated with PP#5F7009. Method AE-003-A04-02 is a revision to Method AE-003-A04-01. The only change was the incorporation of ion-confirmation information for tembotrione.

Using Method AE-003-A04-02, residues of tembotrione in milk, eggs, and beef and poultry tissues are extracted with ACN:H_2O (1:1, v:v) using accelerated solvent extraction. The extracted residues of tembotrione are fortified with the internal standard, diluted, and an aliquot of the diluted extract is filtered and concentrated. A 6% formic acid solution is added to the concentrated sample; the extract is diluted and filtered for LC/MS/MS analysis. Quantitation of tembotrione is done against a known amount of deuterated internal standard. Identification is confirmed by comparing the ion ratio of the analyte to that of the analytical standard. The validated LOQ is 0.01 ppm for all matrices. The calculated LODs for tembotrione were $\leq$0.002 ppm in various livestock matrices.

The initial validation of Method AE-003-A04-02, performed by the petitioner, was conducted using control samples of beef fat, kidney, muscle, liver, whole milk, skim milk, and milk fat. The method recoveries were, overall, adequate and mostly within the acceptable range of 70-120%. Following fortification of samples at 0.010 ppm (LOQ), 0.050 ppm and 0.200 ppm, recoveries of tembotrione ranged 69-85% in beef fat, 70-83% in beef kidney, 81-99% in beef muscle, 83-103% in beef liver, 81-99% in whole milk, 83-99% in skim milk, and 72-100% in milk fat.

The method was also successfully validated by an independent laboratory using beef liver as the matrix at fortification levels of 0.01 ppm, 0.02 ppm, and 0.1 ppm. The fortification levels used in method validations as well as from concurrent analysis of samples from various studies are adequate to bracket expected residue levels. Finally, Method AE-003-A04-02 was adequately radiovalidated using aged samples of beef liver obtained from a previous cattle metabolism study.

LC/MS/MS Method AE-004-A04-02

Method AE-004-A04-02 determines residues of tembotrione *per se* in poultry tissues (skin, muscle, and liver) and eggs (white and yolk). It was the data-collection method used for determination of tembotrione residues in samples collected from the poultry feeding study and is also one of the proposed enforcement methods associated with PP#5F7009.

Using Method AE-004-A04-02, residues in poultry matrices are extracted with ACN:deionized water (1:1,v:v) using accelerated solvent extraction. Extracted residues of tembotrione are fortified with the internal standard, diluted, and an aliquot of the diluted extract is filtered and concentrated. A 6% formic acid solution is added to the concentrated extract. The extract is diluted and filtered for LC/MS/MS analysis. Quantitation of AE 0142747 is done against a known amount of deuterated internal standard. Identifications are confirmed by comparing the ion ratio of the analyte to that of the analytical standard. The validated LOQ reported in the method submission is 0.010 ppm for all matrices. The calculated LODs for whole egg, poultry skin, poultry muscle, and poultry liver were 0.0018 ppm, 0.0031 ppm, 0.0025 ppm, and 0.0025 ppm, respectively.

The initial validation of Method AE-004-A04-02, performed by the petitioner, was conducted using control samples of whole eggs and chicken skin, muscle, and liver. The method recoveries were adequate and within the acceptable range of 70-120%. Following fortification of samples at 0.010 ppm (LOQ), 0.050 ppm and 0.200 ppm, recoveries of tembotrione ranged 77-102% in chicken skin, 71-97% in whole egg, 74-98% in chicken muscle, and 79-106% in chicken liver. The concurrent method recoveries from the analysis of samples from the poultry feeding study were also acceptable and indicate that Method AE-004-A04-02 is adequate for data collection.

Method AE-004-A04-02 was successfully validated by an independent laboratory using whole eggs as the matrix. The mean recoveries were 92.9%, 90.1%, and 92.8% at spike levels of 0.01, 0.02, and 0.10 ppm, respectively. Although not identified by its method designation number, a similar LC/MS/MS method was adequately radiovalidated using aged samples of whole eggs obtained from a laying hen metabolism study; the results of the radiovalidation study which included data for both beef liver and poultry eggs are summarized in 46695536.der.doc.

Conclusions: The petitioner has submitted several LC/MS/MS residue analytical methods for the determination of residues of the parent and its metabolites in/on corn and livestock commodities. Method AE/03/01 determines residues of tembotrione and its metabolites M6, M5, and M2 in/on corn commodities. Method 00967 determines residues of tembotrione and its metabolite M5 in meat, milk, and eggs. Method AE-003-A04-02 determines residues of tembotrione *per se* in beef tissues and milk. Method AE-004-A04-02 determines residues of tembotrione *per se* in poultry tissues (skin, muscle, and liver) and eggs (white and yolk). These methods were used as the data-collection methods in the analysis of samples for residues of concern from the various studies associated with the current petition. Each method has been adequately validated by the petitioner as well as by independent laboratories. Methods AE/03/01 and 00967 were also adequately radiovalidated using weathered samples obtained from metabolism studies.

HED has determined that Methods AE/03/01 and 00967 may be suitable enforcement methods for corn and livestock commodities, respectively, provided the methods pass successful PMVs by Agency chemists at ACL/BEAD and the petitioner addresses the following issues: The methods

should be revised to include a calculation for the conversion of residues of the metabolite(s) to parent equivalents for quantitation. A separate confirmatory method for Method AE/03/01 will not be required provided that two ion transitions are monitored during MS/MS analysis for each analyte. Currently, Method No. 00967 reflects measurement of a second LC/MS/MS ion transition for each analyte. The petitioner has indicated that Method AE/03/01 will be superseded by Revision AE/03/01-01, in which a second ion transition is to be monitored.

860.1360 Multiresidue Methods (MRM)

DER Reference List 46695546.der.doc

The usefulness of the MRM Protocols A, B, C, D, E, and F, as described in the Food and Drug Administration (FDA) Pesticide Analytical Manual (PAM) Vol. I, was evaluated for measuring residues of tembotrione and its metabolites M6, M5, and M2. The decision tree for multiresidue testing (PAM Vol. I, Appendix II-2) was followed as a technical guide for testing the various Protocols.

The parent and its metabolites did not provide a response or viable chromatography under the conditions required for Protocol A. Protocol B is not applicable for tembotrione, M6, and M5 because they are not phenols. However, the metabolites M6 and M2 are acids and were tested using Protocol B; testing on these two metabolites were terminated because they were not soluble in acetone, the solvent required by Protocol B. Protocol G was not considered for testing because tembotrione and its metabolites are not substituted ureas. Tembotrione was not recovered with Florisil column cleanup and was not further tested through Protocols D, E, and F. Protocols D, E, and F, may be used for screening of metabolite M6 in corn grain and oil, if residues are at high levels, but these methods are not adequate for quantitation of M6.

Conclusions: The MRMs are not suitable for the analysis of tembotrione or its metabolites. The multiresidue methods testing data will be forwarded to FDA for further evaluation and inclusion of results in PAM Vol. I.

860.1380 Storage Stability

Plant commodities

DER Reference List 46695601.der.doc (Corn)
46695602.der.doc (Turnip roots, mustard greens, and yellow squash)

Corn

Bayer CropScience has submitted the results of a storage stability study with tembotrione and its metabolites M6, M5, and M2 in/on corn matrices. Untreated samples of corn grain, forage and stover (fodder) were fortified with tembotrione, M6, M5, and M2, each at a level of 0.2 ppm. The fortified and control samples were then stored frozen (≤-10 °C) and analyzed at intervals of 0, 91-99 days (~3 months), 181-188 days (~6 months), and 369-398 days (~12-13 months).

The results indicate that under these conditions, residues of the parent, tembotrione, and metabolites M6 and M2 appear to be stable in/on corn grain, forage, and stover for up to 396-398 days (~13 months). M5 was shown to be stable in corn grain for up to 188 days (~6 months) but declined by 17% after 371 days (61% average corrected recovery). M5 appeared reasonably stable in/on corn forage and stover for up to 369-371 days (~12 months) if the 35% recovery from samples of corn forage at the storage interval of 188 days is deemed an outlier.

Samples of corn grain, forage and stover were analyzed for residues of tembotrione, M6, M5, and M2 using LC/MS/MS Method No. AE/03/01. This method is adequate for data collection based on acceptable method recoveries. The validated LOQ is 0.010 ppm for each analyte in crops. The calculated LODs for the parent and its metabolites were each ≤0.004 ppm in corn matrices.

Turnip roots, mustard greens, and yellow squash

Bayer CropScience has submitted the results of storage stability study with tembotrione and its metabolites M6, M5, and M2 in/on turnip roots, mustard greens, and yellow squash. Untreated samples of mustard greens were fortified with tembotrione and its metabolites each at a level of 0.2 ppm. Untreated samples of turnip roots and yellow squash were fortified with tembotrione and its metabolites each at a level of 0.4 ppm. All fortified and control samples were stored frozen (≤-10 °C) and analyzed at intervals of 0, 91 days (~3 months), 182 days (~6 months), and 350-370 days (~11.5-12 months).

The results indicate that under these conditions, residues of the parent, tembotrione, and its metabolites M6 and M2 appear to be relatively stable in/on turnip roots, mustard greens, and yellow squash for up to 350 days (11.5 months). Residues of metabolite M5 appear to be relatively stable in/on turnip roots, mustard greens, and yellow squash for up to 370 days (~12 months.

Samples of turnip roots, mustard greens, and yellow squash were analyzed for residues of tembotrione and its metabolites using LC/MS/MS Method No. AE/03/01. This method is adequate for data collection based on acceptable method recoveries. The validated LOQ is 0.010 ppm for each analyte in crops. The calculated LODs for the parent and its metabolites were ≤0.0014 ppm in various matrices.

Sample storage conditions and intervals

The storage intervals and conditions of samples from the residue field trials, rotational crop field trials, and processing studies which were submitted to support this petition are presented in Table 7.

Table 7. Summary of Storage Conditions and Intervals of Samples from Crop Field Trial, Processing, and Field Rotational Crop Studies.

Matrix	Storage Temperature (°C)	Actual Storage Duration for Most Samples	Interval of Demonstrated Storage Stability
Field Corn Trials (MRID 46695607)			
Forage	< -15	118–283 days (3.9-9.3 months)	Tembotrione, M6, and M2 are stable for up to 12-13 months in frozen field corn grain, forage, and

Table 7. Summary of Storage Conditions and Intervals of Samples from Crop Field Trial, Processing, and Field Rotational Crop Studies.

Matrix	Storage Temperature (°C)	Actual Storage Duration for Most Samples	Interval of Demonstrated Storage Stability
Grain	< -15	84-250 days (2.8-8.2 months)	fodder. M5 is stable in frozen field corn forage and fodder for up to 12 months. M5 is stable in frozen field corn grain for up to 188 days but declined by 17% after 371 days (61% average corrected recovery).
Stover	< -15	119-260 days (3.9-8.5 months)	
Popcorn Trials (MRID 46695609)			
Grain and stover	< -15	279-307 days (9.2-10.1 months)	See above for field corn.
Sweet Corn Trials (MRID 46695608)			
Forage	< -15	68-372 days (2.2-12.2 months)	See above for field corn.
Kernel plus cob with husks removed	< -15	68-334 days (2.2-11.0 months)	
Stover	< -15	46-313 days (1.5-10.3 months)	
Corn Processing Study (MRID 46695610)			
Grain	< -15	460 days (15.1 months)	See above for field corn.
Grits	< -15	22 days (0.7 months)	No storage stability data for the processed commodities of corn were submitted. These data are not required because most samples were stored for less than 30 days prior to residue analysis.
Meal	< -15	21 days (0.7 months)	
Flour	< -15	38 days (1.3 months)	
Oil	< -15	19 days (0.6 months)	
Starch	< -15	22 days (0.7 months)	
Rotational Wheat Processing Study (MRID 46695611)			
Rotated wheat grain	< -15	120-122 days (4 months)	See above for field corn. Wheat grain was not processed into its components because tembotrione residues were each <LOQ of 0.010 ppm in/on all wheat grain samples treated at an exaggerated rate.
Rotational Crop Study: Wheat as the Rotational Crop (MRID 46695613)			
Forage	< -15	114-381 days (3.8-12.5 months)	See above for field corn.
Hay	< -15	80-147 days (2.6-4.8 months)	
Grain	< -15	55-109 days (1.8-3.6 months)	
Straw	< -15	55-109 days (1.8-3.6 months)	
Rotational Crop Study: Mustard Greens, Turnips, and Summer Squash as the Rotational Crops (MRID 46695614)			
Mustard Greens	-25 to -15	303 days (10.0 months)	Tembotrione, M6, and M2 are stable for up to 11 months in frozen mustard greens, turnip roots, and summer squash. The metabolite M5 is stable in the same matrices for at least 12 months.
Turnip Tops	-25 to -15	294 days (9.7 months)	
Turnip Roots	-25 to -15	294 days (9.7 months)	
Summer Squash	-25 to -15	326 days (10.7 months)	

Livestock commodities

No storage stability data were submitted for livestock commodities, and none are required to support the submitted cattle (MRIDs 46695604 and 46695606) and hen (MRID 46695605) feeding studies because sample integrity was maintained by appropriate freezer storage, and all samples were analyzed within 30 days of collection.

Conclusions: Adequate storage stability data for corn have been submitted. These data indicate that tembotrione and metabolites M6 and M2 are reasonably stable in/on corn grain, forage, and stover for up to 396-398 days (~13 months). Metabolite M5 is stable in corn grain for up to 188 days (~6 months) but declined by 17% after 371 days (61% average corrected recovery), and was reasonably stable in/on corn forage and stover for up to 369-371 days (~12 months). These data support the storage conditions and intervals of samples collected from the various corn trials as well as the rotational crop studies with wheat.

Adequate storage stability data for turnip roots, mustard greens, and yellow squash have also been submitted. Tembotrione and its metabolites M6 and M2 are reasonably stable in/on turnip roots, mustard greens, and yellow squash for up to 350 days (11.5 months). Residues of metabolite M5 are relatively stable in/on turnip roots, mustard greens, and yellow squash for up to 370 days (~12 months). These data support the storage conditions and intervals of samples collected from the rotational crop studies with turnips, mustard greens, and yellow squash.

There are no unresolved storage stability issues, and no corrections need to be applied to the various residue crop studies. No storage stability data are required for corn and wheat processed commodities as well as for livestock commodities because samples from the processing and livestock feeding studies were analyzed within 30 days of collection.

860.1480 Meat, Milk, Poultry, and Eggs

Livestock dietary burdens

The potential for secondary transfer of tembotrione residues of concern in meat, milk, poultry, and eggs exists because there are livestock feedstuffs associated with the proposed uses on field, pop, and sweet corn. The livestock dietary burdens of tembotrione and its metabolite M5 are presented in Tables 8A and 8B, respectively, and reflect the most recent guidance from HED (Personal Communication, J. Stokes, October 2006) concerning revisions of feedstuff percentages in Table 1 and constructing reasonably balanced dietary burdens (RBDBs). The calculated total dietary burdens of tembotrione + M5 (based on tolerance-level residues) are 0.85 ppm for beef cattle, 1.18 ppm for dairy cattle, and 0.024 ppm for swine and poultry. The dietary burdens of metabolite M5 alone are 0.61 ppm for beef cattle, 0.93 ppm for dairy cattle, and 0.006 ppm for swine and poultry.

Table 8A. Livestock Dietary Burdens for Tembotrione and M5.					
Feedstuff	Feedstuff Type[1]	% Dry Matter[2]	% Diet[2]	Recommended Tolerance (ppm)[3]	Dietary Contribution (ppm)[4]
Beef Cattle					
Sweet corn forage	R	48	40	1.0	0.83
Field corn grain	CC	88	60	0.03	0.02
TOTAL BURDEN	--	--	100		**0.85**
Dairy Cattle					
Sweet corn forage	R	48	45	1.0	0.83
Field corn grain	CC	88	45	0.03	0.02
Sweet corn cannery waste	CC	30	10	1.0[5]	0.33
TOTAL BURDEN	--	--	100		**1.18**
Swine					
Field corn grain	CC	N/A	80	0.03	0.024
TOTAL BURDEN	--	--	80[6]		**0.024**
Poultry					
Field corn grain	CC	N/A	70	0.03	0.021
Field corn milled byproducts	CC	N/A	10	0.03[7]	0.003
TOTAL BURDEN	--	--	80[6]		**0.024**

[1] CC = Carbohydrate concentrate; R = Roughage.

[2] Table 1 Feedstuffs (Personal Communieation, J. Stokes, October 2006).

[3] *Total of parent + M5, the residues of concern in the tolerance expression.*

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

[5] Based on residue data for forage as per Table 1 Feedstuffs (October 2006).

[6] The remainder of the diet will be composed of feedstuffs (i.e., protein concentrate sources) derived from crops that do not have registered tembotrione uses/tolerances.

[7] The HED-recommended tolerance for field corn grain will cover expected residues in field corn milled byproducts.

Table 8B. Livestock Dietary Burdens for Metabolite M5.					
Feedstuff	Feedstuff Type[1]	% Dry Matter[2]	% Diet[2]	Maximum M5 Found in the 1x Field Trials (ppm)	Dietary Contribution (ppm)[3]
Beef Cattle					
Sweet corn forage	R	48	40	0.728	0.607
Field corn grain	CC	88	60	0.007	0.005
TOTAL BURDEN	--	--	100		**0.61**
Dairy Cattle					
Sweet corn forage	R	48	45	0.728	0.683
Field corn grain	CC	88	45	0.007	0.004
Sweet corn cannery waste	CC	30	10	0.728[4]	0.243
TOTAL BURDEN	--	--	100		**0.93**
Swine					
Field corn grain	CC	N/A	80	0.007	0.006
TOTAL BURDEN	--	--	80[5]		**0.006**
Poultry					
Field corn grain	CC	N/A	70	0.007	0.005
Field corn milled byproducts	CC	N/A	10	0.007[6]	0.001
TOTAL BURDEN	--	--	80[5]		**0.006**

[1] CC = Carbohydrate concentrate; R = Roughage.
[2] Table 1 Feedstuffs (Personal Communication, J. Stokes, October 2006).
[3] Contribution = (tolerance /% DM x % in diet) for beef and dairy cattle; contribution = (tolerance x % in diet) for poultry and swine.
[4] Based on residue data for forage as per Table 1 Feedstuffs (October 2006).
[5] The remainder of the diet will be composed of feedstuffs (i.e., protein concentrate sources) derived from crops that do not have registered tembotrione uses/tolerances.
[6] The HED-recommended RAC (field corn grain) tolerance will cover expected residues in field corn milled byproducts.

Livestock feeding studies

DER Reference List
46695604.der.doc (Dairy cattle feeding study with tembotrione)
46695606.der.doc (Dairy cattle feeding study with Metabolite M5)
46695605.der.doc (Poultry feeding study with tembotrione)

Dairy cattle feeding study with tembotrione

Three treatment groups of three dairy cows each were dosed orally with gelatin capsules containing tembotrione at target dose rates approximating 3.2 (2.7X), 9.6 (8.1X), and 32 (27X) ppm in the diet (dry feed weight basis) for 29 consecutive days. Cows were milked twice daily, and samples were composited daily for each cow. All cows were sacrificed within 8 hours of the final dose on day 29. Samples of liver (portions of each lobe), kidney (center and ends), fat (composite of available omental, renal, and subcutaneous), and skeletal muscle (composite of loin, round and shank) were collected from each cow. Samples of milk collected on study days 0, 1, 3, 7, 10, 14, 17, 21, 24, 26 and 28, and samples of cream (milk fat) and skim milk collected on day 26 were retained for analysis.

Milk and tissue samples were analyzed for residues of tembotrione using the proposed LC/MS/MS enforcement method, Method AE-003-A04-01. The validated LOQ for tembotrione was 0.01 ppm in milk and tissues, and the estimated LODs ranged 0.0011-0.0024 ppm. The method is adequate for data collection based on acceptable concurrent recovery and method validation data. No storage stability data are required because all milk and tissue samples were stored frozen from collection to analysis and were analyzed within 20 days of collection.

In whole milk, cream, and skim milk, residues of tembotrione were below the LOQ (<0.01 ppm) in all samples from all dose groups. In fat and muscle, residues of tembotrione were below the LOQ (<0.01 ppm) in all samples from the 3.2-, 9.6-, and 32-ppm dose groups, with the exception of samples from one cow from the 32-ppm group which bore quantifiable tembotrione residues of 0.025 ppm in fat and 0.014 ppm in muscle. Maximum residues of tembotrione were 0.454 ppm, 0.486 ppm, and 1.37 ppm in samples of kidney from the 3.2-, 9.6-, and 32-ppm dose groups, respectively, and 2.89 ppm, 2.96 ppm, and 3.35 ppm in samples of liver from the 3.2-, 9.6-, and 32-ppm dose groups, respectively. There appeared to be a slight residue-level dose dependence in kidney samples, but no residue-level dose dependence in liver.

Table 9. Summary of Residue Data from Ruminant Feeding Study with Tembotrione.

Matrix	Feeding Level (ppm)	Residue Levels (ppm)[1]					
		N	Min	Max	Median	Mean	Std. Dev.
Milk Days 10, 14, 17, and 21	3.2	11	<0.010	<0.010	<0.005	<0.005	N/A
Milk Days 0, 1, 3, 7, 10, 14, 17, and 21	9.6	24	<0.010	<0.010	<0.005	<0.005	N/A
Milk Days 0, 1, 3, 7, 10, 14, 17, 21, 24, 26, and 28	32	33	<0.010	<0.010	<0.005	<0.005	N/A
Cream (milk fat) Day 26	32	3	<0.010	<0.010	<0.005	<0.005	N/A
Skim milk Day 26	32	3	<0.010	<0.010	<0.005	<0.005	N/A
Fat Day 29	3.2	3	<0.010	<0.010	<0.005	<0.005	N/A
	9.6	3	<0.010	<0.010	<0.005	<0.005	N/A
	32	3	<0.010	0.025	0.005	0.012	0.012
Kidney Day 29	3.2	3	0.394	0.454	0.446	0.431	0.033
	9.6	3	0.213	0.486	0.477	0.392	0.155
	32	3	0.788	1.37	0.856	1.004	0.317
Musele Day 29	3.2	3	<0.010	<0.010	<0.005	<0.005	N/A
	9.6	3	<0.010	<0.010	<0.005	<0.005	N/A
	32	3	<0.010	0.014	0.005	0.008	0.005
Liver Day 29	3.2	3	2.00	2.89	2.46	2.45	0.448
	9.6	3	1.40	2.96	2.64	2.33	0.825
	32	3	2.93	3.35	3.08	3.12	0.210

[1] For calculation of the minimum and maximum, the LOQ (0.01 ppm) was used for residues reported below the LOQ (or <LOD). In the calculation of the median, mean, and standard deviation, 0.005 ppm (half the LOQ) was used for residues reported as less than the LOD and for residues reported between the LOD and LOQ.

Dairy cattle feeding study with Metabolite M5

Four treatment groups of three dairy cows each were dosed orally with M5 in the feed at target dose rates approximating 0.05 (0.054X), 0.5 (0.54X), 1.5 (1.6X), and 5.0 (5.4X) ppm (dry feed weight) for 28-31 consecutive days; three additional cows were dosed at 5.0 ppm for a depuration study.

Cows were milked twice daily, and samples were composited daily for each cow. Cows were sacrificed within 16-24 hours of the final dose, on Days 30-32; the cows for the depuration study were sacrificed 7, 14, and 28 days after the final dose. Samples of liver (whole organ as two subsamples), kidney (both whole organs as two subsamples), fat (two subsample composites of available omental, perirenal, and subcutaneous), and skeletal muscle (two subsample composites of pectoralis and adductor muscle of thigh) were collected from each cow. Samples of milk collected on Days 4, 7, 10, 14, 18, 21, 25, and 28 from all dose levels were retained for analysis; additional samples from Days 1, 12 and 23 from the 5.0-ppm dose group and from Days 31, 35, 38, 42, 45, 49, 52, and 56 from the depuration study were also retained. Samples of cream (milk fat) and skim milk were collected on Days 14 and 28 (all dose levels).

Milk and tissue samples were analyzed for residues of M5 using a LC/MS/MS method that is essentially the same as the proposed LC/MS/MS enforcement method. The validated LOQs for M5 were 0.002 ppm for milk, skim milk, and cream, and 0.01 ppm for fat, kidney, liver, and muscle, and the estimated LODs were 0.001 ppm for milk, skim milk, and cream, and 0.002 ppm for tissues. The method is adequate for data collection based on acceptable concurrent recovery data. No storage stability data are required because all milk and tissue samples were stored frozen from collection to analysis and were analyzed within ~30 days of collection.

Residues of M5 were nondetectable (<0.001 ppm) in all samples of milk, skim milk, and cream from all dose groups, except for one sample each of Day 4 milk from the 0.05- and 5.0-ppm dose levels, in which residues were <LOQ (<0.002 ppm). In fat and muscle, residues of M5 were below the LOD (<0.002 ppm) in all samples from all dose groups, with the exception of one sample each of fat and muscle from the 5.0-ppm dose group in which residues were <LOQ (<0.01 ppm). In kidney, maximum residues of M5 were <LOQ, 0.017 ppm, 0.049 ppm, and 0.165 ppm in samples from the 0.05-, 0.50-, 1.5-, and 5.0-ppm dose groups, respectively. No residues of M5 above the LOQ were detected in treated kidney samples collected 7, 14 and 28 days after withdrawal of M5. In liver, maximum residues of M5 were <LOQ, 0.036 ppm, 0.163 ppm, and 0.386 ppm in samples from the 0.05-, 0.50-, 1.5-, and 5.0-ppm dose groups, respectively. Residues of M5 in liver declined rapidly over the withdrawal period, to 0.037 ppm, 0.015 ppm, and <LOD, respectively, 7, 14, and 28 days following cessation of dosing. A linear residue-level dose dependence was observed in kidney and liver.

Table 10. Summary of Residue Data from Ruminant Feeding Study with M5.

Matrix	Feeding Level (ppm)	Residue Levels (ppm)					
		n	Min	Max	Median	Mean	Std. Dev.
Milk Days 1-28	0.05	24	<0.002	<0.002	0.001	0.001	N/A
	0.50	24	<0.002	<0.002	0.001	0.001	N/A
	1.5	24	<0.002	<0.002	0.001	0.001	N/A
	5.0	33	<0.002	<0.002	0.001	0.001	N/A
Cream Days 14 and 28	0.05	6	<0.002	<0.002	0.001	0.001	N/A
	0.50	6	<0.002	<0.002	0.001	0.001	N/A
	1.5	6	<0.002	<0.002	0.001	0.001	N/A
	5.0	12	<0.002	<0.002	0.001	0.001	N/A
Skim milk Days 14 and 28	0.05	6	<0.002	<0.002	0.001	0.001	N/A
	0.50	6	<0.002	<0.002	0.001	0.001	N/A
	1.5	6	<0.002	<0.002	0.001	0.001	N/A
	5.0	12	<0.002	<0.002	0.001	0.001	N/A
Fat Days 30-32	0.05	3	<0.01	<0.01	0.005	0.005	N/A
	0.50	3	<0.01	<0.01	0.005	0.005	N/A
	1.5	3	<0.01	<0.01	0.005	0.005	N/A
	5.0	3	<0.01	<0.01	0.005	0.005	N/A
Kidney Days 30-32	0.05	3	<0.01	<0.01	0.005	0.005	N/A
	0.50	3	0.013	0.017	0.015	0.015	0.002
	1.5	3	0.037	0.049	0.040	0.042	0.006
	5.0	3	0.122	0.165	0.139	0.142	0.022
Liver Days 30-32	0.05	3	<0.01	<0.01	0.005	0.005	N/A
	0.50	3	0.029	0.036	0.030	0.032	0.004
	1.5	3	0.084	0.163	0.150	0.132	0.042
	5.0	3	0.305	0.386	0.333	0.341	0.041
Muscle Days 30-32	0.05	3	<0.01	<0.01	0.005	0.005	N/A
	0.50	3	<0.01	<0.01	0.005	0.005	N/A
	1.5	3	<0.01	<0.01	0.005	0.005	N/A
	5.0	3	<0.01	<0.01	0.005	0.005	N/A

[1] For calculation of the minimum and maximum, the LOQ (0.002 ppm for milk, skim milk, and cream, and 0.01 ppm for tissues) was used for residues reported as <LOD. In the calculation of the median, mean, and standard deviation, half the LOQ (0.001 ppm for milk, skim milk, and cream and 0.005 ppm for tissues) was used for residues reported as <LOD or <LOQ.

Expected secondary residues in meat and milk

To determine the need for tolerances for tembotrione residues of concern in milk and tissues, the anticipated secondary residues in cattle matrices were estimated using transfer coefficient factors calculated from the maximum residues of tembotrione and metabolite M5 observed at the dose level closest to the RBDB in the feeding studies. As metabolite M5 was determined in a separate study, residues were not reported in parent equivalents. For purposes of determining tolerances based on combined residues, maximum residue values for liver and kidney were converted to parent equivalents using a molecular weight conversion factor of 0.93; conversion of maximum residues on milk, cream, skim milk, fat, and muscle was not needed because of the low residue values. The transfer coefficients (calculated as residue-level-to-feed ratios) are presented in Table 11. The transfer coefficient for each matrix was then used to calculate the expected secondary residues by multiplying the transfer coefficient by the calculated dietary burden. The

expected combined residues of tembotrione and metabolite M5 and the recommended tolerances based on expected residues are presented in Table 12.

Table 11. Residue-Level-to-Feed Ratios (Transfer Coefficients) in Dairy Cattle Milk and Tissues[1].

Matrix	Tembotrione			M5		
	Maximum Residue, ppm	Feeding Level, ppm	Transfer Coefficient	Maximum Residue, ppm	Feeding Level, ppm	Transfer Coefficient
Milk	<0.010	32	<0.00031	<0.002	5	<0.0004
Cream	<0.010		<0.00031	<0.002		<0.0004
Skim milk	<0.010		<0.00031	<0.002		<0.0004
Fat	0.025		0.00078	<0.01		<0.002
Muscle	0.014		0.00044	<0.01		<0.002
Kidney	0.454	3.2	0.14188	0.046[2]	1.5	0.0304
Liver	2.89		0.90312	0.152[2]		0.1011

[1] Calculated from the maximum residues observed at the dose level closest to the RBDB divided by the dose level.
[2] Expressed in parent equivalents.

Table 12. Expected Secondary Residues in Meat and Milk.

Matrix	Dietary burden (ppm)		Secondary Residues (ppm)[1]		Total Residues (ppm)	Recommended Tolerance (ppm)[2]
	Tembotrione	M5	Tembotrione	M5		
Milk	0.25[3]	0.93	<0.00008	<0.00037	<0.00045	NR
Cream			<0.00008	<0.00037	<0.00045	NR
Skim milk			<0.00008	<0.00037	<0.00045	NR
Fat			0.00020	<0.00186	<0.00211	NR
Kidney			0.03540	0.02825	0.06370	0.07
Muscle			0.00070	<0.00186	<0.00256	NR
Liver			0.22580	0.09400	0.3200	0.40

[1] Calculated from dietary burden x transfer coefficient from Table 10.
[2] NR = not required.
[3] Dietary burden calculated using recommended tolerances (parent + M5) minus dietary burden calculated using M5 alone.

Conclusions: The residue data from the cattle feeding studies are adequate to satisfy data requirements. The feeding study data indicate that tolerances are needed for the combined residues of tembotrione and its metabolite M5 at 0.07 ppm in the meat byproducts, except liver; and at 0.40 ppm in the liver of cattle, goats, horses, and sheep. Based on the transfer coefficients for livestock tissues and the relatively low dietary burdens for swine of 0.024 ppm for tembotrione and M5, tolerances for hogs are not needed.

Poultry feeding study with tembotrione

Three treatment groups consisting of 12 laying hens each were dosed orally with gelatin capsules containing tembotrione at target dose rates of 0.2 (8.3X), 0.6 (25X), and 2.0 (83X) ppm in the diet for 29 consecutive days. Each treatment group consisted of three subgroups of four hens each; samples of eggs and tissues were composited by subgroup for analysis. Eggs were collected twice daily, and samples from study days 0, 1, 3, 7, 10, 14, 17, 21, 24, 26, and 28 were retained for analysis. The hens were sacrificed within 3-5 hours of the final dose on Day 29, and samples of liver (entire), skin (thigh and breast), fat (abdominal and subcutaneous), and muscle (thigh and breast) were collected from each bird.

Samples of eggs (combined yolks and whites; 2.0-ppm dose group only) and tissues were

analyzed for residues of tembotrione using the proposed LC/MS/MS enforcement method, Method AE-004-A04-01. The validated LOQ for tembotrione was 0.01 ppm in eggs and tissues, and the estimated LODs ranged 0.0018-0.0031 ppm. The method is adequate for data collection based on acceptable concurrent recovery and method validation data. No storage stability data are required because all egg and tissue samples were stored frozen from collection to analysis and were analyzed within 23 days of collection.

Residues of tembotrione in eggs were below the LOQ (<0.01 ppm) in all samples from the 2.0-ppm dose group. In fat and muscle, residues of tembotrione were below the LOQ (<0.01 ppm) in all samples from the 0.2- and 0.6-ppm dose groups; maximum residues were 0.034 ppm in fat and 0.020 ppm in muscle from the 2.0-ppm dose group. In skin, residues of tembotrione were below the LOQ (<0.01 ppm), 0.013 ppm, and 0.058 ppm in samples from the 0.2-, 0.6-, and 2.0-ppm dose groups, respectively. Residues of tembotrione were found in significant amounts in the liver, where maximum residues were 0.504 ppm, 0.618 ppm, and 0.702 ppm in samples from the 0.2-, 0.6-, and 2.0-ppm dose groups, respectively. There was a definite residue-level dose dependence in fat, muscle and skin, and that average residues of tembotrione in liver showed evidence of a slight residue-level dose dependence.

A poultry feeding study with the metabolite M5 as the test substance was not conducted.

Table 13. Summary of Residue Data from Poultry Feeding Study with Tembotrione.

Matrix	Feeding Level (ppm)	Residue Levels (ppm)[1]					
		n	Min	Max	Median	Mean	Std. Dev.
Eggs Days 0, 1, 3, 7, 10, 14, 17, 21, 24, 26, and 28	2.0	33	<0.010	<0.010	<0.005	<0.005	N/A
Skin Day 29	0.2	3	<0.010	<0.010	<0.005	<0.005	N/A
	0.6	3	<0.010	0.013	0.011	0.010	0.004
	2.0	3	0.040	0.058	0.052	0.050	0.009
Fat Day 29	0.2	3	<0.010	<0.010	<0.005	<0.005	N/A
	0.6	3	<0.010	<0.010	<0.005	<0.005	N/A
	2.0	3	0.019	0.034	0.023	0.025	0.008
Liver Day 29	0.2	3	0.326	0.504	0.421	0.417	0.089
	0.6	3	0.568	0.618	0.583	0.590	0.026
	2.0	3	0.584	0.702	0.666	0.651	0.060
Muscle Day 29	0.2	3	<0.010	<0.010	<0.005	<0.005	N/A
	0.6	3	<0.010	<0.010	<0.005	<0.005	N/A
	2.0	3	0.016	0.020	0.018	0.018	0.002

[1] For calculation of the minimum and maximum, the LOQ (0.01 ppm) was used for residues reported as <LOD. In the calculation of the median, mean, and standard deviation, 0.005 ppm (half the LOQ) was used for residues reported as <LOD or <LOQ.

Expected secondary residues in poultry eggs and tissues

To determine the need for tolerances for tembotrione residues of concern in poultry eggs and tissues, the anticipated secondary residues in poultry matrices were estimated using transfer coefficient factors calculated from the observed at the dose level closest to the RBDB in the feeding studies. The transfer coefficients (calculated as residue-level-to-feed ratios) are presented in Table 14. The transfer coefficient for each matrix was then used to calculate the

expected secondary residues by multiplying the transfer coefficient by the calculated dietary burden. The expected residues of tembotrione and the recommended tolerances based on expected residues are presented in Table 15.

Table 14. Residue-Level-to-Feed Ratios (Transfer Coefficients) for Tembotrione in Poultry Eggs and Tissues[1].

Matrix	Maximum Residue, ppm	Feeding Level, ppm	Transfer Coefficient
Eggs	<0.01	2.0	<0.005
Skin	0.058		0.029
Fat	0.034		0.017
Muscle	0.020		0.010
Liver	0.504	0.2	2.52

[1] Calculated from the maximum residues observed in each matrix at the highest dose level divided by the highest dose level.

Table 15. Expected Secondary Residues in Poultry Eggs and Tissues.

Matrix	Dietary burden (ppm)	Secondary Residues (ppm)[1]	Recommended Tolerance (ppm)[2]
Eggs	0.024	<0.00012	NR
Skin		0.00070	NR
Fat		0.00041	NR
Liver		0.0605	0.07
Muscle		0.00024	NR

[1] Calculated from dietary burden x the transfer coefficient from Table 10.

[2] NR = not required.

Conclusions: The residue data from the poultry feeding study are adequate to satisfy data requirements. The feeding study data indicate that a tolerance for the combined residues of tembotrione and its metabolite M5 is needed for poultry liver at 0.07 ppm.

860.1500 Crop Field Trials

Corn, field

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Twenty-one field trials were conducted in the United States encompassing Zones 1 (PA; 1 trial), 2 (GA; 1 trial), 5 (IA, IL, IN, KS, MN, MO, NE, OH, SD, and WI; 18 trials), and 6 (TX; 1 trial) during the 2003 growing season. Each trial site included one control plot and two to four treated plots. Two foliar spray applications of a SC formulation (AE 0172747 Herbicide) nominally containing 3.50 lb tembotrione ai/gallon (420 g ai/L), were made to field corn at 24- inch and 36-inch height in treated plot A at a target rate of 0.082 lb ai/A/application (0.092 kg ai/ha/application) (1x the proposed maximum seasonal rate). Field corn in treated plot B received one foliar spray application at 36-inch height and one drop-nozzle (directed) spray one week later at the same target application rates. Additional treated plots (C, D, and E) were included in some trials and these plots received applications at the same use pattern as the treated plot A, but using different spray adjuvants. Applications were made using ground equipment in ~13-17 gal/A (122-161 L/ha). An adjuvant was added to the spray mixture for all applications. The achieved total seasonal rates ranged from 0.160 to 0.174 lb ai/A (0.180 to 0.195 kg ai/ha) for all treated plots at all trial sites. Field corn forage samples were harvested at a PHI of 44 to 53

days after the last application. The grain and stover samples were harvested at commercial maturity (BBCH 87 to 89) at PHIs ranging from 76 to 112 days. At two trial locations, field corn matrices were collected at additional sampling intervals to evaluate residue decline: field corn forage was collected 35, 39-41, 44-45, 50, and 55-56 days and field corn grain and stover were collected 77-85, 84-91, 91-99, 98-106, and 105-112 days following the last application of Treatments A and B.

The harvested field corn RAC samples were analyzed for residues of the parent compound, tembotrione, and the metabolites M2, M5, and M6 using a method entitled "AE 0172747: An Analytical Method for the Determination of Residues of AE 0172747, and its major metabolites M6, AE 1417268, and AE 1392936 in Plant Matrices Using LC/MS/MS." This method is acceptable for data collection based on adequate method validation and concurrent method recovery data. The LOQs for tembotrione, M2, M5, and M6 were each 0.010 ppm in field corn grain, forage and stover; the estimated method LODs were ≤0.004 ppm for each analyte in corn grain, forage, and stover.

The maximum storage intervals of samples from harvest to analysis were 283 days (9.3 months) for field corn forage, 250 days (8.2 months) for field corn grain, and 260 days (8.5 months) for field corn stover. In addition, one forage sample and one stover sample were reanalyzed for tembotrione only, 490 to 512 days after the initial analysis. Results of the reanalyses were not significantly different from the original analyses; therefore, stability may be inferred for the additional storage interval. Adequate storage stability data for field corn commodities (MRID 46695601) are available to support the storage conditions and intervals of samples from the field corn field trials.

In trials reflecting Treatment A (two foliar applications totaling 0.161-0.170 lb ai/A), the maximum combined residues of parent and its metabolites (M5 + M6 + M2), as parent equivalents, were <0.471 ppm in/on field corn forage, <0.155 ppm in/on field corn grain, and <0.554 ppm in/on field corn stover. In treated stover sample which bore the highest combined residues of <0.554 ppm, metabolites M5 and M6 comprised 81% and 17% of the total residues, respectively; individual residues of the parent and metabolite M2 were below the LOQ in the same stover sample.

Following Treatment B (one foliar application and one directed-spray application totaling 0.164-0.174 lb ai/A), the maximum combined residues of parent and its metabolites (M5 + M6 + M2), as parent equivalents, were <0.322 ppm in/on field corn forage, <0.144 ppm in/on field corn grain, and <0.525 ppm in/on field corn stover.

When only residues of the parent and metabolite M5 are summed, the maximum combined residues following Treatment A were <0.375 ppm in/on field corn forage, <0.022 ppm in/on field corn grain, and <0.450 ppm in/on field corn stover. Following Treatment B, the maximum combined residues were <0.290 ppm in/on field corn forage, <0.025 ppm in/on field corn grain, and <0.445 ppm in/on field corn stover.

Overall, the maximum residues of M5 were 0.860 ppm in/on field corn forage, <0.01 ppm in/on field corn grain, and 0.440 ppm in/on field corn stover; maximum residues of M6 were 0.148 ppm in/on field corn forage, 0.125 ppm in/on field corn grain, and 0.129 ppm in/on field corn stover; and maximum residues of M2 were 0.023 ppm in/on field corn forage, <0.01 ppm in/on

field corn grain, and 0.042 ppm in/on field corn stover.

Based on the results of the side-by-side field trials, residues were similar in/on field corn matrices treated with two foliar applications (Treatment A) or treated with one foliar + one directed-spray application (Treatment B). Residues of the parent were nonquantifiable in all field corn matrices from both treatment regimes.

The two residue decline trials indicate that total tembotrione residues do not appear to decline in stover with later sampling intervals, and residues in forage were inconsistent; therefore, no meaningful conclusion could be made regarding a trend. Total residues in grain were near or below the LOQ at all sampling intervals.

The results of the bridging studies, conducted with different spray adjuvant mixtures, indicate that overall the combination of spray adjuvants used had no significant impact on the residue levels in/on treated corn matrices.

Table 16. Summary of Residue Data from Field Corn Field Trials with Tembotrione.

Proposed Use Pattern: Two foliar sprays at 0.08 lb ai/A/application with a minimum RTI of 14 days, for a maximum seasonal rate of 0.16 lb ai/A. The proposed PHI is 45 days for forage; no PHI is listed for grain or stover.

Commodity	Treated[1]	PHI (days)	Sum of Residues: Parent + M5 + M6 + M2 (ppm in parent equivalents)[2]						
			n	Min	Max	HAFT	Median	Mean	Std. Dev.
Forage	A	44-53	42	<0.052	<0.471	<0.455	0.170	0.188	0.111
	B	44-48	42	<0.077	<0.322	<0.305	0.165	0.172	0.067
	C	45-46	12	<0.050	<0.242	<0.213	0.071	0.104	0.073
	D	45-46	6	<0.058	<0.144	<0.136	0.081	0.083	0.033
	E	45	6	<0.059	<0.204	<0.166	0.123	0.121	0.060
Grain	A	83-112	42	<0.04	<0.155	<0.154	0.035	0.043	0.029
	B	76-105	42	<0.04	<0.144	<0.142	0.038	0.046	0.028
	C	91-107	12	<0.04	<0.054	<0.052	0.024	0.027	0.007
	D	91-107	6	<0.04	<0.073	<0.065	0.026	0.032	0.015
	E	93-99	6	<0.04	<0.05	<0.049	0.030	0.028	0.006
Stover (fodder)	A	83-112	42	<0.04	<0.554	<0.479	0.068	0.114	0.119
	B	76-105	42	<0.04	<0.525	<0.501	0.118	0.134	0.112
	C	91-107	12	<0.04	<0.112	<0.110	0.052	0.055	0.027
	D	91-107	6	<0.045	<0.145	<0.114	0.074	0.075	0.039
	E	93-99	6	<0.041	<0.107	<0.090	0.071	0.064	0.030
Commodity	Treated[1]	PHI (days)	Sum of Residues: Parent + M5 (ppm in parent equivalents)[2]						
			n	Min	Max	HAFT	Median	Mean	Std. Dev.
Forage	A	44-53	42	<0.032	<0.375	<0.342	0.140	0.156	0.095
	B	44-48	42	<0.056	<0.290	<0.272	0.133	0.139	0.065
	C	45-46	12	<0.030	<0.215	<0.186	0.061	0.089	0.068
	D	45-46	6	<0.038	<0.124	<0.116	0.071	0.073	0.033
	E	45	6	<0.038	<0.176	<0.143	0.110	0.105	0.057
Grain	A	83-112	42	<0.02	<0.022	<0.021	0.010	0.010	0.001
	B	76-105	42	<0.02	<0.025	<0.023	0.010	0.010	0.002

Table 16. Summary of Residue Data from Field Corn Field Trials with Tembotrione.									
	C	91-107	12	<0.02	<0.02	<0.02	0.010	0.010	0.000
	D	91-107	6	<0.02	<0.02	<0.02	0.010	0.010	0.000
	E	93-99	6	<0.02	<0.02	<0.02	0.010	0.010	0.000
Stover (fodder)	A	83-112	42	<0.02	<0.450	<0.390	0.029	0.072	0.100
	B	76-105	42	<0.02	<0.445	<0.428	0.055	0.083	0.097
	C	91-107	12	<0.02	<0.077	<0.074	0.030	0.034	0.025
	D	91-107	6	<0.02	<0.077	<0.060	0.043	0.040	0.026
	E	93-99	6	<0.02	<0.064	<0.054	0.037	0.032	0.019

[1] Treatment Pattern A: two foliar spray applications at 24-inch and 36-inch corn height, with adjuvants methylated seed oil (MSO) and urea ammonium nitrate (UAN).
Treatment Pattern B: One foliar spray application at 36-inch corn height and one directed-spray application one week later.
Treatment Pattern C: application at the same use pattern as Pattern A except adjuvants added were crop oil concentrate (COC) and UAN.
Treatment Pattern D: application at the same use pattern as Pattern A exeept adjuvants added were MSO and ammonium sulfate (AMS).
Treatment Pattern E: application at the same use pattern as Pattern A except adjuvants added were COC and AMS.
[2] The LOQ (0.01 ppm for each analyte) was used to determine the minimum, maximum, and HAFT. For the calculation of the median, mean and standard deviation ½ the LOQ (0.005 ppm for each analyte) was used for residues reported below the LOQ (or <LOD).

Conclusions: The submitted residue data for field corn are adequate to fulfill data requirements. The number and locations of the crop field trials are in accordance with OPPTS Guideline 860.1500. The available data will support the proposed use pattern.

The residue data for field corn forage and stover from trials reflecting Treatment A or B (whichever had the highest average residues) were entered into the Agency's tolerance spreadsheet as specified by the *Guidance for Setting Pesticide Tolerances Based on Field Trial Data* SOP to determine appropriate tolerance levels; see Appendix II. The Agency's spreadsheet was not used for field corn grain because greater than 95% of the treated samples bore individual or total residues below the LOQ. The recommended tolerances for the combined residues tembotrione and M5, expressed as parent equivalents, are 0.03 ppm for field corn grain, 0.60 ppm for field corn forage, and 0.45 ppm for field corn stover.

No residue data or tolerance for corn aspirated grain fractions are needed for the purpose of this petition because the proposed use on field corn involves applications made prior to the crop's reproductive stage. The proposed use specifies that applications should be made to corn from emergence through the V8 stage of growth; application to corn that is more mature than growth stage V8 (i.e., more than 8 visible leaf collars) is prohibited. This determination is also supported by the results of a field corn processing study which indicates that residues do not concentrate in the processed fractions of corn grain treated at 5x.

Corn, pop

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Four field trials were conducted in the United States encompassing Zones 5 (IL, KS, and NE; 3 trials) and 8 (TX; 1 trial) during the 2003 growing season. Each trial site consisted of one control plot and two treated plots. Two foliar spray applications of a SC formulation (AE 0172747 Herbicide) nominally containing 3.50 lb tembotrione ai/gallon (420 g ai/L), were made to popcorn at 24-inch and 36-inch height in treated plot A at a target rate of 0.082 lb

ai/A/application (0.092 kg ai/ha/application) (1x the proposed maximum seasonal rate). Popcorn in treated plot B received one foliar spray application at the 36-inch height and one drop-nozzle (directed) spray one week later using the same target application rates. Applications were made using ground equipment in ~14-17 gal/A (132-154 L/ha). An adjuvant was added to the spray mixture for all applications. The achieved total seasonal rates ranged from 0.164-0.172 lb ai/A (0.184-0.193 kg ai/ha) for all treated plots at all trial sites.

Popcorn grain and stover samples were harvested at a PHI of 72 to 93 days after the last application. At one trial location, popcorn corn matrices were collected at additional sampling intervals to evaluate residue decline: popcorn grain and stover were collected 69, 77, 83, 90, and 97 days following the last application of Treatment A and collected 63, 71, 77, 84, and 91 days following the last application of Treatment B.

The harvested popcorn RAC samples were analyzed for residues of the parent compound, tembotrione, and the metabolites M2, M5, and M6 using a method entitled "AE 0172747: An Analytical Method for the Determination of Residues of AE 0172747, and its major metabolites M6, AE 1417268, and AE 1392936 in Plant Matrices Using LC/MS/MS." This method is acceptable for data collection based on adequate method validation and concurrent method recovery data. The LOQs for tembotrione, M2, M5, and M6 were each 0.010 ppm based on field corn validation data; the estimated method LODs were ≤0.004 ppm for each analyte in corn grain and stover.

The maximum storage interval of samples from harvest to analysis was 307 days (10.1 months) for popcorn grain and stover. Adequate storage stability data for field corn commodities (MRID 46695601) are available to support the storage conditions and intervals of samples from the popcorn field trials.

In trials reflecting Treatment A (two foliar applications totaling 0.161-0.170 lb ai/A), the maximum combined residues of parent and its metabolites (M5 + M6 + M2), as parent equivalents, were <0.050 ppm in/on popcorn grain and <0.281 ppm in/on popcorn stover. In the treated stover sample which bore the highest combined residues of <0.281 ppm, metabolites M5 and M6 comprised 67% and 24% of the respective total residues; individual residues of the parent and metabolite M2 were either below or slightly above the LOQ in the same stover sample.

Following Treatment B (one foliar application and one directed-spray application totaling 0.165-0.172 lb ai/A), the maximum combined residues of parent and its metabolites (M5 + M6 + M2), as parent equivalents, were <0.048 ppm in/on popcorn grain and <0.302 ppm in/on popcorn stover.

When only residues of the parent and metabolite M5 are summed, as reflected in the proposed tolerance expression, the maximum combined residues from Treatment A trials were <0.02 ppm (combined LOQs) in/on popcorn grain and <0.199 ppm in/on popcorn stover. Following Treatment B, the maximum combined residues were <0.02 ppm in/on popcorn grain and <0.202 ppm in/on popcorn stover.

Based on the results of the side-by-side field trials, residues were similar in/on popcorn matrices treated with two foliar applications or treated with one foliar + one directed-spray application.

Residues of the parent were nondetectable in all popcorn grain and stover samples from both treatment schemes.

In the popcorn decline trial, no total tembotrione residues were found in grain samples above the LOQ of 0.04 ppm at any sampling interval for both Treatments A and B. Total tembotrione residues in popcorn stover in both treatments showed a general tendency to decline with increasing PHIs.

Table 17. Summary of Residue Data from Popcorn Field Trials with Tembotrione.

Proposed Use Pattern: Two foliar sprays at 0.08 lb ai/A/application with a minimum RTI of 14 days, for a maximum seasonal rate of 0.16 lb ai/A. The proposed PHI is 45 days for forage; no PHI is listed for grain or stover.

Commodity	Treated[1]	PHI (days)	Sum of Residues: Parent + M5 + M6 + M2 (ppm in parent equivalents)[2]						
			N	Min	Max	HAFT	Median	Mean	Std. Dev.
Grain	A	81-93	8	<0.04	<0.050	<0.049	0.020	0.023	0.006
	B	72-86	8	<0.04	<0.048	<0.047	0.020	0.023	0.006
Stover	A	81-93	8	<0.04	<0.281	<0.238	0.033	0.081	0.098
	B	72-86	8	<0.04	<0.302	<0.283	0.049	0.102	0.112
Commodity	Treatment Pattern[1]	PHI (days)	Sum of Residues: Parent + M5 (ppm in parent equivalents)[2]						
			N	Min	Max	HAFT	Median	Mean	Std. Dev.
Grain	A	81-93	8	<0.02	<0.02	<0.02	0.01	0.01	N/A
	B	72-86	8	<0.02	<0.02	<0.02	0.01	0.01	N/A
Stover	A	81-93	8	<0.02	<0.199	<0.159	0.018	0.051	0.068
	B	72-86	8	<0.02	<0.202	<0.192	0.026	0.066	0.077

[1] Treatment Pattern A: two foliar spray applications at 24 inch and 36 inch corn height, for a total rate of 0.164-0.170 lb ai/A. Treatment Pattern B: One foliar spray application at 36 inch corn height and one directed spray application one week later, for a total rate of 0.165-0.172 lb ai/A.

[2] The LOQ (0.01 ppm for each analyte) was used to determine the minimum, maximum, and HAFT. For the calculation of the median, mean and standard deviation ½ the LOQ (0.005 ppm for each analyte) was used for residues reported below the LOQ (or <LOD).

Conclusions: The submitted field trial data for popcorn are adequate to fulfill data requirements. The number and locations of the popcorn trials are in accordance with OPPTS Guideline 860.1500. The available data will support the proposed use pattern.

The residue data for popcorn stover from trials reflecting Treatment B were entered into the Agency's tolerance spreadsheet as specified by the *Guidance for Setting Pesticide Tolerances Based on Field Trial Data* SOP to determine appropriate tolerance levels; see Appendix II. The Agency's spreadsheet was not used for popcorn grain because all of the treated samples bore individual or total residues below the LOQ. The recommended tolerances for the combined residues tembotrione and its metabolite M5, expressed as parent equivalents, are 0.02 ppm for popcorn grain and 0.35 ppm for popcorn stover.

Corn, sweet

DER Reference List 46695608.der.doc

Twelve sweet corn trials were conducted in the United States encompassing Zones 1 (NY and

PA; 2 trials), 2 (GA; 1 trial), 3 (FL; 1 trial), 5 (IA, IL, IN, NE, and WI; 5 trials), 10 (CA; 1 trial), 11 (ID; 1 trial), and 12 (OR; 1 trial) during the 2003 and 2004 growing seasons. Each trial site consisted of one control plot and two treated plots. Two foliar spray applications of a SC formulation (AE 0172747 Herbicide) nominally containing 3.50 lb tembotrione ai/gallon (420 g ai/L), were made to sweet corn at 24-inch and 36-inch height in treated plot A at a target rate of 0.082 lb ai/A/application (0.092 kg ai/ha/application) (1x the proposed maximum seasonal rate). Sweet corn in treated plot B received one foliar spray application at the 36-inch height and one drop-nozzle (directed) spray one week later at the same target application rates. Applications were made using ground equipment in ~13-17 gal/A (122-163 L/ha). An adjuvant was added to the spray mixture for all applications. The achieved total seasonal rates ranged from 0.162 to 0.170 lb ai/A (0.182 to 0.190 kg ai/ha) for all treated plots at all trial sites.

Sweet corn forage and kernels plus cob with husk removed (K+CWHR) samples were harvested at a PHI of 44 to 46 days after the last application. Stover was harvested at commercial maturity (BBCH 87 to 89) at PHIs ranging from 46 to 95 days. At one trial location, sweet corn matrices were collected at additional sampling intervals to evaluate residue decline: sweet corn forage and K+CWHR were collected 35/36, 39, 44/45, 49/50, and 56 days and sweet corn stover was collected 42/49, 50/57, 56/63, 64/71, and 70/77 days following the last application of Treatments A and B.

The harvested sweet corn RAC samples were analyzed for residues of the parent compound, tembotrione, and the metabolites M2, M5, and M6 using a method entitled "AE 0172747: An Analytical Method for the Determination of Residues of AE 0172747, and its major metabolites M6, AE 1417268, and AE 1392936 in Plant Matrices Using LC/MS/MS." This method is acceptable for data collection based on adequate method validation and concurrent method recovery data. The LOQs for tembotrione, M2, M5, and M6 were each 0.010 ppm in corn grain, forage and stover based on field corn validation data; the estimated method LODs were ≤0.004 ppm for each analyte in corn grain, forage, and stover.

The maximum storage intervals of samples from harvest to analysis were 372 days (12.2 months) for sweet corn forage, 334 days (11.0 months) for sweet corn K+CWHR, and 313 days (10.3 months) for sweet corn stover. In addition, several forage and stover samples were reanalyzed 321-334 days after the initial analysis; the maximum storage intervals of these samples was 641 days (21.1 months) for forage and 635 days (20.9 months) for stover. Results of the reanalyses were not significantly different from the original analyses; therefore, stability may be inferred for the additional storage interval. Adequate storage stability data for field corn commodities (MRID 46695601) are available to support the storage conditions and intervals of samples from the sweet corn field trials.

In trials reflecting Treatment A (two foliar applications totaling 0.162-0.170 lb ai/A), the maximum combined residues of parent and its metabolites (M5 + M6 + M2), as parent equivalents, were <0.864 ppm in/on sweet corn forage, <0.082 ppm in/on sweet corn K+CWHR, and <0.973 ppm in/on sweet corn stover. In the treated stover sample which bore the highest combined residues of <0.973 ppm, metabolites M5, M6, and M2 comprised 76%, 12%, and 10% of the total residues, respectively; residues of the parent were below the LOQ in the same stover sample.

Following Treatment B (one foliar application and one directed-spray application totaling 0.164-

0.170 lb ai/A), the maximum combined residues of parent and its metabolites (M5 + M6 + M2), as parent equivalents, were <1.384 ppm in/on sweet corn forage, <0.082 ppm in/on sweet corn K+CWHR, and <0.720 ppm in/on sweet corn stover.

When only residues of the parent and metabolite M5 are summed, the maximum combined residues following Treatment A were <0.738 ppm in/on sweet corn forage, <0.035 ppm in/on sweet corn K+CWHR, and <0.754 ppm in/on sweet corn stover. Following Treatment B, the maximum combined residues were <0.911 ppm in/on sweet corn forage, <0.02 ppm (combined LOQs) in/on sweet corn K+CWHR, and <0.465 ppm in/on sweet corn stover.

Based on the results of the side-by-side field trials, residues were similar in/on sweet corn K+CWHR treated with two foliar applications or treated with one foliar + one directed-spray application; however, residues were higher in forage treated with the two foliar applications but higher in stover treated with the one foliar + one directed-spray applications. Residues of the parent were below the LOQ in all sweet corn matrices from both treatment regimes.

For sweet corn forage and stover, the total tembotrione residue declined with time by the later sampling intervals; residues initially increased in forage and then declined. The minimal total tembotrione residue in grain was not observed to decline with time; however, overall residues were nondetectable or very low.

Table 18. Summary of Residue Data from Sweet Corn Field Trials with Tembotrione.

Proposed Use Pattern: Two foliar sprays at 0.08 lb ai/A/application with a minimum RTI of 14 days, for a maximum seasonal rate of 0.16 lb ai/A. The proposed PHI is 45 days for forage; no PHI is listed for grain or stover.

Commodity	Treated[1]	PHI (days)	Sum of Residues: Parent + M5 + M6 + M2 (ppm in parent equivalents)[2]						
			N	Min	Max	HAFT	Median	Mean	Std. Dev.
Forage	A	44-46	24	<0.110	<0.864	<0.856	0.341	0.361	0.208
	B	44-46	24	<0.04	<1.384	<1.242	0.256	0.373	0.345
K+CWHR	A	44-46	24	<0.04	<0.082	<0.080	0.029	0.031	0.013
	B	44-46	24	<0.04	<0.082	<0.078	0.031	0.032	0.013
Stover (fodder)	A	47-95	24	<0.04	<0.973	<0.904	0.077	0.176	0.246
	B	46-88	24	<0.04	<0.720	<0.690	0.083	0.164	0.196
Commodity	Treated[1]	PHI (days)	Sum of Residues: Parent + M5 (ppm in parent equivalents)[2]						
			N	Min	Max	HAFT	Median	Mean	Std. Dev.
Forage	A	44-46	24	<0.085	<0.738	<0.738	0.248	0.279	0.174
	B	44-46	24	<0.02	<0.911	<0.751	0.181	0.222	0.195
K+CWHR	A	44-46	24	<0.02	<0.035	<0.028	0.010	0.011	0.004
	B	44-46	24	<0.02	<0.02	<0.02	0.010	0.010	NA
Stover (fodder)	A	47-95	24	<0.02	<0.754	<0.664	0.034	0.116	0.188
	B	46-88	24	<0.02	<0.465	<0.426	0.037	0.087	0.126

[1] Treatment Pattern A: two foliar spray applications at 24 inch and 36 inch corn height, for a total rate of 0.162-0.170 lb ai/A. Treatment Pattern B: One foliar spray application at 36 inch corn height and one directed spray application one week later, for a total rate of 0.164-0.170 lb ai/A.

[2] The LOQ (0.01 ppm for each analyte) was used to determine the minimum, maximum, and HAFT. For the calculation of the median, mean and standard deviation ½ the LOQ (0.005 ppm for each analyte) was used for residues reported below the LOQ (or <LOD).

Conclusions: The submitted field trial data for sweet corn are adequate to fulfill data requirements. The number and locations of the sweet corn trials are in accordance with OPPTS Guideline 860.1500. The available data will support the proposed use pattern.

The residue data for sweet corn forage and stover from trials reflecting Treatment A were entered into the Agency's tolerance spreadsheet as specified by the *Guidance for Setting Pesticide Tolerances Based on Field Trial Data* SOP to determine appropriate tolerance levels; see Appendix II. The Agency's spreadsheet was not used for sweet corn K + CWHR because greater than 95% of the treated samples bore individual or total residues below the LOQ. The recommended tolerances for the combined residues tembotrione and its metabolite M5, expressed as parent equivalents, are 0.04 ppm for sweet corn K + CWHR, 1.0 ppm for sweet corn forage, and 1.2 ppm for sweet corn stover.

860.1520 Processed Food and Feed

DER Reference List 46695610.der.doc (Corn)
46695611.der.doc (Rotated wheat)

Corn, field

In one trial conducted in IL during the 2003 growing season, field corn grain was harvested 71 days following the last of two foliar broadcast applications of the SC formulation for a total rate of 0.82 lb ai/A (0.914 kg ai/ha; 5x the nominal field trial rate). Corn grain samples were processed into dry milled commodities (grits, meal, flour, and refined oil) and wet milled commodities (starch and refined oil).

Samples of corn grain and its processed commodities were analyzed for residues of the parent compound, tembotrione, and the metabolites M2, M5, and M6. The analytical method was entitled "AE 0172747: An Analytical Method for the Determination of Residues of AE 0172747, and its major metabolites M6, AE 1417268, and AE 1392936 in Plant Matrices Using LC/MS/MS." This method is acceptable for data collection based on adequate method validation and concurrent method recovery data. The LOQ for tembotrione, M2, M5, and M6 were 0.010 ppm for each analyte in corn grain and all processed corn commodities. The calculated method LODs were ≤0.003 ppm for each analyte in corn grain and its processed commodities.

The maximum storage intervals of crop samples from harvest/processing to analysis were 460 days (15.1 months) for corn grain and 19-38 days (0.6-1.3 months) for corn processed commodities. Adequate storage stability data for field corn commodities (MRID 46695601) are available to support the storage conditions and intervals of RAC samples from the processing study. No storage stability data are required for processed commodities because samples were stored less than approximately 30 days prior to analysis.

The average total residues of tembotrione plus M5 (as parent equivalents) were 0.046 ppm in/on field corn grain (RAC) treated at a total rate of 0.82 lb ai/A (0.914 kg ai/ha). Following processing of the treated RAC, total residues concentrated slightly in meal (0.053 ppm; 1.2x processing factor) but did not concentrate in oil (0.001 ppm; 0.02x), flour (0.037 ppm; 0.80x), grits (0.046 ppm; 1.0x), and starch (0.001 ppm; 0.02x). Residues were significantly reduced in

starch and in corn oil. The observed processing factors are less than the theoretical concentration factors of 25x for corn oil (based on separation into components; OPPTS 860.1520, Table 3).

Table 19. Residue Data from Field Corn Processing Study with Tembotrione.

RAC	Processed Commodity	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Total Tembotrione + M5 Residues[1] (ppm in parent equivalents)	Processing Factor[2]
Grain	RAC	0.82 (0.914)	71	0.046	--
	Refined oil (dry milled)			0.001	0.02x
	Refined oil (wet milled)			0.001	0.02x
	Flour			0.037	0.80x
	Grits			0.046	1.0x
	Meal			0.053	1.2x
	Starch			0.001	0.02x

[1] Individual analyte residues reported as "<LOD" were assigned a finite value of ½ the respective analyte LOD. The LOD values for tembotrione (parent), and M5 in field corn grain (also used for flour, grits, meal, and starch) were 0.0011 ppm, and 0.0025 ppm, respectively; LODs for refined oil were 0.0012 ppm, and 0.0011 ppm, respectively.

[2] Processing factor = Average residue in processed sample/residue in unproeessed sample.

Rotated Wheat

In one trial conducted in IL during the 2003 growing season, two foliar applications of AE 0172747 Herbicide, a SC formulation nominally containing 3.50 lb tembotrione ai/gallon (420 g ai/L), were made to the primary crop (field corn) at a seasonal rate of 0.82 lb ai/A (0.913 kg ai/ha). This rate is equivalent to 5x the seasonal field trial rates for corn. After normal harvest of the primary crop, the rotational crop winter wheat was planted in the test plot with a 107-day PBI. The winter wheat crop was allowed to grow according to good agricultural practices, and grain was harvested at commercial maturity (253 days after planting).

Samples of rotated wheat grain were analyzed for residues of the parent compound, tembotrione, and the metabolites M2, M5, and M6. The analytical method was entitled "AE 0172747: An Analytical Method for the Determination of Residues of AE 0172747, and its major metabolites M6, AE 1417268, and AE 1392936 in Plant Matrices Using LC/MS/MS." This method is acceptable for data collection based on adequate method validation and concurrent method recovery data. The LOQs for tembotrione, M2, M5, and M6 were 0.010 ppm each in wheat grain. The calculated method LODs were ≤0.003 ppm for each analyte in grain.

The maximum storage interval of wheat grain samples from harvest to analysis was 122 days (4 months). Adequate storage stability data for field corn commodities (MRID 46695601) are available to support the storage conditions and intervals of RAC samples from the processing study.

Residues of tembotrione and each of its metabolites (M5, M6 and M2) were below the method LOQ (<0.010 ppm) in rotated wheat grain. Since all residues were <LOQ, the petitioner determined that processing of the bulk wheat grain samples to representative processed commodities was not necessary.

Conclusions: The submitted corn and wheat grain processing data are adequate to fulfill data requirements. The corn study shows that following processing of field corn grain bearing

quantifiable residues, total residues of tembotrione plus M5 (as parent equivalents) concentrated slightly in meal (0.053 ppm; 1.2x processing factor) but did not concentrate in oil (0.001 ppm; 0.02x), flour (0.037 ppm; 0.80x), grits (0.046 ppm; 1.0x), or starch (0.001 ppm; 0.02x). A tolerance for corn meal need not be established as the recommended RAC tolerance will cover any expected residues in corn meal as a result of the proposed use. The wheat study shows that total residues of tembotrione and its metabolites were below the method LOQ (<0.010 ppm) in/on rotated wheat grain following treatment of the primary crop at 5x. As residues in the RAC were <0.010 ppm, data on the processed commodities of wheat as a rotated crop are not required.

860.1650 Submittal of Analytical Reference Standards

Analytical standards for tembotrione and its metabolite M5 are currently not available in the National Pesticide Standards Repository [Source: personal communication with D. Wright Jr. of ACL/BEAD, 11/13/2006]. Analytical reference standards of tembotrione and M5 (including the deuterated internal standards) should be supplied, and supplies replenished as requested by the Repository. The reference standards should be sent to the Analytical Chemistry Lab, which is located at Fort Meade, to the attention of either Theresa Cole or Frederic Siegelman at the following address:

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

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

860.1850 Confined Accumulation in Rotational Crops

DER Reference List *46695612.der.doc*

Bayer CropScience has submitted a confined rotational crop study with [phenyl-U-^{14}C]tembotrione. The radiolabeled test substance was combined with nonlabeled tembotrione and diluted with ACN, then applied to bare sandy loam soil at a rate equivalent to 0.189 lb ai/A (212 g ai/ha) (1.2x the proposed maximum seasonal rate). Rotational crops, Swiss chard, turnips, and spring wheat, were planted 90 days after soil treatment.

TRR, determined by summing extractable and nonextractable residues in wheat grain and by combustion/LSC in remaining matrices, accumulated at ≥0.01 ppm in all rotated crop matrices. TRR were 0.134 ppm in Swiss chard, 0.050 and 0.013 ppm, respectively, in turnip tops and roots, and 0.031, 0.246, 0.188, and 0.178 ppm, respectively, in wheat forage, hay, straw, and grain.

Approximately 74-97% TRR were extracted from rotational crop matrices using ACN/water; additional residues (~10-13% TRR) were extracted from wheat hay and straw by refluxing with methanol/water. The nonextractable residues of wheat straw and grain were also subjected to mild acid or base hydrolysis procedures which released ~5% TRR (acid hydrolysis) or ~11-13%

TRR (base hydrolysis). Nonextractable residues following extraction and hydrolysis procedures accounted for ≤0.009 ppm in all rotational crop matrices except wheat hay, in which nonextractable residues accounted for 7.3% TRR (0.018 ppm). These procedures adequately extracted the majority of residues from rotational crop matrices. Extraction values were normalized; reported accountabilities before normalization were 85.5% for Swiss chard and 77.4% and 91.8%, respectively for turnip tops and roots. In wheat matrices, accountabilities before normalization were 98.2%, 92.0%, and 94.2%, respectively, for wheat forage, hay, and straw. TRR in wheat grain were determined by summing extractable and nonextractable residues; therefore, accountability was 100%. Residues were identified and quantitated by HPLC, TLC, and HPLC/MS and HPLC/MS/MS analyses.

Total identified residues ranged ~22-25% TRR in turnip tops and roots, and 80-91% TRR in remaining matrices. The parent, tembotrione, was not identified in any rotational crop commodity. The major identified residue in all rotational crop matrices was metabolite M6, which accounted for 90.6% TRR (0.121 ppm) in Swiss chard, 22.0% and 15.5% TRR (0.011 and 0.002 ppm) in turnip tops and roots, respectively, 51.0% TRR (0.016 ppm) in wheat forage, 70.6% TRR (0.173 ppm) in wheat hay, 59.7% TRR (0.112 ppm) in wheat straw, and 86.4% TRR (0.154 ppm) in wheat grain. The only other identified metabolite was M2, which was not found in Swiss chard, turnip tops, or wheat grain, but accounted for 9.4% TRR (0.001 ppm) in turnip roots, 35.1% TRR (0.011 ppm) in wheat forage, and 20.2% and 20.3% TRR (0.050 and 0.038 ppm) in wheat hay and straw, respectively. The petitioner characterized a number of unknowns in Swiss chard and turnip matrices. These unknowns, designated A1-A10, were generally determined at individual levels ≤8.4% TRR and ≤0.006 ppm; however, unknowns A2 and A3 were present at 15.0% and 15.7% TRR (0.007 and 0.008 ppm) in turnip tops, and unknowns A1 and A2 were present at 21.3% and 25.5% TRR (0.003 ppm each) in turnip roots, where they constituted the major components of the residue. Unknowns designated R1 and R2 were found in the methanol reflux extract of wheat straw at ≤0.003 ppm. Because no individual unknown accounted for 0.010 ppm, no further analysis is required.

The petitioner did not provide the dates of sample extraction and profiling, but did provide storage intervals for the RACs and extracts. Based on these data, sample extraction and metabolite profiling were completed within ≤97 days of collection. Because samples were stored for <6 months prior to analysis, supporting storage stability data are not required.

The metabolic profile of tembotrione in confined rotational crops involves cleavage of the complete cyclohexyl moiety from the parent compound leaving the benzoic acid moiety of the molecule, M6, and to a lesser extent subsequent cleavage of the ether bond to form M2. Both M6 and M2 are significant soil degradates, hence, the presence of these degradates in the confined rotational crops is consistent with the uptake of these metabolites from soil by the rotational crops. The metabolic pathway seen in this study is consistent with the pathway observed in the corn metabolism study.

Conclusions: The submitted confined rotational crop study is adequate to satisfy data requirements. The two residue components identified in the study, M6 and M2, were also identified in the primary crop (corn) metabolism study. The metabolism of tembotrione in rotational crops appears to be consistent with the pathway observed in the corn metabolism study. The residue of concern for rotational crops is tembotrione *per se* (Memo, L. Austin *et al.*, 7/18/07; D325935).

860.1900 Field Accumulation in Rotational Crops

DER Reference List 46695613.der.doc (Winter wheat)
46695614.der.doc (Mustard greens, turnips, and summer squash)

Winter wheat

A SC formulation (AE 0172747 Herbicide) nominally containing 3.50 lb tembotrione ai/gallon, was applied to the primary crop in 10 corn field trials (field corn, sweet corn, or popcorn) at a seasonal rate ranging from 0.164 to 0.174 lb ai/A (~1.0-1.1x the maximum proposed seasonal rate). Once the primary crops were harvested, the plots were prepared according to local commercial practice for planting of winter wheat. Using the same plots where corn was grown, winter wheat was planted approximately 90-120 days after the last application of the test formulation. The winter wheat crops were allowed to grow according to good agricultural practices, and appropriate winter wheat commodities were harvested at commercial maturity.

The harvested wheat RACs were analyzed for residues of the parent compound, tembotrione, and the metabolites M2, M5, and M6 using a method entitled "AE 0172747: An Analytical Method for the Determination of Residues of tembotrione, and its major metabolites M6, AE 1417268, and AE 1392936 in Plant Matrices Using LC/MS/MS." This method is acceptable for data collection based on adequate method validation and concurrent method recovery data. The LOQs for tembotrione, M2, M5, and M6 were each 0.010 ppm in all matrices; the estimated LODs were $\leq$0.004 ppm for each analyte.

Samples of winter wheat hay, grain, and straw were held in frozen storage for intervals of 109-147 days prior to extraction; wheat forage was stored for up to 381 days prior to extraction. All extracts were analyzed within 5 days of extraction. Adequate storage stability data for field corn commodities (MRID 46695601) are available to support the storage conditions and intervals of samples from the wheat rotational crop trials.

The results from this study indicate that the total residues of tembotrione, M2, M5, and M6 were <0.04 ppm in/on all samples of rotated wheat forage, hay, grain, and straw planted at the 83-158 day PBI.

Mustard greens, turnips, and summer squash

A SC formulation (AE 0172747 Herbicide) nominally containing 3.50 lb tembotrione ai/gallon, was applied in three trials as broadcast foliar sprays to a target primary crop of either field corn or sweet corn at a total rate ranging from 0.165 to 0.166 lb ai/A (~1x the maximum proposed seasonal rate). Once the corn was harvested, the plots were prepared according to local commercial practice for each rotated crop. Using the same plots where corn was grown, rotational crops (mustard greens, turnips, and summer squash) were planted approximately 90-120 days after the last application for the "fall" PBI. The rotational crops were allowed to grow according to good agricultural practices and were harvested at commercial maturity. In addition, rotational crops (mustard greens, turnips, and bell peppers) were planted 273-349 days after the last application for the "spring" PBI.

The harvested rotational crop RACs were analyzed for residues of the parent compound,

tembotrione, and the metabolites M2, M5, and M6 using a method entitled "AE 0172747: An Analytical Method for the Determination of Residues of AE 0172747, and its major metabolites M6, AE 1417268, and AE 1392936 in Plant Matrices Using LC/MS/MS." This method is acceptable for data collection based on adequate method validation and concurrent method recovery data. The LOQs for tembotrione, M2, M5, and M6 were each 0.010 ppm in all matrices; the estimated method LODs were ≤0.004 ppm for each analyte.

The rotational crop commodities were held in frozen storage for a maximum of 10.7 months (326 days) prior to extraction. All extracts were analyzed within 5 days of extraction. Adequate storage stability data for mustard greens, turnip roots, and summer squash (MRID 46695602) are available to support the storage conditions and intervals of samples from the rotational crop trials.

The results from this study indicate that residues of the parent and its metabolites (M2, M5, and M6) were each <0.010 ppm in/on all rotated crop commodities (mustard greens, turnip top, turnip root, and summer squash) planted at the 91-117 day PBI. Additional rotational crops (mustard greens, turnips, and bell peppers) planted 273-349 days after the last application for the "spring" PBI were not analyzed since residues of tembotrione and its metabolites M2, M5, and M6 were nonquantifiable in crop samples from the earlier PBI..

Conclusions: The submitted field rotational crop data are adequate to satisfy data requirements. The available data indicate that residues of the parent and its metabolites (M2, M5, and M6) were each <0.010 ppm in/on: (i) all samples of rotated wheat forage, hay, grain, and straw at PBI of 83-158 days; and (ii) all samples of rotated mustard greens, turnip top, turnip root, and summer squash at PBIs of 91-117 days. These data support the proposed rotational crop restrictions listed in Table 5. Unless the petitioner requests for PBIs shorter than 90 days for non-labeled crops (the shortest interval tested in confined rotational crop study), no additional data are required, and tolerances for inadvertent residues need not be established.

860.1550 Proposed Tolerances

Bayer CropScience has proposed a tolerance expression in terms of the residues of tembotrione (2-[2-chloro-4-(methylsulfonyl)-3-[(2,2,2-(trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione) and its metabolite M5 (2-[2-chloro-4-(methylsulfonyl)-3-[(2,2,2-(trifluoroethoxy)methyl]benzoyl]-4,6-dihydroxy-1,3-cyclohexanedione) for the establishment of tolerances for corn commodities. HED has determined that the residues of concern in corn commodities are tembotrione and its metabolite M5. The petitioner is requested to submit a revised Section F to specify the tolerance expression in terms of the combined residues of tembotrione and its metabolite M5, expressed as tembotrione equivalents.

For the establishment of tolerances on livestock commodities, the petitioner has proposed a tolerance expression in terms of the residues of M5 (2-[2-chloro-4-(methylsulfonyl)-3-[(2,2,2-(trifluoroethoxy)methyl]benzoyl]-4,6-dihydroxy-1,3-cyclohexanedione). HED has determined that the residues of concern in dairy cattle and poultry are tembotrione and its metabolite M5. The petitioner is requested to submit a revised Section F to specify the tolerance expression in terms of the combined residues of tembotrione and its metabolite M5, expressed as tembotrione equivalents.

There are no Codex, Canadian, or Mexican maximum residue limits (MRLs) established for residues of tembotrione in crop or livestock commodities.

A summary of the recommended tolerances for the current petition are listed in Table 20. The petitioner should submit a revised section F reflecting the recommended tolerances and commodity definitions presented in Table 20.

The Agency's *Guidance for Setting Pesticide Tolerances Based on Field Trial Data* was utilized for determining appropriate tolerance levels for field corn forage, field corn stover, popcorn stover sweet corn forage, and sweet corn stover; see Appendix II for tolerance calculations. The Agency's tolerance spreadsheet was not used to determine tolerance levels for the remainder of various corn commodities since greater than 95% of the treated samples bore individual or total residues below the LOQ.

A tolerance for corn aspirated grain fractions is not needed because the proposed use on field corn involves applications prior to the crop's reproductive stage. Tolerances for the processed commodities of corn are not needed because the submitted corn processing study shows that residues do not concentrate. Residues of tembotrione and its metabolites are not likely to concentrate in the processed commodities of rotated wheat grain because residues of tembotrione and its metabolites were nonquantifiable following treatments at 5x the proposed seasonal rate. Tolerances for inadvertent residues of tembotrione and its metabolites in/on rotational crops are not needed because the limited field rotational crop trials show that residues were below the LOQ in/on various rotational crop commodities.

A detailed discussion of the assessment of livestock commodity tolerances is presented in the "860.1480 Meat, Milk, Poultry, and Eggs" section of this Summary Document.

Table 20. Tolerance Summary for Tembotrione.

Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments; *Correct Commodity Definition*
Corn Commodities			
Field Corn, grain	0.01	0.03	*Corn, field, grain*
Field Corn, forage	0.6	0.60	*Corn, field, forage*
Field Corn, stover	0.7	0.45	*Corn, field, stover*
Sweet Corn, K + CWHR	0.03	0.04	*Corn, sweet, kernel plus cob with husks removed*
Sweet Corn, forage	1.0	1.0	*Corn, sweet, forage*
Sweet Corn, stover	1.5	1.2	*Corn, sweet, stover*
Popcorn, grain	0.01	0.02	*Corn, pop, grain*
Popcorn, stover	0.20	0.35	*Corn, pop, stover*
Livestock Commodities			
Cattle Liver	0.5	0.40	*Cattle, liver*
Cattle Kidney	0.07	0.07	*Cattle, meat byproducts, except liver*
Goat Liver	0.5	0.40	*Goat, liver*
Goat Kidney	0.07	0.07	*Goat, meat byproducts, except liver*
Hog Liver	0.5	Not required	Based on the transfer coefficients for livestock tissues and relatively low dietary burdens for swine of 0.024
Hog Kidney	0.07	Not required	

			ppm for tembotrione and 0.006 ppm for metabolite M5, tolerances for hogs are not needed.
Sheep Kidney	0.07	0.07	*Sheep, meat byproducts, except liver*
Sheep, meat by products	0.5	0.40	*Sheep, liver*
Horse Kidney	0.07	0.07	*Horse, meat byproducts, except liver*
Horse, meat by products	0.5	0.40	*Horse, liver*
Additional Livestock Commodity Tolerance That Needs to be Established			
Poultry, liver	None	0.07	

Attachments:
International Residue Limit Status sheet
Appendix I - Chemical Name and Structure Table
Appendix II - Tolerance Assessment Calculations

cc: G. Kramer (RAB1)
RDI: P.V. Shah (2/21/07), RAB1 Chemists (2/21/07), HED ChemSAC (2/28/07)
G.F. Kramer:S10781:PY-S:(703)305-5079:7509P:RAB1

INTERNATIONAL RESIDUE LIMIT STATUS

Chemical Name: 2-[2-Chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione	Common Name: Tembotrione (experimental code: AE 0172747)	X Proposed tolerance 9 Reevaluated tolerance 9 Other	Date: 11/9/06

Codex Status (Maximum Residue Limits)	U. S. Tolerances
X No Codex proposal step 6 or above ☐Codex proposal step 6 or above for the crops requested	Petition Numbers: PP#5F7009 DP Barcodes: D325349, D325663, D331222, & D332977 Other Identifier:
Residue definition (step 8/CXL): N/A	Reviewer/Branch: G. Kramer/RAB1
	Residue definition: see below

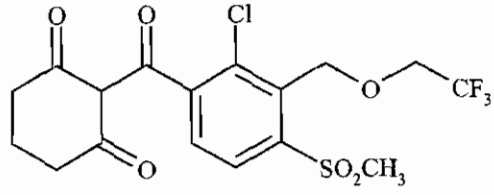
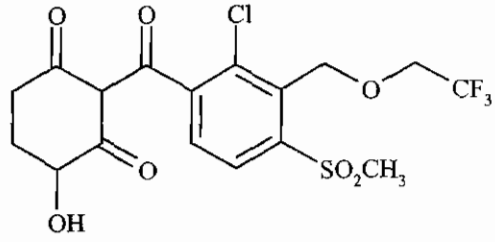
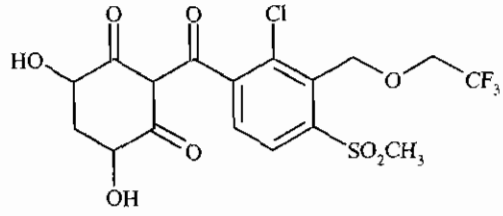
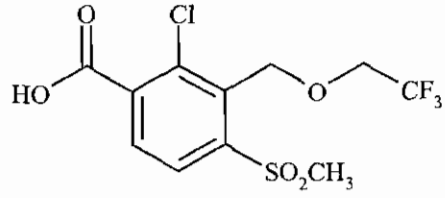
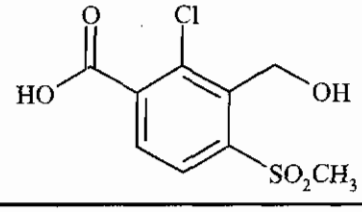
Crop (s)	MRL (mg/kg)	Crop(s)	Tolerance (ppm)
		Residue definition for plant commodities: Tembotrione (AE 0172747) and its metabolite M5	
		Field corn, grain	0.01
		Field corn, forage	0.6
		Field corn, stover	0.7
		Sweet corn, K + CWHR	0.03
		Sweet corn, forage	1.0
		Sweet corn, stover	1.5
		Popcorn, grain	0.01
		Popcorn, stover	0.20
		Residue definition for livestock commodities: M5 *per se*	
		Cattle liver	0.5
		Cattle kidney	0.07
		Goat liver	0.5
		Goat kidney	0.07
		Hog liver	0.5
		Hog kidney	0.07
		Sheep kidney	0.07
		Sheep, meat by products	0.5
		Horse kidney	0.07
		Horse meat by products	0.5

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

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

Notes/Special Instructions: S. Funk, 11/14/2006.

APPENDIX I. Chemical Names and Structures of Tembotrione and Metabolites.

Common name/code *Matrix*	Chemical name	Chemical structure
Tembotrione/AE 0172747 (parent) *Immature corn plants* *Bovine muscle, fat, kidney, liver and milk* *Poultry muscle, fat, liver, skin, egg yolk, and egg whites*	2-[2-Chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione	
Monohydroxy Tembotrione/ AE 1444744 (M10) *Early immature corn plants*	2-[2-Chloro-4-(methylsulfonyl)-3-[(trifluoroethoxy)methyl]benzoyl]-4-hydroxy-1,3-cyclohexanedione	
Dihydroxy Tembotrione/ AE 1417268 (M5) *Corn immature plants, forage, stover and grain* *Bovine kidney and liver*[1]	2-[2-Chloro-4-(methylsulfonyl)-3-[2,2,2-trifluoroethoxy)methyl]benzoyl]-4,6-dihydroxycyclohexan-1,3-dione	
Descyclohexadione Tembotrione/ AE 0456148 (M6) *Corn immature plants, forage, stover and grain* *Rotated swiss chard leaves, turnip tops and roots, and wheat forage, hay, straw and grain*	2-Chloro-4-mesyl-3-[(2,2,2-trifluoroethoxy)methyl]benzoic acid	
Tembotrione Hydroxyacid/ AE 1392936 (M2) *Corn immature plants, forage, stover and grain* *Rotated turnip roots, and wheat forage, hay and straw*	2-Chloro-3-hydroxymethyl-4-mesyl-benzoic acid	

[1] Only in bovine matrices from cattle fed the metabolite M5.

Appendix II. Tolerance-Assessment Calculations.

Field Corn

The dataset used to establish a tolerance for tembotrione on **field corn forage** consisted of field trial data representing application rates of 0.161-0.170 lb ai/A (Treatment A, 2 foliar applications at 0.082 lb ai/A/application) with a 44- to 53-day PHI. As specified by the *Guidance for Setting Pesticide Tolerances Based on Field Trial Data* SOP, the field trial application rates and PHIs are within 25% of the maximum label application rate and minimum label PHI, respectively. The residue values (total of parent + M5, as parent equivalents) used to calculate the tolerance are provided in Table II-1.

All 42 field trial sample results were above the combined LOQ of 0.02 ppm. Since there were no values (combined residues) reported below the LOQ, maximum likelihood estimation (MLE) procedures were not needed to impute censored values.

The tembotrione-field corn forage dataset was entered into the tolerance spreadsheet as specified by the *Guidance for Setting Pesticide Tolerances Based on Field Trial Data* SOP. Visual inspection of the lognormal probability plot (Figure II-1) provided in the spreadsheet indicates that the dataset is reasonably lognormal. The result from the approximate Shapiro-Francia test statistic (Figure II-2) confirmed that the assumption of lognormality should not be rejected.

Since the field trial data for tembotrione on field corn forage represent a large dataset (i.e., more than 15 samples) and are reasonably lognormal, the minimum of the 95% upper confidence limit (UCL) on the 95th percentile and the point estimate of the 99th percentile should be selected as the tolerance value. Using the rounding procedure as outlined in the *Guidance for Setting Pesticide Tolerances Based on Field Trial Data* SOP, the 95% UCL on the 95th percentile and the point estimate of the 99th percentile round to the value 0.60 ppm (Figure II-2). Therefore, 0.60 ppm is the recommended tolerance level for tembotrione (parent + M5) on field corn forage.

The dataset used to establish a tolerance for tembotrione on **field corn stover** consisted of field trial data representing application rates of 0.161-0.170 lb ai/A (Treatment B, one foliar spray application at 36-inch corn height and one directed-spray application one week later) with a 76- to 105-day PHI. As specified by the *Guidance for Setting Pesticide Tolerances Based on Field Trial Data* SOP, the field trial application rates and PHIs are within 25% of the maximum label application rate and minimum label PHI, respectively. The residue values (total of parent + M5, as parent equivalents) used to calculate the tolerance are provided in Table II-2.

As 7 of 42 field trial sample results were below the combined LOQ of 0.02 ppm, MLE procedures were needed to impute censored values.

The tembotrione-field corn stover dataset was entered into the tolerance spreadsheet as specified by the *Guidance for Setting Pesticide Tolerances Based on Field Trial Data* SOP. Visual inspection of the lognormal probability plot (Figure II-3) provided in the spreadsheet indicates that the dataset is reasonably lognormal. The result from the approximate Shapiro-Francia test statistic (Figure II-4) confirmed that the assumption of lognormality should not be rejected.

Since the field trial data for tembotrione on field corn forage represent a large dataset (i.e., more

than 15 samples) and are reasonably lognormal, the minimum of the 95% UCL on the 95th percentile should be selected as the tolerance value. Using the rounding procedure as outlined in the *Guidance for Setting Pesticide Tolerances Based on Field Trial Data* SOP, the 95% UCL on the 95th percentile rounds to the value 0.45 ppm (Figure II-4). Therefore, 0.45 ppm is the recommended tolerance level for tembotrione (parent + M5) on field corn stover.

Sweet Corn

The dataset used to establish a tolerance for tembotrione on **sweet corn forage** consisted of field trial data representing application rates of 0.162-0.170 lb ai/A (Treatment A, 2 foliar applications at 0.082 lb ai/A/application) with a 44- to 46-day PHI. As specified by the *Guidance for Setting Pesticide Tolerances Based on Field Trial Data* SOP, the field trial application rates and PHIs are within 25% of the maximum label application rate and minimum label PHI, respectively. The residue values (total of parent + M5, as parent equivalents) used to calculate the tolerance are provided in Table II-3.

All 24 field trial sample results were above the combined LOQ of 0.02 ppm. Since there were no values (combined residues) reported below the LOQ, MLE procedures were not needed to impute censored values.

The tembotrione-sweet corn forage dataset was entered into the tolerance spreadsheet as specified by the *Guidance for Setting Pesticide Tolerances Based on Field Trial Data* SOP. Visual inspection of the lognormal probability plot (Figure II-5) provided in the spreadsheet indicates that the dataset is reasonably lognormal. The result from the approximate Shapiro-Francia test statistic (Figure II-6) confirmed that the assumption of lognormality should not be rejected.

Since the field trial data for tembotrione on sweet corn forage represent a large dataset (i.e., more than 15 samples) and are reasonably lognormal, the minimum of the 95% UCL on the 95th percentile and the point estimate of the 99th percentile should be selected as the tolerance value. Using the rounding procedure as outlined in the *Guidance for Setting Pesticide Tolerances Based on Field Trial Data* SOP, the 95% UCL on the 95th percentile and the point estimate of the 99th percentile round to the value 1.0 ppm (Figure II-6). Therefore, 1.0 ppm is the recommended tolerance level for tembotrione (parent + M5) on sweet corn forage.

The dataset used to establish a tolerance for tembotrione on **sweet corn stover** consisted of field trial data representing application rates of 0.162-0.170 lb ai/A (Treatment A, 2 foliar applications at 0.082 lb ai/A/application) with a 47- to 95-day PHI. As specified by the *Guidance for Setting Pesticide Tolerances Based on Field Trial Data* SOP, the field trial application rates and PHIs are within 25% of the maximum label application rate and minimum label PHI, respectively. The residue values (total of parent + M5, as parent equivalents) used to calculate the tolerance are provided in Table II-4.

As 6 of 24 field trial sample results were below the combined LOQ of 0.02 ppm, MLE procedures were needed to impute censored values.

The tembotrione-sweet corn stover dataset was entered into the tolerance spreadsheet as specified by the *Guidance for Setting Pesticide Tolerances Based on Field Trial Data* SOP. Visual

inspection of the lognormal probability plot (Figure II-7) provided in the spreadsheet indicates that the dataset is reasonably lognormal. The result from the approximate Shapiro-Francia test statistic (Figure II-8) confirmed that the assumption of lognormality should not be rejected.

Since the field trial data for tembotrione on field corn forage represent a large dataset (i.e., more than 15 samples) and are reasonably lognormal, the minimum of the 95% UCL on the 95th percentile should be selected as the tolerance value. Using the rounding procedure as outlined in the *Guidance for Setting Pesticide Tolerances Based on Field Trial Data* SOP, the 95% UCL on the 95th percentile rounds to the value 1.2 ppm (Figure II-8). Therefore, 1.2 ppm is the recommended tolerance level for tembotrione (parent + M5) on sweet corn stover.

Popcorn

The dataset used to establish a tolerance for tembotrione on **popcorn stover** consisted of field trial data representing application rates of 0.165-0.172 (Treatment B, one foliar spray application at 36-inch corn height and one directed-spray application one week later) with a 72- to 86-day PHI. The residue values (total of parent + M5, as parent equivalents) used to calculate the tolerance are provided in Table II-5.

As 25% of the values (combined residues) reported below the LOQ, the MLE procedure was needed to impute censored values.

The tembotrione-field corn forage dataset was entered into the tolerance spreadsheet as specified by the *Guidance for Setting Pesticide Tolerances Based on Field Trial Data* SOP. Visual inspection of the lognormal probability plot (Figure II-9) provided in the spreadsheet indicates that the dataset is reasonably lognormal. The result from the approximate Shapiro-Francia test statistic (Figure II-10) confirmed that the assumption of lognormality should not be rejected.

Using the rounding procedure as outlined in the *Guidance for Setting Pesticide Tolerances Based on Field Trial Data* SOP, the UPLMedian95th round to the value 0.35 ppm (Figure II-10). Therefore, 0.35 ppm is the recommended tolerance level for tembotrione (parent + M5) on popcorn stover.

Table II-1. Residue data used to calculate tolerance for combined residues of tembotrione (parent + M5) in/on field corn forage.

Chemical:	Tembotrione
Crop:	Field corn forage
PHI:	44-53 Days
App. Rate:	Treatment Pattern A
Submitter:	Bayer CropScience
MRID Citation:	MRID 46695607
	Total Residues of tembotrione + M5
	<0.258
	<0.236
	<0.043
	<0.061
	<0.133

	<0.094
	<0.356
	<0.315
	<0.191
	<0.199
	<0.142
	<0.131
	<0.088
	<0.071
	<0.051
	<0.067
	<0.234
	<0.195
	<0.206
	<0.049
	<0.084
	<0.099
	<0.152
	<0.231
	<0.216
	<0.249
	<0.148
	<0.112
	<0.101
	<0.158
	<0.080
	<0.075
	<0.063
	<0.108
	<0.328
	<0.356
	<0.160
	<0.173
	<0.074
	<0.032
	<0.375
	<0.279

Figure II-1. Lognormal probability plot of tembotrione field trial data for field corn forage.

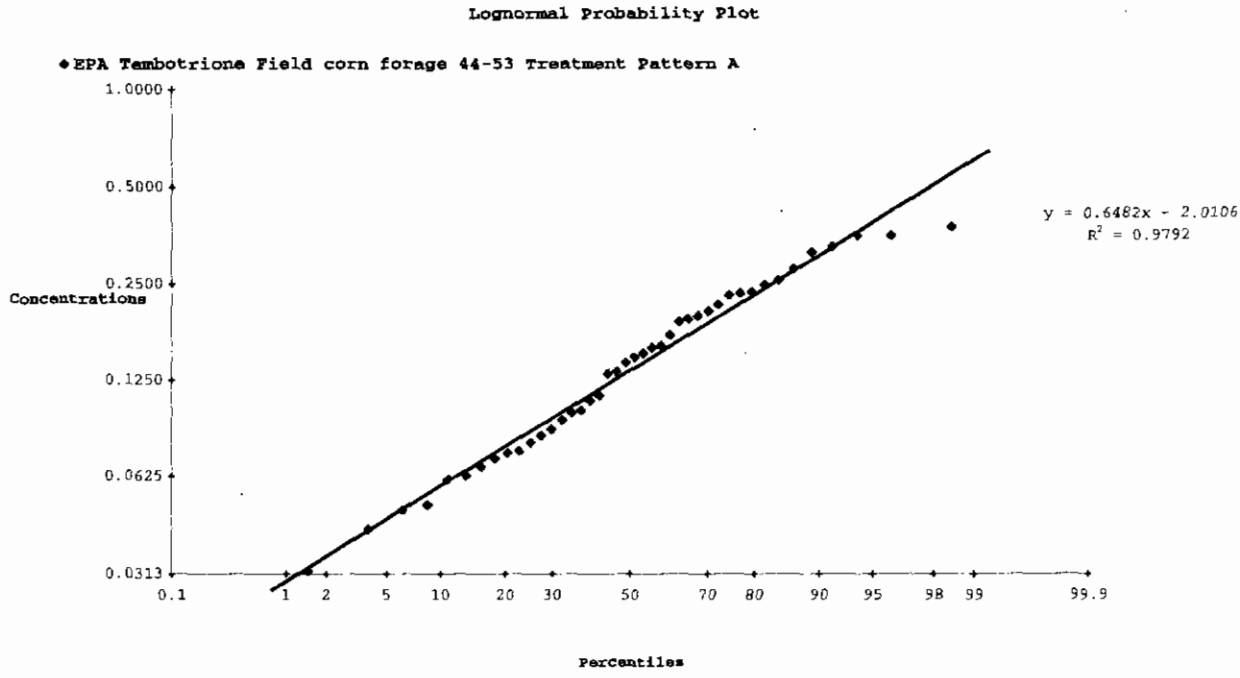


Figure II-2. Tolerance spreadsheet summary of tembotrione field trial data for field corn forage.

	Regulator: EPA **Chemical:** Tembotrione **Crop:** Field corn forage **PHI:** 44-53 **App. Rate:** 2 at 0.082 lb ai/A/application **Submitter:** Bayer CropScience **MRID Citation:** MRID 46695607 ***n:*** 42 **min:** 0.03 **max:** 0.38 **median:** 0.15 **average:** 0.16		
	95th Percentile	**99th Percentile**	**99.9th Percentile**
EU Method I Normal	0.35 (0.40)	0.40 (0.45)	0.50 (--)
EU Method I Log Normal	0.40 (0.50)	0.60 (0.90)	1.0 (--)
EU Method II Distribution-Free	0.50		
California Method μ+ 3σ	**0.45**		
UPLMedian95th	**0.80**		
Approximate Shapiro-Francia Normality Test	0.9792 p-value > 0.05 : Do not reject lognormality assumption		

Would you like the above values
rounded? (Y or N)==> Y

Table II-2. Residue data used to calculate tolerance for combined residues of tembotrione (parent + M5) in/on field corn stover.

Chemical: Tembotrione

Crop: field corn stover

PHI: 76-105 Days

App. Rate: Treatment Pattern B

Submitter:

Residues
0.026
0.041
0.007
0.009
0.102
0.069
0.287
0.227
0.124
0.178
0.445
0.411
0.095
0.133
0.066
0.057
0.098
0.094
0.102
0.083
0.023
0.011
0.041
0.081
0.080
0.099
0.013
0.015
0.054
0.168
0.034
0.027
0.017
0.018
0.025
0.026
0.042

0.062
0.030
0.029
0.054
0.087

Figure II-3. Lognormal probability plot of tembotrione field trial data for field corn stover.

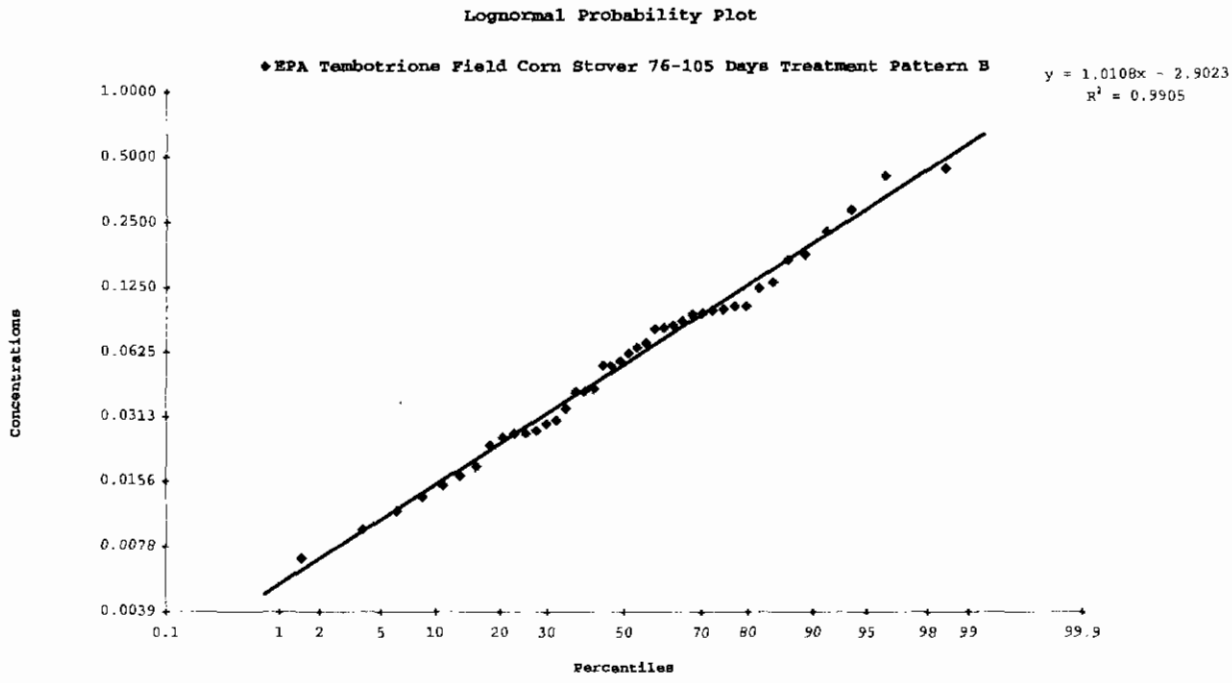


Figure II-4. Tolerance spreadsheet summary of tembotrione field trial data for field corn stover.

	Regulator:	EPA	
	Chemical:	Tembotrione	
	Crop:	Field Corn Stover	
	PHI:	76-105 Days	
	App. Rate:	Treatment Pattern B	
	Submitter:		
	n:	42	
	min:	0.01	
	max:	0.45	
	median:	0.06	
	average:	0.09	
	95th Percentile	99th Percentile	99.9th Percentile
EU Method I Normal	0.25 (0.30)	0.35 (0.40)	0.40 (--)
EU Method I Log Normal	0.30 (0.45)	0.60 (1.1)	1.2 (--)
EU Method II Distribution-Free		0.20	
California Method $\mu + 3\sigma$		0.40	
UPLMedian95th		0.35	
Approximate Shapiro-Francia Normality Test		0.9905 p-value > 0.05 : Do not reject lognormality assumption	

Table II-3. Residue data used to calculate tolerance for combined residues of tembotrione (parent + M5) in/on sweet corn forage.	
Regulator:	EPA
Chemical:	Tembotrione
Crop:	Sweet corn forage
PHI:	44-46 Days
App. Rate:	Treatment Pattern A
Submitter:	Bayer CropScience
MRID Citation:	MRID 46695608
	Total Residues of tembotrione + M5
	<0.303
	<0.324
	<0.118
	<0.110
	<0.220
	<0.210
	<0.364
	<0.214
	<0.230
	<0.298
	<0.738
	<0.738
	<0.113
	<0.085
	<0.209
	<0.235
	<0.360
	<0.303
	<0.270
	<0.327
	<0.096
	<0.102
	<0.477
	<0.362

Figure II-5. Lognormal probability plot of tembotrione field trial data for sweet corn forage.

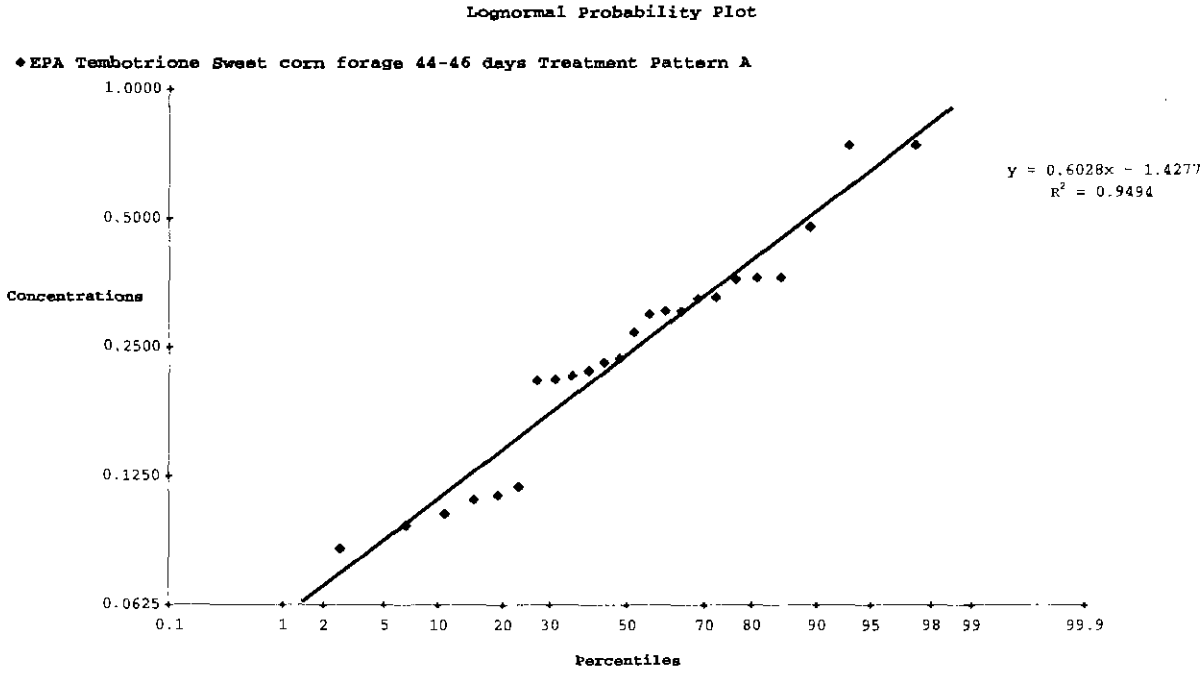


Figure II-6. Tolerance spreadsheet summary of tembotrione field trial data for sweet corn forage.

	Regulator: EPA **Chemical:** Tembotrione **Crop:** Sweet corn forage **PHI:** 44-46 days **App. Rate:** 2 at 0.082 lb ai/A/application **Submitter:** Bayer CropScience **MRID Citation:** MRID 46695608 **n:** 24 **min:** 0.09 **max:** 0.74 **median:** 0.25 **average:** 0.28		
	95th Percentile	**99th Percentile**	**99.9th Percentile**
EU Method I Normal	0.60 (0.70)	0.70 (0.90)	0.90 (--)
EU Method I Log Normal	0.70 (1.0)	1.0 (1.7)	1.6 (--)
EU Method II Distribution-Free	0.80		
California Method μ+ 3σ	**0.90**		
UPLMedian95th	**1.5**		
Approximate Shapiro-Francia Normality Test	0.9494 p-value > 0.05 : Do not reject lognormality assumption		

Would you like the above values
rounded? (Y or N)==> Y

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Table II-4. Residue data used to calculate tolerance for combined residues of tembotrione (parent + M5) in/on sweet corn stover.

Chemical: Tembotrione

Crop: Sweet Corn Stover

PHI: 79-95 Days

App. Rate: Treatment Pattern A

Submitter:

Residues
0.022
0.004
0.048
0.065
0.021
0.006
0.217
0.300
0.754
0.574
0.008
0.011
0.041
0.036
0.022
0.032
0.047
0.123
0.236
0.194
0.014
0.017
0.027
0.040

Figure II-7. Lognormal probability plot of tembotrione field trial data for sweet corn stover.

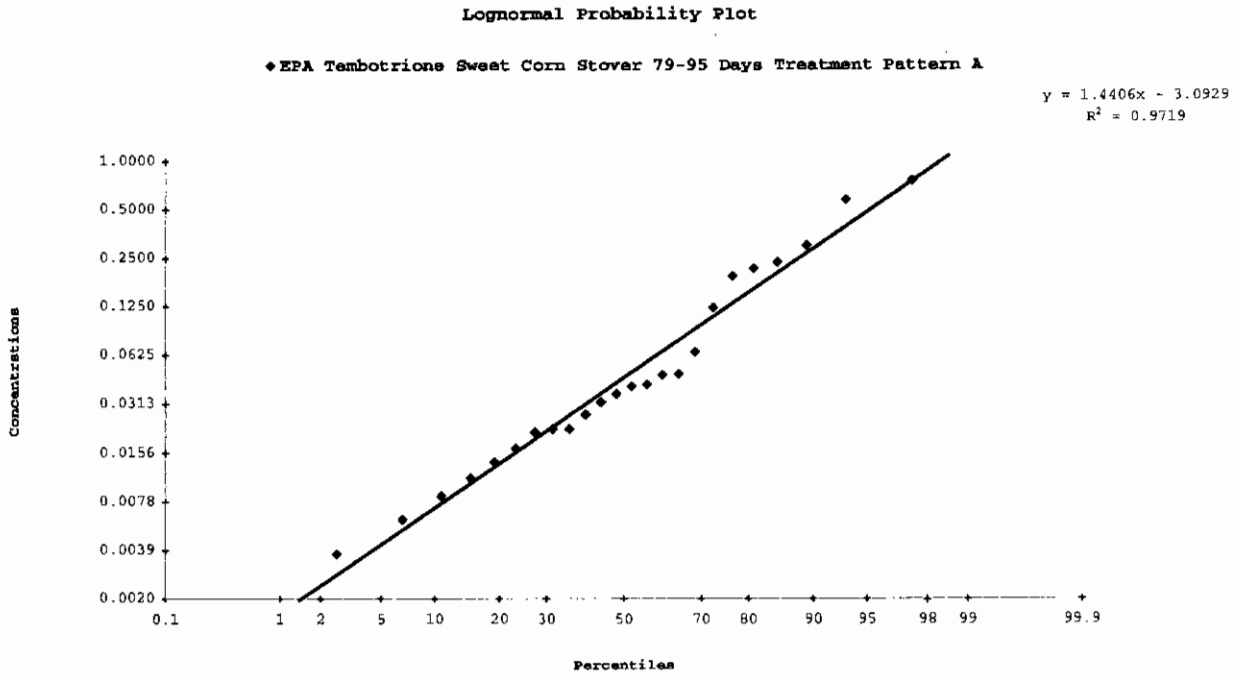


Figure II-8. Tolerance spreadsheet summary of tembotrione field trial data for sweet corn stover.

	Regulator:	EPA	
	Chemical:	Tembotrione	
	Crop:	Sweet Corn Stover	
	PHI:	79-95 Days	
	App. Rate:	Treatment Pattern A	
	Submitter:		
	n:	24	
	min:	0.00	
	max:	0.75	
	median:	0.04	
	average:	0.12	
	95th Percentile	99th Percentile	99.9th Percentile
EU Method I Normal	0.45 (0.60)	0.60 (0.80)	0.80 (--)
EU Method I Log Normal	0.50 (1.7)	1.3 (4.5)	4.0 (--)
EU Method II Distribution-Free		0.40	
California Method $\mu + 3\sigma$		0.70	
UPLMedian95th		0.25	
Approximate Shapiro-Francia Normality Test		0.9719	
	p-Value > 0.05 : Do not reject lognormality assumption		

Table II-5. Residue data used to calculate tolerance for combined residues of tembotrione (parent + M5) in/on popcorn stover.

Chemical: Tembotrione

Crop: Popcorn Stover

PHI: 72-86 Days

App. Rate Treatment Pattern B

Residues
0.026
0.036
0.181
0.202
0.051
0.041
0.009
0.015

Figure II-9. Lognormal probability plot of tembotrione field trial data for popcorn stover.

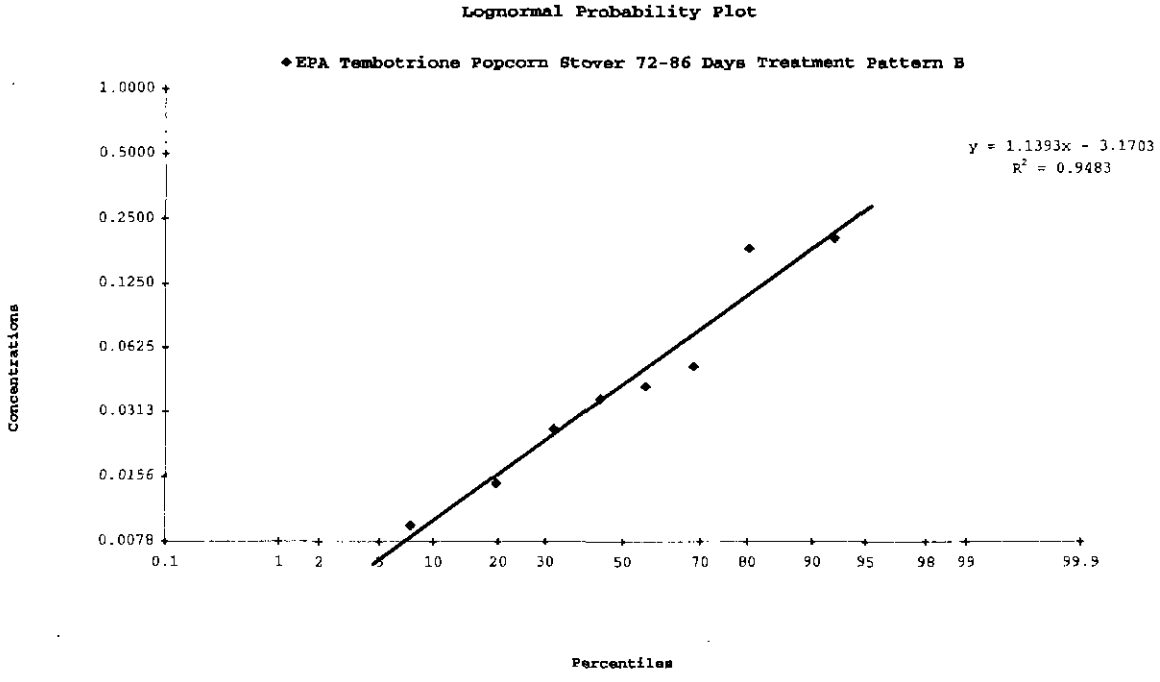


Figure II-10. Tolerance spreadsheet summary of tembotrione field trial data for popcorn stover.

	Regulator:	EPA	
	Chemical:	Tembotrione	
	Crop:	Popcorn Stover	
	PHI:	72-86 Days	
	App. Rate:	Treatment Pattern B	
	Submitter:		
	n:	8	
	min:	0.01	
	max:	0.20	
	median:	0.09	
	average:	0.07	
	95th Percentile	99th Percentile	99.9th Percentile
EU Method I Normal	0.20 (0.35)	0.25 (0.45)	0.35 (--)
EU Method I Log Normal	0.30 (1.4)	0.60 (5.0)	1.3 (--)
EU Method II Distribution-Free		0.30	
California Method $\mu + 3\sigma$		0.30	
UPLMedian95th		0.35	
Approximate Shapiro-Francia Normality Test	p-value > 0.05 :	0.9483 Do not reject lognormality assumption	

Tembotrione/AE 0172747/PC Code 012801/Bayer CropScience/264
DACO 6.3/OPPTS 860.1300/OECD II 6.2.2, 6.2.3 & IIIA 8.2, 8.4.1, 8.4.2
Nature of the Residues in Plants - Corn

Primary Evaluator	George F. Kramer, Ph.D., Senior Chemist Registration Action Branch (RAB1) Health Effects Division (HED) (7509P)	Date: 18-JUL-2007
Approved by	P.V. Shah, Ph.D., Branch Senior Scientist RAB1/HED (7509P)	Date: 18-JUL-2007

This DER was originally prepared under contract by Dynamac Corporation (2275 Research Boulevard, Suite 300; Rockville, MD 20850; submitted 10/31/2006). The DER has been reviewed by HED and revised to reflect current Office of Pesticide Programs (OPP) policies.

STUDY REPORT:

46695529 Brueckner, H.; Haas, M. (2004) Metabolism of [cyclohexyl-UL-(Carbon 14)]-AE 0172747 in Corn (Zea mays) after Treatment with an Application Rate of 200 g. a.i./ha in Presence of Safener (Inert Ingredient) (AE F122006). Project Number: CM/02/010, MO/04/006607, MEF/221/03. Unpublished study prepared by Aventis Crop Science and Bayer Ag, Institute of Product Info. & Residue Anal. 116 p.

The petitioner has submitted an evaluation template for the study (Bayer CropScience DER for Study MEF- 221-03), which was used to generate this DER; selected sections were copied without alteration or were copied and modified to more specifically reflect HED's data evaluation requirements.

EXECUTIVE SUMMARY:

Bayer CropScience has submitted a study investigating the metabolism of [cyclohexyl-U-^{14}C]tembotrione (CY label; specific activity 6.968 mBq/mg) in corn. The radiolabeled test substance was formulated as a 5% ai oil-based suspension concentrate (SC) containing the safener, isoxadifen-ethyl, for dilution in water. The formulated test substance was applied as a broadcast foliar application to container-grown corn (growth stage BBCH 14-15) at a rate equivalent to 0.153 lb ai/A (171 g ai/ha) in ~43 gal/A (400 L/ha). Whole plants were harvested at several intervals after application (days after treatment; DAT). The sampling intervals were: 0, 14, 29, and 49 DAT (immature plants); 89 DAT (forage); and at maturity, 113 DAT (stover and grain).

Total radioactive residues (TRR) in corn matrices except grain were determined by summing the radioactivity in the rinses (0- and 14-DAT immature plants) and extractable and nonextractable fractions; TRR in grain were determined by combustion/liquid-scintillation counting (LSC). Following application of CY-labeled tembotrione, TRR were 13.721, 0.715, 0.120, and 0.019 ppm in immature plants harvested 0, 14, 29, and 49 DAT, respectively, and TRR were 0.035 ppm in forage, 0.025 ppm in stover, and 0.003 ppm in grain. Grain samples were not extracted or further analyzed because of low radioactivity.

Plants collected at 0 and 14 DAT were rinsed with acetonitrile (ACN)/water before homogenization, which released ~24% and 8% TRR, respectively. Solvent extraction with

ACN/water (all samples) released ~75-87% TRR in immature whole plants (0-49 DAT), 67% TRR in forage, and 62% TRR in stover. Nonextractable residues in immature plants (0-49 DAT) ranged from 1.2% TRR (0.159 ppm) in 0-DAT plants to 20.9% TRR (0.004 ppm) in 49-DAT plants. Nonextractable residues in forage and stover, were subjected to acid or base hydrolysis; acid hydrolysis released little radioactivity (5.6-6.5% TRR), but base hydrolysis released 21-22% TRR in forage and stover. Nonextractable residues after exhaustive extractions were 9.7% and 10.2% TRR (0.003 ppm) in forage and stover, respectively.

These procedures adequately extracted the majority of the residues from corn matrices. Because TRR were determined by summing extractable and nonextractable radioactivity, accountabilities were 100% in all matrices except forage (98.4%) and stover (94.0%), where additional hydrolysis procedures were performed. Residues were identified and quantitated by high-performance liquid chromatography (HPLC) and confirmed by thin-layer chromatography (TLC). HPLC/mass spectrometry (MS), HPLC/MS/MS, and nuclear-magnetic resonance (NMR) analyses were also used for structure elucidation and identification/confirmation of metabolites. Adequate storage stability data were submitted to support the storage intervals and conditions of samples of immature plants and forage from the study. No additional storage stability data are required because all samples were stored for <6 months prior to initial analysis.

The parent, tembotrione, was only identified in early immature plants, decreasing from ~30% TRR in 0-DAT samples to <1% TRR in 29-DAT samples; tembotrione was not found in 49-DAT immature plants, forage or stover. Metabolite AE 1417268 was identified as the major residue in all corn matrices: 41.7% TRR (5.723 ppm) in 0-DAT immature plants; 62.7% TRR (0.449 ppm) in 14-DAT immature plants; 60.0% TRR (0.072 ppm) in 29-DAT immature plants; 44.1% TRR (0.008 ppm) in 49-DAT immature plants; 33.9% TRR (0.012 ppm) in forage; and 24.9% TRR (0.006 ppm) in stover. The metabolite AE 1444744 was also identified as a major residue in 0-DAT immature plants at 20% TRR and as a minor residue in 14-DAT immature plants at <1% TRR. The remaining solvent-extractable residues, accounting for ~7-37% TRR, were characterized by the polarity of the residue according to its behavior on HPLC. None of the peaks or regions that were characterized as very polar, polar, or medium polar exceeded 9.9% TRR (0.003 ppm) in forage or 14.1% TRR (0.003 ppm) in stover.

Based on the corn metabolism study with CY-labeled tembotrione, tembotrione is metabolized in corn by the hydroxylation of the cyclohexyl moiety to form the monohydroxy metabolite (AE 1444744) and dihydroxy metabolite (AE 1417268). The cyclohexyl portion of the molecule appeared to be metabolized very rapidly and was apparently incorporated or bound to natural compounds, if not mineralized.

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the plant metabolism data are classified as scientifically acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document [DP# 325349].

COMPLIANCE:

Signed and dated Good Laboratory Practice (GLP), Quality Assurance and Data Confidentiality statements were provided. No GLP deviations were reported which would impact the study results or their interpretation.

A. BACKGROUND INFORMATION

Tembotrione, a new herbicide with broad use against mono- and dicotyledons in selected crops such as corn, is a 4-hydroxyphenylpyruvate deoxygenase (HPPD) inhibitor (bleacher). The test compound nomenclature and physiochemical properties of the test compound are presented in Tables A.1 and A.2, respectively.

TABLE A.1. Test Compound Nomenclature for Tembotrione.

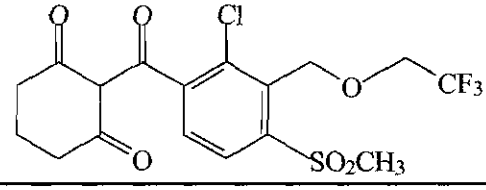
Compound: Tembotrione	Chemical Structure 
Proposed common name	Tembotrione
Company experimental name	AE 0172747
IUPAC name	2-{2-chloro-4-mesyl-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl}cyclohexane-1,3-dione
CAS name	2-[2-chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione
CAS #	335104-84-2
End-use product/EP	AE 0172747 Herbicide, EPA Reg No. 264-xxx

TABLE A.2. Physicochemical Properties of Technical Grade Tembotrione.

Parameter	Value	Reference (MRID#)
Melting point	117 °C	46695402
pH @ 24 °C	3.63	
Density (g/mL @ 20 °C)	1.56	
Water solubility (mg/L @ 20 °C)	0.22 at pH4 28.3 at pH 7 29.7 at pH 9	
Solvent solubility (g/L at 20 °C) *DMSO* Methylene Chloride Acetone Ethyl Acetate Toluene Hexane Ethanol	 >600 >600 300-600 180.2 75.7 47.6 8.2	
Vapor pressure (Torr, 20 °C)	8.25×10^{-11}	
Dissociation constant (pK_a)	3.2	

TABLE A.2. Physicochemical Properties of Technical Grade Tembotrione.		
Parameter	Value	Reference (MRID#)
Octanol/water partition coefficient (P_{ow} @ 23 °C) (P_{ow} @ 24 °C) (P_{ow} @ 23 °C)	 0.0430 at pH 9.0 0.0807 at pH 7.0 144.9 at pH 2.0	
UV/visible absorption spectrum (nm)	Primary: 205 Secondary: 284 Tertiary: 240	

B. EXPERIMENTAL DESIGN

B.1. Test Site and Crop Information

Corn plants were grown in stainless steel containers (height 50 cm, width 70 cm, and length 100 cm) equipped with a device for irrigation from below. The bottom of the container was covered up to a height of approx. 5 cm with a gravel layer. The gravel was topped with a 40-cm layer of sandy loam soil. The untreated controls were grown in 20-L Kick-Brauckmann pots with a similar soil profile. The planting containers and pots were placed in an outdoor vegetation hall surrounded by wire-mesh fencing to keep off birds and covered with a glass roof to prevent flooding in case of extensive rainfall. Placing the containers and pots close to the fence of the vegetation hall ensured direct irradiation with sunlight from the side. The plants were artificially irrigated, fertilized, and treated with other pesticides, if needed, to ensure growth under optimal conditions. Daily climatic conditions (temperature maximums and minimums and weather conditions) were reported. There were no meteorological abnormalities that may have impacted the study.

TABLE B.1.1. Test Site Information.					
Type	Method	Soil characteristics[1]			
		Type	%OM	pH	CEC
Foliar Treatment	Hand-held spray pistol.	Sandy loam (US soil taxonomy) SL3 (DIN 4220)	2.5	6.8 (0.01 M $CaCl_2$)	6.6 *meq*/100 g

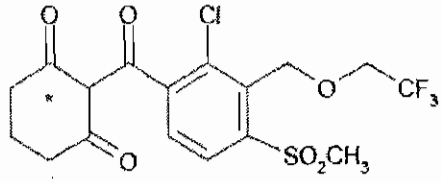
[1] OM = Organic matter, CEC = Cation-exchange capacity.

TABLE B.1.2. Crop Information.				
Crop/crop group	Variety	Growth stage at application	Growth stage at harvest	Harvested Matrix
Corn (*Zea mays*)/ Grain, cereal, group 15, and Grain, cereal, forage, fodder, and straw, group 16	Dea (Pioneer)	BBCH 14-15 (leaf development)	BBCH 14-15; 4-5 leaves unfolded	0 DAT immature plants
			BBCH 17-18; 7-8 leaves unfolded	14 DAT immature plants
			BBCH 32; stem elongation, 2 nodes detectable	29 DAT immature plants
			BBCH 55-61; heading/flowering	49 DAT immature plants
			BBCH 85; dough stage	89 DAT forage
			BBCH 99; mature stover/grain	113 DAT stover and grain

B.2. Test Materials

The radiolabeled test substance was formulated as a 5% oil-based SC with formulation blank containing the safener, isoxadifen-ethyl. The ratio of the test substance to the safener was 1:1 (w:w). The test material characteristics are presented in Table B.2.1.

TABLE B.2.1. Test Material Characteristics.

Chemical structure	
Radiolabel position	[cyclohexyl-UL-^{14}C]Tembotrione
Lot or Batch No.	Z31010-1
Purity	99.3% (HPLC)
Specific activity (Bq)*	6.968 mBq/mg (418,080 dpm/µg)

* Bq = disintegrations per second

B.3. Study Use Pattern

The formulated test substance was diluted with water for application. The foliar broadcast application was made in a plastic tent using a Walther Pilot ND spray pistol. After application, the corn plants were moved to a secured outdoor area to continue their growth. The study use pattern is summarized in Table B.3.1.

TABLE B.3.1. *Use Pattern Information*

Chemical	[cyclohexyl-U-^{14}C]Tembotrione
Application method	The test substance, formulated as an oil-based SC formulation, was diluted with water and applied to corn plants as a broadcast foliar spray using a hand-held spray pistol.
Application rate, Nominal	200 g ai/ha (0.178 lb ai/A)
Application rate, Actual	171 g ai/ha (0.153 lb ai/A)
Number of applications	1 broadcast foliar
Timing of applications	BBCH 14-15 (4-5 leaves unfolded)
Preharvest Interval (PHI)	Immature plants: 0, 14, 29 and 49 days after application Forage: 89 days after application Grain and stover: 113 days after application

B.4. Identification/Characterization of Residues

B.4.1. Sample Handling and Preparation

Corn plants were harvested at several intervals after application of the test formulation. The sampling intervals were: 0 DAT (BBCH 14-15, 4-5 leaves unfolded), 14 DAT (BBCH 17-18, 7-8 leaves unfolded), 29 DAT (BBCH 32, stem elongation, 2 nodes detected), 49 DAT (BBCH 55-61, heading-flowering), 89 DAT (BBCH 85, dough stage) and 113 DAT (BBCH 99, stover and grain). Plants were cut 5 to 10 cm above the soil surface. Immature plants were processed without separation into different plant parts. Mature plants were separated into the raw agricultural commodities of grain and stover (which included the cobs) prior to processing. The processing was carried out immediately after sampling. At each sampling interval, the fresh weight was recorded. Whole plants from the 0- and 14-DAT intervals were rinsed with ACN:water (1:1, v:v), and the rinse was reserved for HPLC and TLC analysis. The rinsed plants, 29- and 49-DAT immature plants, forage, stover, and grain were cut into small pieces with scissors before homogenization in a cutter mill with dry ice. Subsamples were removed for analysis, with the remaining material stored in a freezer at ≤-18 °C. The in-life and analytical phases of the study were conducted at the same facility (Bayer CropScience GmbH, Frankfurt, Germany); therefore, samples were not shipped.

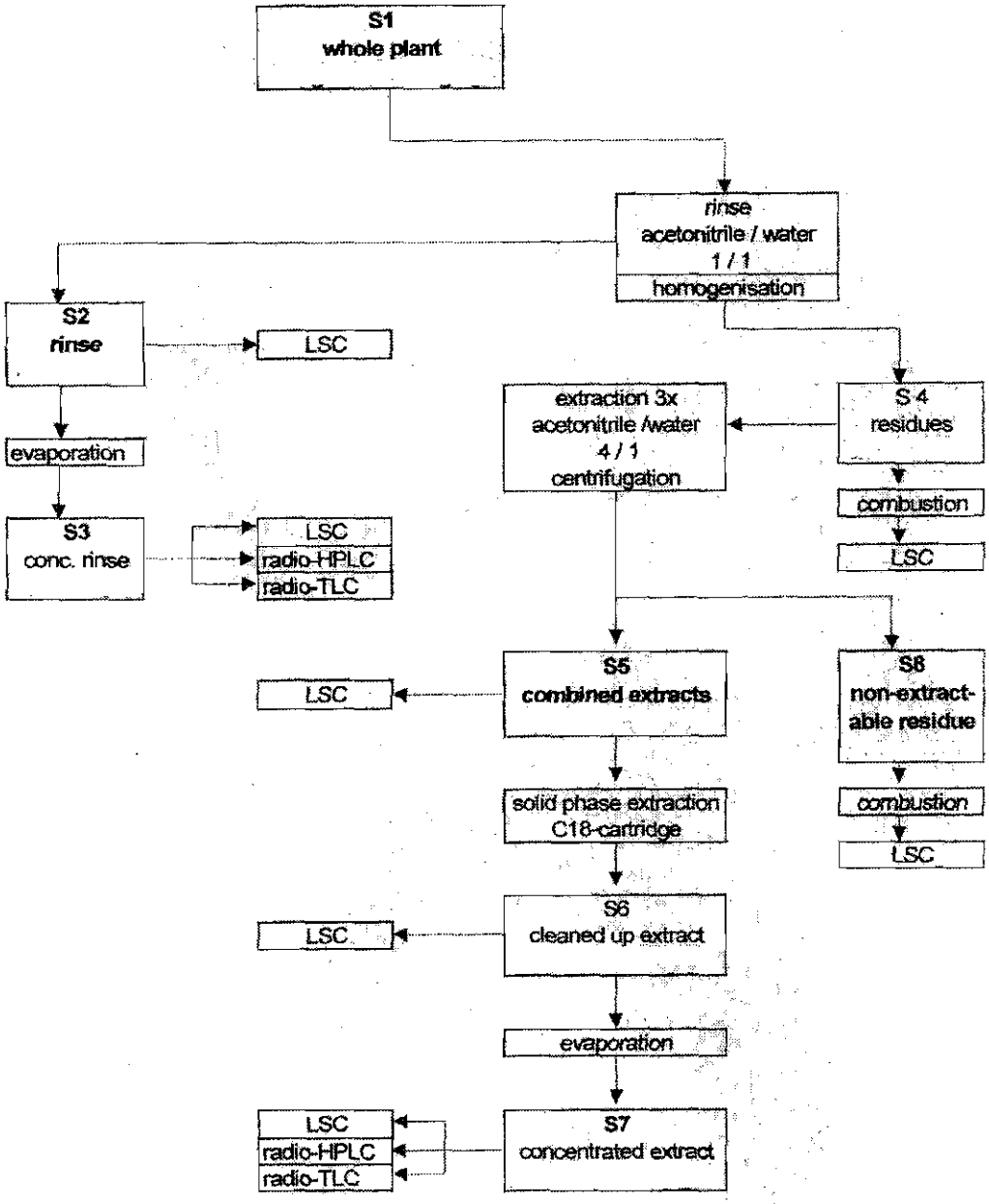
A generalized extraction scheme is presented in Figure 1; samples of corn grain were not extracted due to low radioactivity (<0.01 ppm).

Subsamples of **immature plants** were extracted 3-4x with ACN:water (4:1, v:v) using an Ultra-Turrax high speed blender, then centrifuged. The supernatants were combined and passed through a C-18 solid-phase extraction (SPE) cartridge; residues were eluted with ACN. The resulting ACN eluates were concentrated and reserved for HPLC and TLC analysis. A subsample of the concentrated ACN eluate of 0-DAT immature plants was acidified to pH 2 with H_2SO_4 and partitioned with ethyl acetate. The resulting organic phase was concentrated and reserved for HPLC.

Subsamples of **84-DAT forage** and **stover** were extracted 5x with ACN:water (4:1, v:v) and purified on a C-18 SPE cartridge as described above for immature plants. The resulting eluates were concentrated by rotary evaporation. The evaporation flasks were rinsed with ACN:water (1:1, v:v), and the rinses were combined with the concentrated samples and reserved for HPLC and TLC analysis (fraction S5).

Separate subsamples of nonextractable residues remaining after solvent extraction of corn forage and stover were subjected to acid (1 M HCl) or base (1 M NaOH) hydrolysis. Hydrolyses were conducted at room temperature for 24.5 hours. The hydrolysates were centrifuged and partitioned with ethyl acetate to characterize the polarity of the hydrolyzed residues.

Figure 1 : Work-up scheme for whole plant



TRR = S2 + S5 + S8

B.4.2. Analytical Methodology

The TRR were initially estimated in representative subsamples using combustion/liquid scintillation counting techniques; these data were not reported, except for grain. Radioactivity in the liquid samples (i.e., rinses, extracts, and concentrates) was quantified by LSC. The nonextractable residues were determined by combustion/LSC. The TRR that were used for all further determinations for immature plants, forage, and stover, were calculated by summing the radioactivity from the rinses (0- and 14-DAT immature plants only), the extracts, and nonextractable residues. The limit of quantitation (LOQ) for TRR determinations was not reported.

Analytical separations of the extracted radioactivity, as well as identification of the metabolites, were established by reverse-phase HPLC and TLC as two independent analytical systems.

Aliquots of the concentrated rinses, extracts, and purified eluates were analyzed by reversed phase HPLC using a C-18 column (150 x 4.6 mm, stainless steel), UV detection at 254 nm, and a gradient mobile phase of water (acidified to pH 2 with formic or sulfuric acid)/ACN. Residues were quantitated using a flow-through radioactivity detector. The reported LOQ for HPLC determinations was 0.001 ppm. An additional HPLC system was used for purification of metabolite AE 1417268, isolated from 0-DAT immature plants. This system was equipped with a diol column, UV detector (254 nm), and flow-through radiodetector, and used a gradient mobile phase of n-hexane/ethanol + 3.0% ammonia (25%). For characterization of metabolites, the retention times of the non-labeled reference standards were compared with the retention times of radioactive fractions in sample extracts. The reference standards used in the study are presented in Appendix I.

TLC analysis was conducted with representative samples as a second independent analytical system to confirm the characterization of metabolites obtained by HPLC. TLC analyses were conducted using silica-gel plates, and a mobile phase of chloroform:methanol:toluene:acetic acid (50:35:15:1, v:v:v:v). Radioactivity was detected by autoradiography, and nonlabeled standards were detected by UV fluorescence detection.

HPLC/MS and HPLC/MS/MS (daughter-ion scan) were conducted with representative sample extracts of 0-DAT plants. Electrospray ionization in the positive- and negative-ion modes was used for HPLC/MS, and argon was used as the collision gas for MS/MS determinations. NMR analysis was also used for structure elucidation.

C. RESULTS AND DISCUSSION

Actual extraction and analysis dates were not provided; however, based on the harvest dates and dated HPLC chromatograms included in the submission, samples were stored from harvest to initial analysis for <5 months for immature plants and for 1-2 months for forage and stover. The petitioner demonstrated storage stability in immature plants by re-extracting and analyzing 14-DAT immature plants from the high rate treatment 4.6 months after the sample was first analyzed. Stability of the residues in extracts was investigated by re-analyzing the 0-DAT

extract 4.3 months after initial analysis. Adequate storage stability data were submitted to support the storage intervals and conditions of samples of immature plants and forage from the study. No additional storage stability data are required because all samples were stored for <6 months prior to initial analysis. The petitioner should note for future submissions that the critical study dates are required for each sample.

TRR in corn matrices except grain were determined by summing the radioactivity in the rinses (0- and 14-DAT immature plants) and extractable and nonextractable fractions; TRR in grain were determined by combustion/LSC. TRR are reported in Table C.2.1. Following foliar application of CY-labeled tembotrione at 0.153 lb ai/A, TRR were 13.721, 0.715, 0.120, and 0.019 ppm in immature corn plants harvested 0, 14, 29, and 49 DAT, respectively, and TRR were 0.035 ppm in forage, 0.025 ppm in stover, and 0.003 ppm in grain. Grain samples were not extracted or further analyzed because of low radioactivity.

The distribution of the radioactivity in corn matrices is presented in Tables C.2.2.1 (0-29 DAT immature plants) and C.2.2.2 (49-DAT immature plants, forage, and stover). Plants collected at 0 and 14 DAT were rinsed with ACN/water before homogenization, which released ~24% and 8% of the TRR, respectively. Solvent extraction with ACN/water (all samples) released ~75-87% TRR in immature whole plants (0-49 DAT), 67% TRR in forage, and 62% TRR in stover. Nonextractable residues in immature plants (0-49 DAT) ranged from 1.2% TRR (0.159 ppm) in 0-DAT plants to 20.9% TRR (0.004 ppm) in 49-DAT plants. Nonextractable residues in forage and stover, were subjected to acid or base hydrolysis; acid hydrolysis released little radioactivity (5.6-6.5% TRR), but base hydrolysis released 21-22% TRR in forage and stover. Nonextractable residues after exhaustive extractions were 9.7% and 10.2% TRR (0.003 ppm) in forage and stover, respectively.

These procedures adequately extracted the majority of the residues from corn matrices. Because TRR were determined by summing extractable and nonextractable radioactivity, accountabilities were 100% in all matrices except forage (98.4%) and stover (94.0%), where additional hydrolysis procedures were performed. Residues were identified and quantitated by HPLC and confirmed by TLC. HPLC/MS, HPLC/MS/MS, and NMR analyses were also used for structure elucidation and identification/confirmation of metabolites.

The characterization and identification of residues in corn matrices is summarized in Table C.2.3.1 (0-29 DAT immature plants) and C.2.3.2 (49-DAT immature plants, forage, and stover). The parent, tembotrione, was only identified in early immature plants, decreasing from ~30% TRR in 0-DAT samples to <1% TRR in 29-DAT samples; tembotrione was not found in 49-DAT immature plants, forage or stover. Metabolite AE 1417268 was identified as the major residue in all corn matrices: 41.7% TRR (5.723 ppm) in 0-DAT immature plants; 62.7% TRR (0.449 ppm) in 14-DAT immature plants; 60.0% TRR (0.072 ppm) in 29-DAT immature plants; 44.1% TRR (0.008 ppm) in 49-DAT immature plants; 33.9% TRR (0.012 ppm) in forage; and 24.9% TRR (0.006 ppm) in stover. The metabolite AE 1444744 was also identified as a major residue in 0-DAT immature plants at 20% TRR and as a minor residue in 14-DAT immature plants at <1% TRR. The remaining solvent-extractable residues, accounting for ~7-37% TRR, were characterized by the polarity of the residue according to its behavior on HPLC. None of the peaks or regions that were characterized as very polar, polar, or medium polar exceeded 9.9%

TRR (0.003 ppm) in forage or 14.1% TRR (0.003 ppm) in stover.

The parent was identified in early immature corn plants by comparison of the spectra with the retention time of the tembotrione reference standard, and by co-chromatography of the 0-DAT plant extract with reference standard. Metabolite AE 1417268 in 0-DAT immature plants was isolated and identified by HPLC/MS, HPLC/MS/MS and NMR analyses. Metabolites AE 1417268 and AE 1444744 in 0-DAT immature plants were also identified by co-chromatography with metabolites that had been isolated from a cell culture study (refer to the DER for MRID 46695530). Furthermore, the 0-DAT plant extract was co-chromatographed with 0-DAT extracts from the other phenyl-label corn metabolism study (refer the DER for MRID 46695530) and a study reflecting application of phenyl-labeled tembotrione at 100 g ai/ha (Study No. MEF 190/03) that does not appear to have been submitted. The identity of these metabolites in other matrices (14- and 29-DAT immature plants, forage, and stover) was confirmed by co-chromatography or retention time comparisons with the 0-DAT extract.

C.1. Storage Stability

The petitioner stated that samples were processed and extracted immediately after sampling. Subsamples were removed for analysis, and the remaining material, including bulk extracts and leaf rinses, was stored in a freezer at ≤-18 °C. Actual extraction and analysis dates were not provided; however, based on the harvest and dated HPLC chromatograms included in the submission, samples were stored from harvest to initial analysis for ~5 months for immature plants, and 1-2 months for forage and stover.

The petitioner demonstrated storage stability by re-extracting and analyzing 14-DAT immature plants ~4.6 months after the sample was first analyzed. Stability of the residues in extracts was investigated by re-analyzing the 0-DAT immature plant extract ~4.3 months after initial analysis. No significant changes were observed in the matrix or the extract following frozen storage. A comparison of the initial analysis and re-analysis results for the 14-DAT plants is presented in Table C.1.2.

TABLE C.1.1. Summary of Storage Conditions.

Matrix	Storage Temperature (°C)	Actual Storage Duration[1]	Interval of Demonstrated Storage Stability
Immature plant (0-49 DAT)	-18	13-159 days (≤5.2 months)	None required because samples were initially analyzed (for quantitation) <6 months after harvest.
Forage		63 days (2.1 months)	
Stover		39 days (1.3 months)	

[1] Storage interval from harvest to initial HPLC analysis of the extract, based on the dates of the representative chromatograms; extraction dates were not provided.

TABLE C.1.2. Comparison of Results following Initial and Re-analysis of 14-DAT Immature Corn Plants After Application of [Cyclohexyl-^{14}C]Tembotrione at 0.153 lb ai/A.

Fraction[1]	Initial extraction (7/1/02)		Re-analysis (11/19/02)	
	%TRR	ppm	%TRR	ppm
Extractable	91.0	0.651	90.8	0.638
Nonextractable	9.0	0.064	9.3	0.065
HPLC Separation				
P1	2.1	0.015	3.0	0.022
P2	2.0	0.014	0.8	0.005
P3	0.9	0.006	1.4	0.010
P4	2.0	0.014	1.3	0.009
P5	1.6	0.011	1.5	0.011
P6	2.2	0.016	3.5	0.025
P7	2.7	0.019	3.3	0.024
P8	62.3	0.445	58.3	0.417
P9	2.1	0.015	--	--
P11	--	--	0.8	0.006
R2	1.9	0.013	1.6	0.011
R4	3.6	0.026	7.4	0.053
Accountability	83.4	0.594	82.9	0.593

[1] Refer to Table C.2.2.1 for identification of peaks (P) and regions (R).

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

TABLE C.2.1. TRR in Corn Matriees.

Matrix	Timing and Applic. No.	PHI (days)	TRR (ppm)
Immature plant	One broadcast foliar application to corn plants at the BBCH 14-15 growth stage.	0	13.721
Immature plant		14	0.715
Immature plant (stem elongation)		29	0.120
Immature plant (flowering/heading)		49	0.019
Forage		89	0.035
Stover (including cobs)		113	0.025
Grain		113	0.003

[1] Determined in all matrices except grain by summing the radioactivity in the rinses (0- and 14-DAT immature plants) and extraetable and nonextractable fractions; TRR in grain were determined by combustion/LSC

TABLE C.2.2.1. Distribution of the Parent and the Metabolites in Immature Corn Plants After Application of [Cyclohexyl-U-^{14}C]Tembotrione at 0.153 lb ai/A.

Metabolite Fraction[1]	Whole Plant, 0 DAT		Whole Plant, 14 DAT		Whole Plant, 29 DAT	
	TRR = 13.721 ppm		TRR = 0.715 ppm		TRR = 0.120 ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm
ACN/water surface wash	23.7	3.245	7.7	0.054		
ACN/water extract	75.2	10.317	83.3	0.596	87.1	0.104
Total Extractable (wash + extract)[2]	98.8	13.562	91.0	0.651	87.1	0.104
P1, unknown, very polar	0.8	0.113	2.7	0.019	2.2	0.003

TABLE C.2.2.1. Distribution of the Parent and the Metabolites in Immature Corn Plants After Application of [Cyclohexyl-U-^{14}C]Tembotrione at 0.153 lb ai/A.

Metabolite Fraction[1]	Whole Plant, 0 DAT		Whole Plant, 14 DAT		Whole Plant, 29 DAT	
	TRR = 13.721 ppm		TRR = 0.715 ppm		TRR = 0.120 ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm
P2, unknown, very polar	0.3	0.046	2.3	0.016	1.1	0.001
P3, unknown, polar	0.3	0.045	1.7	0.012	0.6	0.001
P4, unknown, polar	--	--	2.0	0.014	4.2	0.005
P5, unknown, polar	--	--	1.6	0.011	3.0	0.004
P6, unknown, polar	0.3	0.046	2.2	0.016	3.4	0.004
P7, unknown, polar	0.5	0.067	2.7	0.019	4.2	0.005
P8, AE 1417268 (M5)	41.7	5.723	62.7	0.449	60.0	0.072
P9, unknown, medium polar	0.7	0.099	2.3	0.017	1.0	0.001
P10, AE 1444744 (M10)	20.0	2.741	0.3	0.002	--	--
P11, Tembotrione (parent)	29.9	4.104	2.8	0.020	0.8	0.001
R2, polar region	0.2	0.032	2.9	0.021	2.4	0.003
R3, medium polar region	2.4	0.329	0.6	0.004	--	--
R4, medium polar region	1.2	0.170	3.9	0.028	4.3	0.005
R5, non-polar region	0.3	0.046	0.3	0.002	--	--
Nonextractable	1.2	0.159	9.0	0.064	12.9	0.015

[1] Shading indicates that the extraction step and/or characterization analysis was not conducted for the matrix in question.
P = peak; R = region. R1 – R5 = chromatographic regions with several unidentified components.
[2] The surface wash and extract (after SPE cleanup and concentration) were separately analyzed by HPLC; however, the petitioner reported the combined residues.

TABLE C.2.2.2. Distribution of the Parent and the Metabolites in Immature Corn Plants, Forage, and Stover After Application of [Cyclohexyl-U-^{14}C]Tembotrione at 0.153 lb ai/A.

Metabolite Fraction[1]	Whole Plant, 49 DAT		Forage, 89 DAT		Stover, 113 DAT	
	TRR = 0.019 ppm		TRR = 0.035 ppm		TRR = 0.025 ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm
ACN/water extract	79.1	0.015	67.3	0.023	61.8	0.015
P1, unknown, very polar	8.0	0.001	9.9	0.003	14.1	0.003
P4, unknown, polar	2.0	<0.001	--	--	--	--
P5, unknown, polar	3.6	0.001	4.0	0.001	3.5	0.001
P6, unknown, polar	5.6	0.001	4.1	0.001	5.0	0.001
P7, unknown, polar	3.6	0.001	5.2	0.002	6.0	0.001
P8, AE 1417268 (M5)	44.1	0.008	33.9	0.012	24.9	0.006
P9, unknown, medium polar	1.3	<0.001	1.6	0.001	1.8	<0.001
R1, very polar region	2.6	<0.001	--	--	--	--
R2, polar region	2.8	0.001	4.2	0.001	2.2	0.001
R4, medium polar region	5.4	0.001	4.5	0.002	4.3	0.001
Nonextractable	20.9	0.004	32.7	0.011	38.2	0.009
1. Acid hydrolysis			5.6	0.002	6.5	0.002
Organosoluble			1.7	<0.001	1.6	<0.001
Water soluble			4.4	0.002	4.6	0.001
Nonextractable			22.7	0.008	25.2	0.006
2. Base hydrolysis			21.4	0.007	22.0	0.005
Organosoluble			0.5	<0.001	0.8	<0.001

TABLE C.2.2.2. Distribution of the Parent and the Metabolites in Immature Corn Plants, Forage, and Stover After Application of [Cyclohexyl-U-^{14}C]Tembotrione at 0.153 lb ai/A.

Metabolite Fraction[1]	Whole Plant, 49 DAT		Forage, 89 DAT		Stover, 113 DAT	
	TRR = 0.019 ppm		TRR = 0.035 ppm		TRR = 0.025 ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm
Water soluble			17.8	0.006	19.8	0.005
Nonextractable			9.7	0.003	10.2	0.003

[1] Shading indicates that the extraction step and/or characterization analysis was not conducted for the matrix in question.
P = peak; R = region. R1 – R5 = chromatographic regions with several unidentified components.

TABLE C.2.3.1. Summary of Characterization and Identification of Radioactive Residues in Immature Corn Plants Following Application of [Cyclohexyl-U-^{14}C]Tembotrione at 0.153 lb ai/A.

Compound	Whole Plant, 0 DAT		Whole Plant, 14 DAT		Whole Plant, 29 DAT	
	TRR = 13.721 ppm		TRR = 0.715 ppm		TRR = 0.120 ppm	
	% TRR	ppm	% TRR	ppm	% TRR	ppm
Tembotrione	29.9	4.104	2.8	0.020	0.8	0.001
AE1444744	20.0	2.741	0.3	0.002	--	--
AE 1417268 (M5)	41.7	5.723	62.7	0.449	60.0	0.072
Very polar fraction (peaks + region)	1.1	0.159	5.0	0.035	3.3	0.004
Polar fraction (peaks + region)	1.3	0.190	13.1	0.093	17.8	0.022
Medium polar fraction (peaks + region)	4.3	0.598	6.8	0.049	5.3	0.006
Non-polar fraction (region)	0.3	0.046	0.3	0.002	--	--
Total identified	91.6	12.568	65.8	0.471	60.8	0.073
Total characterized	7.0	0.993	25.2	0.179	26.4	0.032
Total extractable	98.8	13.562	91.0	0.651	87.1	0.104
Unextractable[1]	1.2	0.159	9.0	0.064	12.9	0.015
Accountability[2]	100		100.0		99.2	

[1] Residues remaining after exhaustive extractions.
[2] Accountability = (Total extractable + Total unextractable); TRR determined by summing extractable and nonextractable fractions.

TABLE C.2.3.2. Summary of Characterization and Identification of Radioactive Residues in Immature Corn Plants, Forage, and Stover Following Application of [Cyclohexyl-U-^{14}C]Tembotrione at 0.153 lb ai/A.

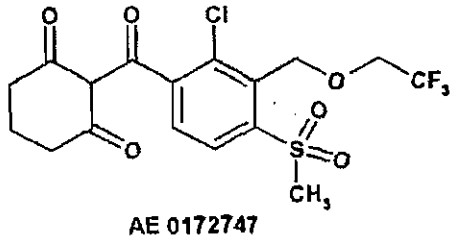
Compound	Whole Plant, 49 DAT		Forage, 89 DAT		Stover, 113 DAT	
	TRR = 0.019 ppm		TRR = 0.035 ppm		TRR = 0.025 ppm	
	% TRR	ppm	% TRR	ppm	% TRR	ppm
AE 1417268 (M5)	44.1	0.008	33.9	0.012	24.9	0.006
Very polar fractions (peaks + regions)	10.6	<0.002	9.9	0.003	14.1	0.003
Polar fractions (peaks + regions)	17.6	<0.004	17.5	0.005	16.7	0.004
Medium polar fractions (peaks + regions)	6.7	<0.002	6.1	0.003	6.1	<0.002
Base hydrolysate	--	--	21.4	0.007	22.0	0.005
Total identified	44.1	0.008	33.9	0.012	24.9	0.006
Total characterized	34.9	<0.007	54.9	0.018	58.9	<0.014
Total extractable	79.1	0.015	88.7	0.030	83.8	0.020
Unextractable[1]	20.9	0.004	9.7	0.003	10.2	0.003
Accountability[2]	100		98.4		94.0	

[1] Residues remaining after exhaustive extractions (i.e., base hydrolysis of forage and stover).
[2] Accountability = (Total extractable + Total unextractable); TRR determined by summing extractable and nonextractable fractions.

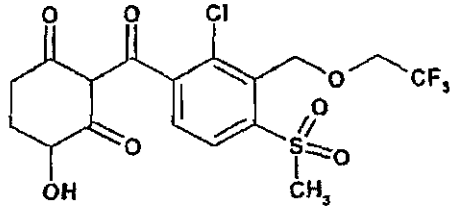
C.3. Proposed Metabolic Profile

Based on the CY-labeled corn metabolism study, tembotrione is metabolized in corn by the hydroxylation of the cyclohexyl moiety to form the monohydroxy metabolite (AE 1444744) and dihydroxy metabolite (AE 1417268). The cyclohexyl portion of the molecule appeared to be metabolized very rapidly and was apparently incorporated or bound to natural compounds, if not mineralized.

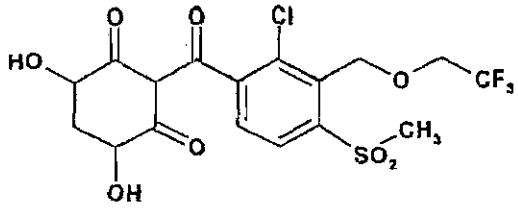
FIGURE C.3.1. Proposed Metabolic Profile of Tembotrione in Corn



AE 0172747

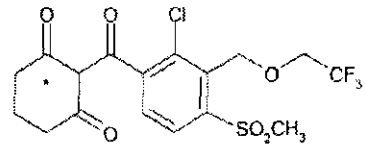
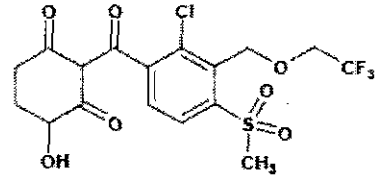
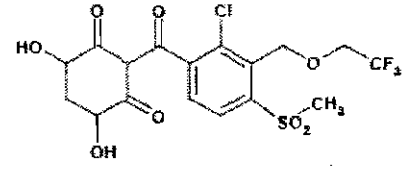


AE 1444744 (=P10)



AE 1417268 (=P8)

TABLE C.3.1. Identification of Compounds from Metabolism Study

Common name/code	Chemical name	Chemical structure
Tembotrione [1] (parent)	2-[2-Chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione	
AE 1444744 (M10)[1]	2-[2-Chloro-4-(methylsulfonyl)-3-[((2,2,2-trifluoroethoxy)methyl]benzoyl]-4-hydroxy-1,3-cyclohexanedione	
AE 1417268 (M5)	2-[2-Chloro-4-(methylsulfonyl)-3-[((2,2,2-trifluoroethoxy)methyl]benzoyl]-4,6-dihydroxy-1,3-cyclohexanedione	

[1] Only identified in early immature corn plants.

D. CONCLUSION

Following foliar application of CY-labeled tembotrione at 0.153 lb ai/A, TRR were 13.721, 0.715, 0.120, and 0.019 ppm in immature corn plants harvested 0, 14, 29, and 49 DAT, respectively, and 0.035 ppm in forage, 0.025 ppm in stover, and 0.003 ppm in grain. Grain samples were not extracted or further analyzed because of low radioactivity.

Plants collected at 0 and 14 DAT were rinsed with ACN/water before homogenization. Rinsed immature plants and remaining matrices were extracted with ACN/water, and nonextractable residues in forage and stover, were subjected to acid or base hydrolysis. These procedures adequately extracted the majority of the residues from corn matrices. Because TRR were determined by summing extractable and nonextractable radioactivity, accountabilities were 100% in all matrices except forage (98.4%) and stover (94.0%), where additional hydrolysis procedures were performed.

Residues were identified and quantitated by HPLC and confirmed by TLC. HPLC/MS, HPLC/MS/MS, and NMR analyses were also used for structure elucidation and identification/confirmation of metabolites. Adequate storage stability data were submitted to support the storage intervals and conditions of samples of immature plants and forage from the study. No additional storage stability data are required because all samples were stored for <6 months prior to initial analysis.

The parent herbicide, tembotrione, was only identified in early immature plants, decreasing from ~30% TRR in 0-DAT samples to <1% TRR in 29-DAT samples; tembotrione was not found in 49-DAT immature plants, forage or stover. Metabolite AE 1417268 was identified as the major residue in all corn matrices, accounting for ~42-63% TRR in immature plants, 34% TRR in

forage, and 25% TRR in stover. The metabolite AE 1444744 was also identified as a major residue in 0-DAT immature plants at 20% TRR and as a minor residue in 14-DAT immature plants at <1% TRR. The remaining solvent extractable residues accounting for ~7-37% TRR were characterized by the polarity of the residue according to its behavior on HPLC.

Based on the CY-labeled corn metabolism study, tembotrione is metabolized in corn by the hydroxylation of the cyclohexyl moiety to form the monohydroxy metabolite (AE 1444744) and dihydroxy metabolite (AE 1417268). The cyclohexyl portion of the molecule appeared to be metabolized very rapidly and was apparently incorporated or bound to natural compounds, if not mineralized.

The submitted study is acceptable and successfully delineates the amount and distribution of TRR in corn tissues.

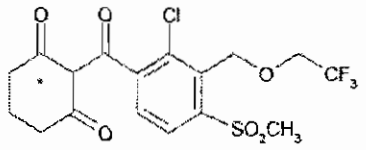
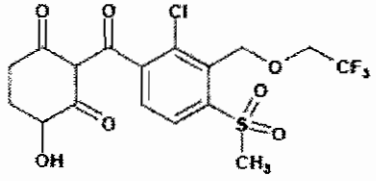
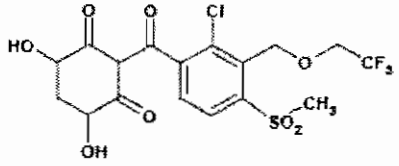
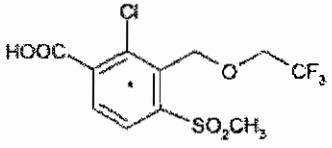
E. REFERENCES

46695530 Brueckner, H.; Haas, M. (2004) Metabolism of [phenyl-UL-(Carbon 14)]-AE 0172747 in Corn (Zea mays) after Treatment with an Application Rate of 100 g ai/ha and 200 g ai/ha in Presence of Safener (Inert Ingredient). Project Number: 36050, CM/01/014, MEF/220/03. Unpublished study prepared by Aventis Crop Science and Bayer Ag, Institute of Product Info. & Residue Anal. 229 p.

F. DOCUMENT TRACKING

RDI: RAB1 Chemists (12/6/06)
Petition Number: PP#5F7009
DP#s: 325349, 325663, and 331222
PC Code: 012801

Template Version June 2005

APPENDIX I. Chemical Names and Structures of Reference Standards Used in Corn Metabolism Study.		
Common name; Company code	Chemical name	Chemical structure
Tembotrione[1]	2-[2-Chloro-4-(methylsulfonyl)-3-[((2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione	
AE 1444744[2]	2-[2-Chloro-4-(methylsulfonyl)-3-[((2,2,2-trifluoroethoxy)methyl]benzoyl]-4-hydroxy-1,3-cyclohexanedione	
AE 1417268[2]	2-[2-Chloro-4-(methylsulfonyl)-3-[((2,2,2-trifluoroethoxy)methyl]benzoyl]-4,6-dihydroxy-1,3-cyclohexanedione	
AE 0456148[3]	2-Chloro-4-mesyl-3-[(2,2,2-trifluoroethoxy)methyl]benzoic acid	

[1] Radiolabeled and non-labeled standards were used.
[2] Isolated from cell culture experiment.
[3] Based on the label site, not expected to be found in this study; used only for testing and co-chromatography comparisons with samples from other studies.

Tembotrione/AE 0172747/PC Code 012801/Bayer CropScience/264
DACO 6.3/OPPTS 860.1300/OECD II 6.2.2, 6.2.3 & IIIA 8.2, 8.4.1, 8.4.2
Nature of the Residues in Plants - Corn

Primary Evaluator	George F. Kramer, Ph.D., Senior Chemist Registration Action Branch (RAB1) Health Effects Division (HED) (7509P)	Date: 18-JUL-2007
Approved by	P.V. Shah, Ph.D., Branch Senior Scientist RAB1/HED (7509P)	Date: 18-JUL-2007

This DER was originally prepared under contract by Dynamac Corporation (2275 Research Boulevard, Suite 300; Rockville, MD 20850; submitted 10/31/2006). The DER has been reviewed by HED and revised to reflect current Office of Pesticide Programs (OPP) policies.

STUDY REPORT:

46695530 Brueckner, H.; Haas, M. (2004) Metabolism of [phenyl-UL-(Carbon 14)]-tembotrione in Corn (Zea mays) after Treatment with an Application Rate of 100 g a.i./ha and 200 g a.i./ha in Presence of Safener (Inert Ingredient). Project Number: 36050, CM/01/014, MEF/220/03. Unpublished study prepared by Aventis Crop Science and Bayer Ag, Institute of Product Info. & Residue Anal. 229 p.

The petitioner has submitted an evaluation template for the study (Bayer CropScience DER for Study MEF-220-03), which was used to generate this DER; selected sections were copied without alteration or were copied and modified to more specifically reflect the Agency's data evaluation requirements.

EXECUTIVE SUMMARY:

Bayer CropScience has submitted a study investigating the metabolism of [phenyl-U-^{14}C]tembotrione (PH label; specific activity 4,793 MBq/g) in corn. The radiolabeled test substance was formulated as a 5% ai oil-based suspension concentrate (SC), containing the safener, isoxadifen-ethyl, for dilution in water. The formulated test substance was applied as a broadcast foliar application to container-grown corn (growth stage BBCH 12-14) at a rate equivalent to 0.103 lb ai/A (116 g ai/ha) or 0.181 lb ai/A (203 g ai/ha) in ~43 gal/A (400 L/ha). Plants were harvested at several intervals after application (days after treatment; DAT). The sampling intervals were: 0, 14, and 49 DAT (immature plants); 84 DAT (forage); and maturity, 124 DAT (stover and grain).

Total radioactive residues (TRR) in corn matrices were determined by summing the radioactivity in rinses (0- and 14-DAT immature plants) and extractable and nonextractable fractions. Following foliar application of PH-labeled tembotrione at 0.103 lb ai/A, TRR were 16.389, 1.516, and 0.013 ppm in immature plants harvested 0, 14, and 49 DAT, respectively, and TRR were 0.023 ppm in forage, 0.046 ppm in stover, and 0.011 ppm in grain. Following foliar application of PH-labeled tembotrione at 0.181 lb ai/A, TRR were 53.747, 3.785, and 0.053 ppm in immature corn plants harvested 0, 14, and 49 DAT, respectively, and TRR were 0.066 ppm in forage, 0.124 ppm in stover, and 0.029 ppm in grain.

Plants collected at 0 and 14 DAT were rinsed with acetonitrile (ACN)/water, which released 12-13% TRR and 4-5% TRR, respectively. Samples were homogenized and extracted with ACN/water (all samples) which released ~85-97% TRR in immature plants (0-49 DAT), 91-93% TRR in forage, 78-79% TRR in stover, and 82-88% TRR in grain. Nonextractable residues in immature plants (0-49 DAT), forage, and grain were <0.1-12.3% TRR. Nonextractable residues in stover were subjected to acid or base hydrolysis; acid hydrolysis released little radioactivity (2.2-2.5% TRR), but base hydrolysis released 13.0-13.4% TRR in stover. Nonextractable residues after exhaustive extractions were 7.6-8.6% TRR (0.004-0.009 ppm) in stover.

These procedures adequately extracted the majority of the residues from corn matrices. Because TRR were determined by summing extractable and nonextractable radioactivity, accountabilities were ~100%. Residues were identified and quantitated by high-performance liquid chromatography (HPLC) and confirmed by thin-layer chromatography (TLC). The petitioner reported significant loss of radioactivity (~18-19% TRR) on HPLC analysis of grain; no significant losses were observed for the other matrices. HPLC/mass spectrometry (MS), HPLC/MS/MS, and nuclear magnetic resonance (NMR) analyses were also used for structure elucidation and identification/confirmation of metabolites. Adequate storage stability data were submitted to support the storage intervals and conditions of samples of immature plants and forage from the study. No additional storage stability data are required because all samples were stored frozen for <6 months prior to initial analysis.

The identified metabolites and their relative distributions were similar for each matrix at both treatment levels. No residues of the parent, tembotrione, were found in 84-DAT forage, stover, or grain samples. Metabolite AE 0456148 was identified as the major residue in forage, stover, and grain, at 38.8-40.9% TRR (0.009 and 0.027 ppm) in forage, 33.1-39.6% TRR (0.015 and 0.049 ppm) in stover, and 47.1-59.5% TRR (0.005 and 0.017 ppm) in grain. Other identified residues included AE 1392936 at 10.2-10.3% TRR (0.002 and 0.007 ppm) in forage, and 11.6% TRR (0.005 and 0.014 ppm) in stover; and AE 1417268 at 9.3-9.8% TRR (0.002 and 0.006 ppm) in forage, and 5.5-6.2% TRR (0.003 and 0.007 ppm) in stover. Both of these metabolites were present at ≤1% TRR (<0.001 ppm) in grain. The unknowns in forage, stover, and grain accounted for ~10-40% TRR and were characterized by the polarity of the residue according to its behavior on HPLC analysis. None of the peaks or regions that were characterized exceeded a level of 14% TRR (0.008 ppm) in forage, 11.5% TRR (0.014 ppm) in stover, or 9.5% TRR (0.002 ppm) in grain.

The parent, tembotrione, was identified in immature corn plants, decreasing from ~27-43% TRR in 0-DAT samples to ≤0.6% TRR in 49-DAT samples. The metabolite AE 1444744 was also only identified in immature plants, decreasing from ~28-30% TRR in 0-DAT samples to ≤1.2% TRR in 49-DAT samples. Metabolite AE 1417268 was the major residue identified in 14-DAT plants at 64-66% TRR (0.999 and 2.438 ppm), and was also a significant residue in 0-DAT plants (12-24% TRR) and 49-DAT plants (11-14% TRR). Metabolite AE 0456148 (the major residue in forage and mature matrices) increased in immature plants with later sampling intervals (≤7% TRR at 0 DAT to 60-65% TRR at 49 DAT). Residues of AE 1392936 also increased in immature plants with later sampling intervals (<0.1% TRR at 0 DAT to <8% TRR at 49 DAT).

Based on the PH-labeled corn metabolism study, tembotrione is metabolized in corn by hydroxylation of the cyclohexyl moiety to form the monohydroxy (AE 1444744) and dihydroxy (AE 1417268) metabolites, followed by cleavage to the benzoic acid derivative (AE 0456148). Formation of this metabolite, AE 0456148, directly from the parent herbicide could not be ruled out. The metabolite AE 1392936 is formed by the subsequent cleavage of the trifluoroethoxy ether bond of AE 0456148.

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the plant metabolism data are classified as scientifically acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document [DP# 325349].

COMPLIANCE:

Signed and dated Good Laboratory Practice (GLP), Quality Assurance and Data Confidentiality statements were provided. No GLP deviations were reported which would impact the study results or their interpretation.

A. BACKGROUND INFORMATION

Tembotrione, a new herbicide with broad use against mono- and dicotyledons in selected crops such as corn, is a 4-hydroxyphenylpyruvate deoxygenase (HPPD) inhibitor (bleacher). The test compound nomenclature and physiochemical properties of the test compound are presented in Tables A.1 and A.2, respectively.

TABLE A.1. Test Compound Nomenclature for Tembotrione.

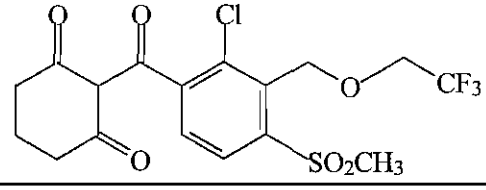
Compound: Tembotrione	Chemical Structure 
Proposed common name	Tembotrione
Company experimental name	AE 0172747
IUPAC name	2-{2-chloro-4-mesyl-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl}cyclohexane-1,3-dione
CAS name	2-[2-chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione
CAS #	335104-84-2
End-use product/EP	AE 0172747 Herbicide, EPA Reg No. 264-xxx

TABLE A.2. Physicochemical Properties of Technical Grade Tembotrione.		
Parameter	Value	Reference (MRID#)
Melting point	117 °C	46695402
pH @ 24 °C	3.63	
Density (g/mL @ 20 °C)	1.56	
Water solubility (mg/L @ 20 °C)	0.22 at pH4 28.3 at pH 7 29.7 at pH 9	
Solvent solubility (g/L at 20 °C) DMSO Methylene Chloride Acetone Ethyl Acetate Toluene Hexane Ethanol	 >600 >600 300-600 180.2 75.7 47.6 8.2	
Vapor pressure (Torr, 20 °C)	8.25×10^{-11}	
Dissociation constant (pK_a)	3.2	
Octanol/water partition coefficient (P_{ow} @ 23 °C) (P_{ow} @ 24 °C) (P_{ow} @ 23 °C)	 0.0430 at pH 9.0 0.0807 at pH 7.0 144.9 at pH 2.0	
UV/visible absorption spectrum (nm)	Primary: 205 Secondary: 284 Tertiary: 240	

B. EXPERIMENTAL DESIGN

B.1. Test Site and Crop Information

Corn plants were grown in stainless steel containers (height 50 cm, width 70 cm, and length 100 cm) equipped with a device for irrigation from below. The bottom of the container was covered up to a height of approx. 5 cm with a gravel layer. The gravel was topped with a 40-cm layer of sandy loam soil. The untreated controls were grown in 20-L Kick-Brauckmann pots with a similar soil profile. The planting containers and the pots were placed in an outdoor vegetation hall surrounded by wire-mesh fencing to keep off birds and covered with a glass roof to prevent flooding in case of extensive rainfall. Placing the containers and pots close to the fence of the vegetation hall ensured direct irradiation with sunlight from the side. The plants were artificially irrigated, fertilized, and treated with other pesticides, if needed, to ensure growth under optimal conditions. Daily climatic conditions (temperature maximums and minimums and weather conditions) were reported. There were no meteorological abnormalities that may have impacted the study.

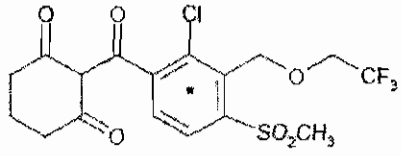
TABLE B.1.1. Test Site Information.					
Type	Method	Soil characteristics[1]			
		Type	%OM	pH	CEC
Foliar Treatment	Hand-held spray pistol	Sandy loam (US soil taxonomy) SL3 (DIN 4220)	1.1	5.8 (0.01 M $CaCl_2$)	6.15 meq/100 g

[1] OM = Organic matter, CEC = Cation-exchange capacity

TABLE B.1.2. *Crop Information.*				
Crop/crop group	Variety	Growth stage at application	Growth stage at harvest	Harvested Matrix
Corn (*Zea mays*)/ Grain, cereal, group 15, and Grain, cereal, forage, fodder, and straw, group 16	Dea (Pioneer)	BBCH 12-14 (leaf development)	BBCH 12-14; 2-3 leaves unfolded	0-DAT immature plants
			BBCH 16-17; 6-7 leaves unfolded	14-DAT immature plants
			BBCH 55-63; heading/flowering	49-DAT immature plants
			BBCH 85; dough stage	84-DAT forage
			BBCH 97; mature	124-DAT stover and grain

B.2. Test Materials

The radiolabeled test substance was isotopically diluted with nonlabeled tembotrione, and formulated as a 5% oil-based SC with formulation blank containing the safener, isoxadifen-ethyl. The test substance was applied with the safener in a 1:1 (w:w) ratio. The test material characteristics are presented in Table B.2.1.

TABLE B.2.1. Test Material Characteristics.	
Chemical structure	
Radiolabel position	[phenyl-U-^{14}C]Tembotrione
Lot or Batch No.	CFQ12575
Purity	97.7% (by HPLC)
Specific activity (Bq)[1]	9.76 mBq/mg (585,600 dpm/µg) 4,793 mBq/g (isotopically diluted test substance)

[1] Bq = disintegrations per second

B.3. Study Use Pattern

The formulated test substance was diluted with water for application. The foliar broadcast application was made in a plastic tent using a Walther Pilot ND spray pistol. After application, the corn plants were moved to a secured outdoor area to continue their growth. The study use pattern is summarized in Table B.3.1.

TABLE B.3.1. Use Pattern Information	
Chemical	[phenyl-U-^{14}C]Tembotrione
Application method	The test substance, formulated as an oil-based SC formulation, was diluted with water and applied to corn plants as a broadcast foliar spray using a handheld spray pistol.
Application rate, Nominal	100 g ai/ha (0.089 lb ai/A) or 200 g ai/ha (0.178 lb ai/A)
Application rate, Actual	116 g ai/ha (0.103 lb ai/A) or 203 g ai/ha (0.181 lb ai/A)
Number of applications	1 broadcast foliar (each)
Timing of applications	BBCH 12-14 (2-3 leaves unfolded)
Preharvest Interval (PHI)	Immature plants: 0, 14, and 49 days after application Forage: 84 days after application Grain and stover: 124 days after application

B.4. Identification/Characterization of Residues

B.4.1. Sample Handling and Preparation

Corn plants were harvested at several intervals after application. The sampling intervals were: 0 DAT (BBCH 12-14, 2-3 leaves unfolded), 14 DAT (BBCH 16-17, 6-7 leaves unfolded), 49 DAT (BBCH 55-63, heading-flowering), 84 DAT (BBCH 85, dough stage, forage) and 124 DAT (BBCH 97, mature stover and grain). Plants were cut 5 to 10 cm above the soil surface. Immature plants were processed without separation into different plant parts. Mature plants were separated into the raw agricultural commodities of grain and stover (which included the cobs) prior to processing. Processing was carried out immediately after sampling. At each sampling interval, the fresh weight was recorded. Whole plants from the 0- and 14-DAT intervals were rinsed with ACN:water (1:1, v:v), and the rinse was reserved for HPLC and TLC analysis. The rinsed plants, 49-DAT immature plants, forage, stover, and grain were cut into small pieces with scissors before homogenization in a cutter mill with dry ice. Subsamples were removed for analysis, and the remaining material was stored in a freezer at ≤-18 °C. The in-life and analytical phases of the study were conducted at the same facility (Bayer CropScience GmbH, Frankfurt, Germany); therefore, samples were not shipped.

Samples from both applications rates were subjected to the extraction procedures described below. Representative extraction schemes are presented for immature plants (Figure 1) and forage, stover, and grain (Figure 2).

Subsamples of **immature plants** were extracted 3-4x with ACN:water (4:1, v:v) using an Ultra-Turrax high speed blender, then centrifuged. The supernatants were combined and passed through a C-18 solid-phase extraction (SPE) cartridge; residues were eluted with ACN. The resulting ACN eluates were concentrated and reserved for HPLC and TLC analysis.

Subsamples of **84-DAT forage** and **stover** were extracted 5x with ACN:water (4:1, v:v) and purified on a C-18 SPE cartridge as described above for immature plants. The resulting eluates were concentrated by rotary evaporation, and the stover eluates (fraction S5) were reserved for HPLC analysis. For forage, the evaporation flasks were rinsed with ACN:water (1:1, v:v), and the rinses were combined with the concentrated sample and applied to a second C-18 SPE

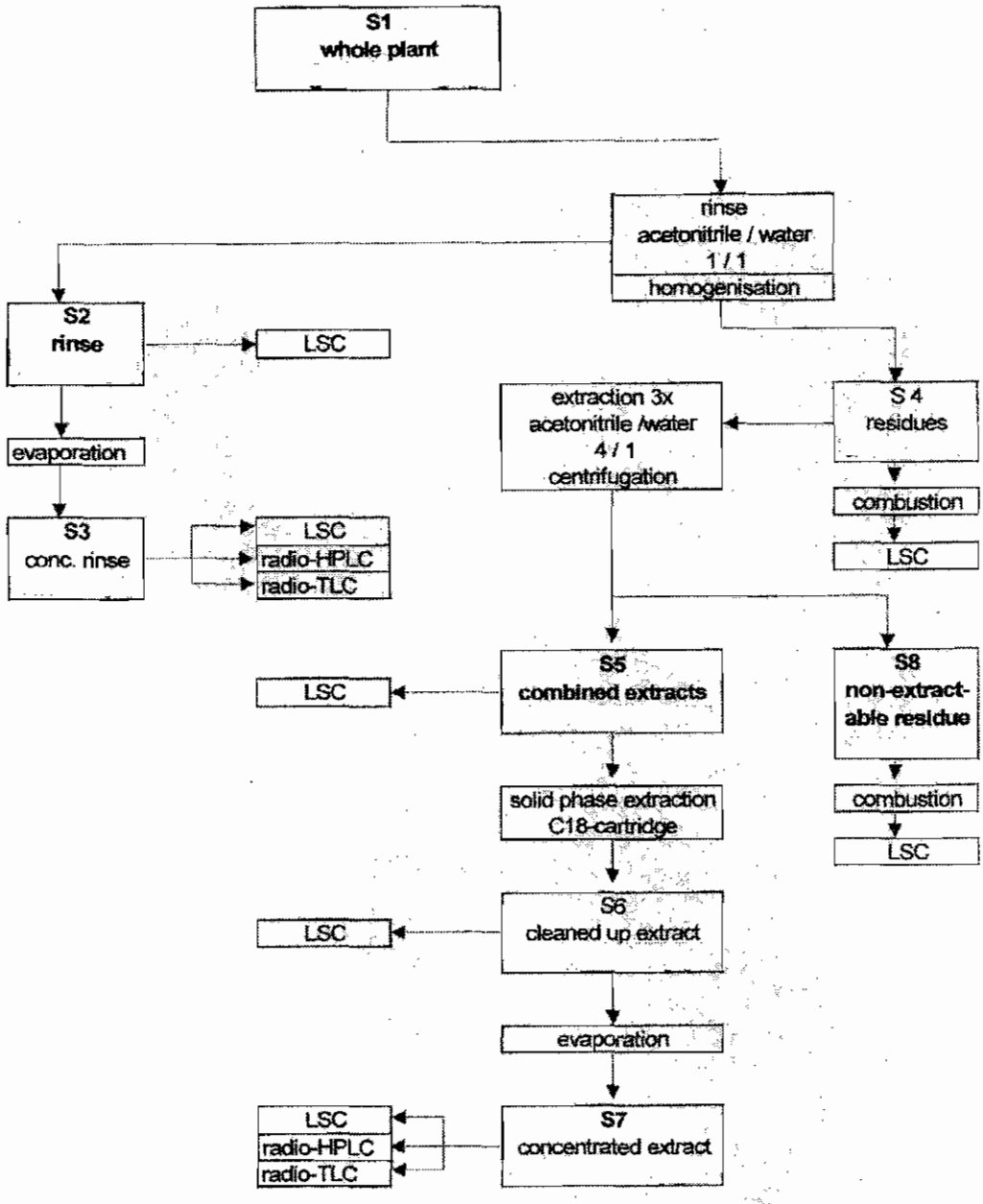
cartridge. The ACN eluates (fraction S7) were concentrated and reserved for HPLC analysis. Because of high levels of matrix byproducts, subsamples of the concentrated ACN eluates for forage and stover were acidified to pH 2 with H_2SO_4 and partitioned with ethyl acetate. The resulting organic phases (fraction S9 for forage and S7 for stover) were concentrated and reserved for HPLC and TLC analysis. The aqueous phase for forage was subjected to additional purification via C-18 SPE; residues were eluted with water, water:ACN (4:1, v:v), water:ACN (1:1, v:v), and ACN. The water fraction was discarded, and the three remaining fractions were combined and concentrated. The combined eluates for forage and the concentrated aqueous phase for stover were neutralized to pH 6 with 10 M NaOH, concentrated, and reserved for HPLC analysis.

Subsamples of **grain** were extracted 4x with ACN:water (4:1, v:v) and purified on a C-18 SPE cartridge as described above for immature plants. The resulting ACN eluate was concentrated by rotary evaporation and partitioned with ethyl acetate. Due to low radioactivity, the aqueous phase was not further analyzed. The organic phase was concentrated, resuspended in water:ACN (4:1, v:v) and subjected to a second C18 SPE purification. The resulting eluate was concentrated and resuspended in water (fraction S7) and ACN:water (1:1, v:v; fraction S8). Fractions S7 and S8 were combined and analyzed by HPLC and TLC.

Fractions S9 from forage, S7 from stover, and S7 + S8 from grain from the high rate application (organic phases following ethyl acetate partitioning) were subjected to acid and base hydrolysis with 1 M HCl and 1 M NaOH, each for 6 hours at 35 °C. The S7 fraction from stover was also subjected to enzyme hydrolysis with α-glucosidase, β-glucosidase, and β-glucuronidase (each in 0.1 M sodium acetate buffer, pH 4.5, for 27 hours at 37 °C). The resulting hydrolysates from all procedures were reserved for HPLC analysis.

Separate subsamples of nonextractable residues remaining after solvent extraction of corn stover were subjected to acid (1 M HCl) or base (1 M NaOH) hydrolysis. Hydrolyses were conducted at room temperature for 46 hours. The hydrolysates were centrifuged and partitioned with ethyl acetate to characterize the polarity of the hydrolyzed residues.

Figure 1 : Work-up scheme for whole plant



TRR = S2 + S5 + S8

Figure 2: *Work-up scheme for 84-DAT forage*

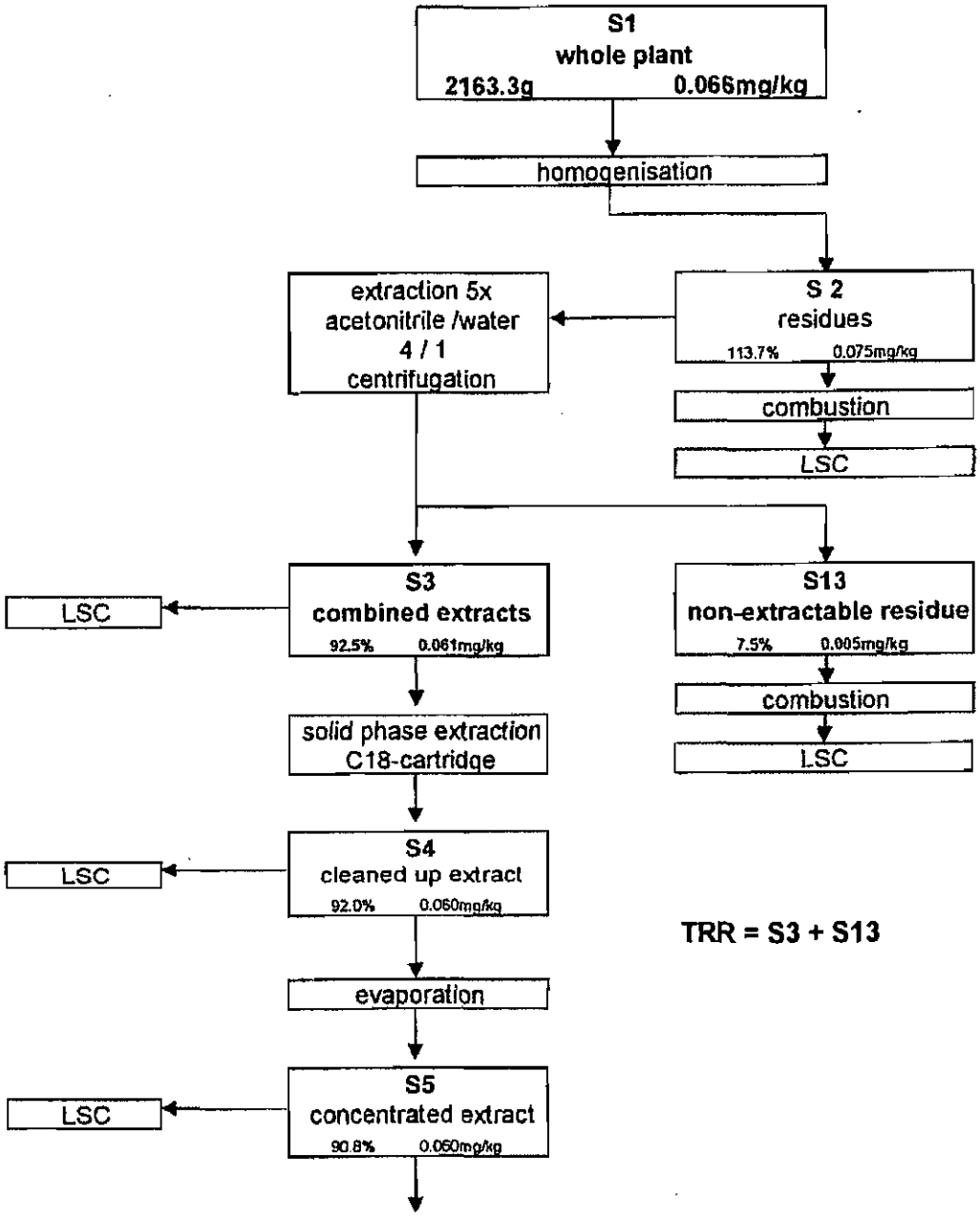
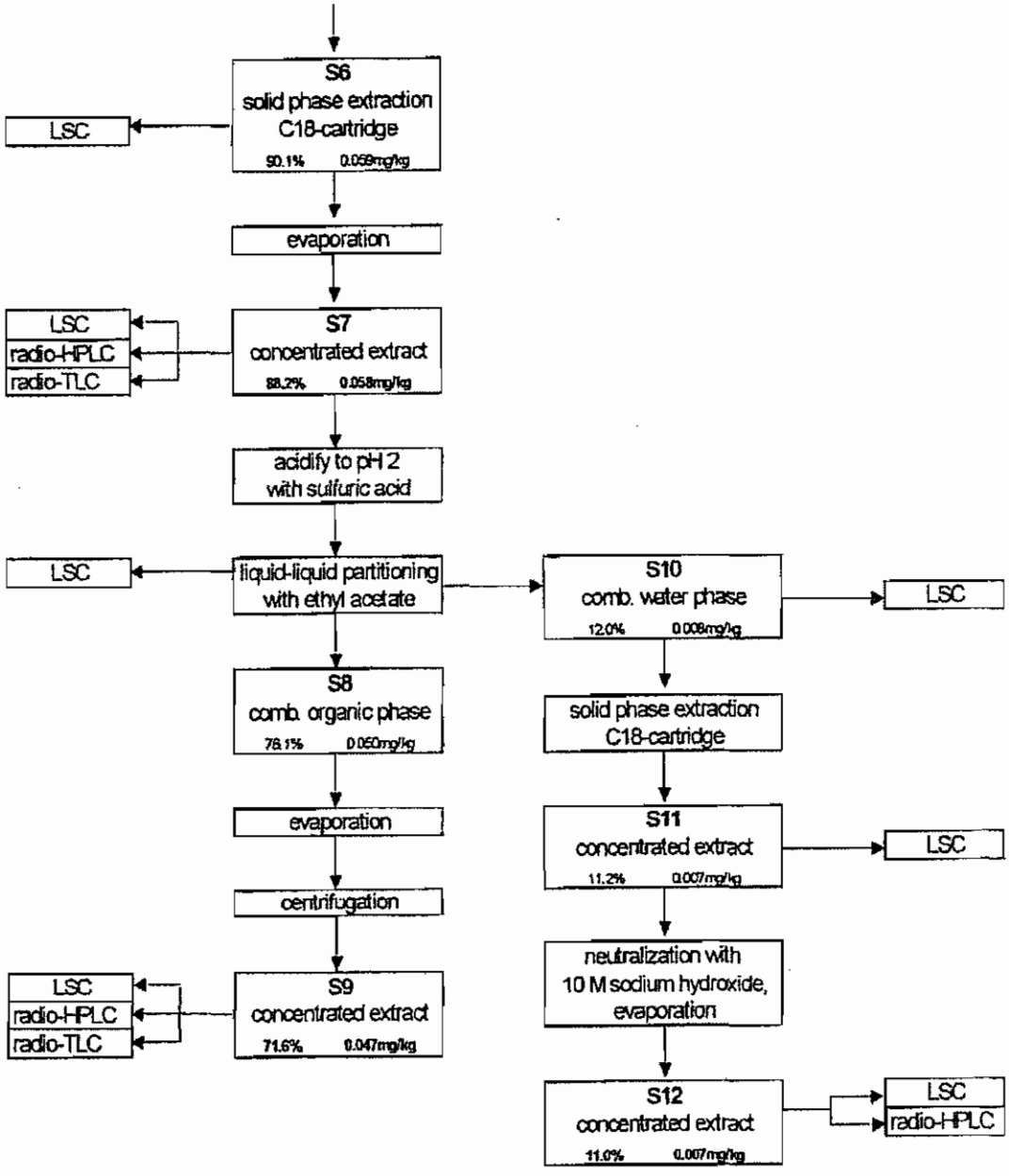


Figure 2 (continued): *Work-up scheme for 84-DAT forage*



B.4.2. Analytical Methodology

The TRR were initially estimated in representative subsamples using combustion/liquid scintillation counting (LSC) techniques; these data were not reported. Radioactivity in the liquid samples (i.e., rinses, extracts, and concentrates) was quantified by LSC. The nonextractable residues were determined by combustion/LSC. The TRR, used for all further determinations, were calculated by summing the radioactivity from the rinses (0- and 14-DAT immature plants only) and extractable and nonextractable residues. The limit of quantitation (LOQ) for TRR determinations was not reported.

Analytical separations of the extracted radioactivity, as well as identification of the metabolites, were established by reverse-phase HPLC and TLC as two independent analytical systems.

Aliquots of the concentrated rinses, extracts, and purified eluates were analyzed by reversed phase HPLC using a C-18 column (150 x 4.6 mm, stainless steel), UV detection at 254 nm, and a gradient mobile phase of water (acidified to pH 2 with formic or sulfuric acid)/ACN. Residues were quantitated using a flow-through radioactivity detector. The reported LOQ for HPLC determinations was 0.001 ppm. For characterization of metabolites, the retention times of the non-labeled reference standards were compared with the retention times of radioactive fractions in sample extracts. The reference standards used in the study are presented in Appendix I.

Additional preparative and semi-preparative HPLC analyses for the isolation of metabolites were conducted using similar systems. Selected metabolites were also purified using HPLC analysis on a system equipped with a diol column, UV detector (254 nm), and flow-through radiodetector, and using a gradient mobile phase of n-hexane/ethanol + 3.0% ammonia (25%).

TLC analysis was conducted with representative samples as a second independent analytical system to confirm the characterization of metabolites obtained by HPLC. TLC analyses were conducted using silica gel plates, and a mobile phase of chloroform:methanol:toluene:acetic acid (50:35:15:1, v:v:v:v). Radioactivity was detected by autoradiography, and nonlabeled standards were detected by UV fluorescence detection.

HPLC/MS and HPLC/MS/MS (daughter-ion scan) were conducted with representative sample extracts of 0-DAT whole plant and the 14-DAT ACN/water rinse (both from the high rate treatment). Electrospray ionization in the positive- and negative-ion modes was used for HPLC/MS, and argon was used as the collision gas for MS/MS determinations.

Cell cultures of corn, wheat and/or apple were also used to isolate metabolites for identification. Limited details of the cell culture study were provided. Samples were extracted 3x with ACN:water (80:20, v:v), and the extracts were combined and partitioned with ethyl acetate. The metabolites were isolated using two different semi-preparative HPLC methods from cell cultures incubated with [phenyl-U-^{14}C]tembotrione for 14 days (7 days for apple cell cultures). After purification, the major metabolites were isolated and identified by NMR and HPLC/MS/MS. Data concerning the cell culture studies were referenced to Bayer Report Number MR-691/98.

C. RESULTS AND DISCUSSION

The storage conditions and intervals for corn matrices are presented in Table C.1.1. Actual extraction and analysis dates were not provided; however, based on the harvest dates and dated HPLC chromatograms included in the submission, samples were stored from harvest to initial analysis for <6 months for immature plants and for 2-3 months for forage, stover, and grain. The petitioner demonstrated storage stability in immature plants by re-extracting and analyzing 49-DAT immature plants from the high rate treatment 6 months after the sample was first analyzed. Stability of the residues in extracts was investigated by re-analyzing the stover extract from the high rate treatment ~2.5 months after initial analysis. Adequate storage stability data were

submitted to support the storage intervals and conditions of samples of immature plants and forage from the study. No additional storage stability data are required because all samples were stored for <6 months prior to initial analysis. The petitioner should note for future submissions that the critical study dates are required for each sample.

TRR in corn matrices were determined by summing the radioactivity in rinses (0- and 14-DAT immature plants) and extractable and nonextractable fractions; TRR are reported in Table C.2.1. Following foliar application of PH-labeled tembotrione at 0.103 lb ai/A, TRR were 16.389, 1.516, and 0.013 ppm in immature corn plants harvested 0, 14, and 49 DAT, respectively, and TRR were 0.023 ppm in forage, 0.046 ppm in stover, and 0.011 ppm in grain. Following foliar application of PH-labeled tembotrione at 0.181 lb ai/A, TRR were 53.747, 3.785, and 0.053 ppm in immature corn plants harvested 0, 14, and 49 DAT, respectively, and TRR were 0.066 ppm in forage, 0.124 ppm in stover, and 0.029 ppm in grain.

The distribution of the radioactivity in corn matrices is presented in Tables C.2.2.1 (0-49 DAT immature plants treated at 0.103 lb ai/A), C.2.2.2 (forage, stover, and grain treated at 0.103 lb ai/A), C.2.2.3 (0-49 DAT immature plants treated at 0.181 lb ai/A), and C.2.2.4 (forage, stover, and grain treated at 0.181 lb ai/A). Plants collected at 0 and 14 DAT were rinsed with ACN/water before homogenization, which released 12-13% TRR and 4-5% TRR, respectively. Solvent extraction with ACN/water (all samples) released ~85-97% TRR in immature plants (0-49 DAT), 91-93% TRR in forage, 78-79% TRR in stover, and 82-88% TRR in grain. Nonextractable residues in immature plants (0-49 DAT), forage, and grain were <0.1-12.3% TRR. Nonextractable residues in stover were subjected to acid or base hydrolysis; acid hydrolysis released little radioactivity (2.2-2.5% TRR), but base hydrolysis released 13.0-13.4% TRR in stover. Nonextractable residues after exhaustive extractions were 7.6-8.6% TRR (0.004-0.009 ppm) in stover.

These procedures adequately extracted the majority of the residues from corn matrices. Because TRR were determined by summing extractable and nonextractable radioactivity, accountabilities were ~100%. Residues were identified and quantitated by HPLC and confirmed by TLC. The petitioner reported significant loss of radioactivity (~18-19% TRR) on HPLC analysis of grain; no significant losses were observed for the other matrices. HPLC/MS, HPLC/MS/MS, and NMR analyses were also used for structure elucidation and identification/confirmation of metabolites.

The characterization and identification of residues in corn matrices are summarized in Tables C.2.3.1 (0-49 DAT immature plants treated at 0.103 lb ai/A), C.2.3.2 (forage, stover, and grain treated at 0.103 lb ai/A), C.2.3.3 (0-49 DAT immature plants treated at 0.181 lb ai/A), and C.2.3.4 (forage, stover, and grain treated at 0.181 lb ai/A). The metabolites identified and their relative distributions were similar for each matrix at both treatment levels. No residues of the parent, tembotrione, were found in forage, stover, or grain samples. Metabolite AE 0456148 was identified as the major residue in forage, stover, and grain, at 38.8-40.9% TRR (0.009 and 0.027 ppm) in forage, 33.1-39.6% TRR (0.015 and 0.049 ppm) in stover, and 47.1-59.5% TRR (0.005 and 0.017 ppm) in grain. Other identified residues included AE 1392936 at 10.2-10.3% TRR (0.002 and 0.007 ppm) in forage, and 11.6% TRR (0.005 and 0.014 ppm) in stover; and AE 1417268 at 9.3-9.8% TRR (0.002 and 0.006 ppm) in forage, and 5.5-6.2% TRR (0.003 and 0.007 ppm) in stover. Both of these metabolites were present at ≤1% TRR (<0.001 ppm) in grain

The parent, tembotrione, was identified in immature corn plants, decreasing from ~27-43% TRR in 0-DAT samples to ≤0.6% TRR in 49-DAT samples. The metabolite AE 1444744 was also only identified in immature plants, decreasing from ~28-30% TRR in 0-DAT samples to ≤1.2% TRR in 49-DAT samples. Metabolite AE 1417268 was the major residue identified in 14-DAT plants at 64-66% TRR (0.999 and 2.438 ppm), and was also a significant residue in 0-DAT plants (12-24% TRR) and 49-DAT plants (11-14% TRR). Metabolite AE 0456148 (the major residue in forage and mature matrices) increased in immature plants with later sampling intervals (≤7% TRR at 0 DAT to 60-65% TRR at 49 DAT). Residues of AE 1392936 also increased in immature plants with later sampling intervals (<0.1% TRR at 0 DAT to <8% TRR at 49 DAT).

Approximately 13% TRR in stover was base hydrolyzed. The remaining solvent-extractable residues in forage, stover, and grain, accounting for ~10-40% TRR, were characterized by the polarity of the residue according to its behavior on HPLC analysis. None of the peaks or regions that were characterized as very polar, polar, or medium polar exceeded a level of 14% TRR (0.008 ppm) in forage, 11.5% TRR (0.014 ppm) in stover, or 9.5% TRR (0.002 ppm) in grain.

Metabolites AE 1392936 (P2) and AE 1417268 (P5) were isolated from stover and 14-DAT immature plants, respectively, from the high-rate treatment and identified by HPLC/MS, HPLC/MS/MS, and NMR analyses. Identification of parent (tembotrione) and metabolites AE 0456148, AE 1417268 and AE 1444744 was confirmed in high-rate treated 0- and 14-DAT plant rinses/extracts by HPLC/MS. Metabolite AE 0456148 was further identified in corn forage, stover, and grain by co-chromatography with radiolabeled reference standard. Metabolite AE 1417268 was identified in stover by co-chromatography with the rinsate of 14-DAT plants. Metabolite AE 1392936 isolated from stover was identified by HPLC/MS, and identified in the 14-DAT rinse by co-chromatography with the stover extract. Metabolites in the other extracts were identified by retention time comparison with reference standards, the 0- and 14-DAT extracts, or the stover extract (AE 1392936). Co-chromatography of metabolites isolated and identified in the cell culture study, further confirmed identifications of AE 1444744 and AE 1417268 in 0- and 14-DAT plants. Metabolites in cell cultures were identified by HPLC/MS, HPLC/MS/MS, and NMR.

Acid, base, and enzyme hydrolysis (α-glucosidase, β-glucosidase, and β-glucoronidase) of forage, stover and grain residues did not change the metabolic pattern; therefore, none of the metabolites were considered to be cleavable conjugates.

C.1. Storage Stability

The petitioner stated that samples were processed and extracted immediately after sampling. Subsamples were removed for analysis, and the remaining material was stored in a freezer at ≤-18 °C. The petitioner stated that bulk extracts and leaf rinses were also stored frozen at -18 °C. Actual extraction and analysis dates were not provided; however, based on the harvest dates and dated HPLC chromatograms included in the submission, samples were stored from harvest to initial analysis for <6 months for immature plants, and 2-3 months for forage, stover, and grain.

The petitioner demonstrated storage stability by re-extracting and analyzing 49-DAT immature plants from the high rate treatment 6 months after the sample was first analyzed. Stability of the residues in extracts was investigated by re-analyzing the stover extract from the high rate treatment ~2.5 months after initial analysis. In addition, a sample of untreated stover was fortified with tembotrione and metabolite AE 0456148 and analyzed before and after processing to check stability during sample processing prior to extraction. The metabolite profiles were comparable for all matrices tested. A comparison of the original analysis and re-analysis results for 49-DAT plants is presented in Table C.1.2.

TABLE C.1.1. Summary of Storage Conditions.

Matrix	Storage Temperature (°C)	Aetual Storage Duration [1]	Interval of Demonstrated Storage Stability
Immature plant (0-49 DAT)	-18	33-168 days (≤5.5 months)	None required because samples were initially analyzed (for quantitation) within 6 months after harvest.
Forage		104 days (3.4 months)	
Stover		64 days (2.1 months)	
Grain		93 days (3.1 months)	

[1] Storage interval for samples from both treatment rates from harvest to initial HPLC analysis of the extraet, based on the dates of the representative chromatograms; extraction dates were not provided.

TABLE C.1.2. Comparison of Results Following Initial and Re-analysis of 49-DAT Immature Corn Plants After Application of [Phenyl-U-^{14}C]Tembotrione at 0.181 lb ai/A.

Fraction[1]	Initial analysis (8/28/01)[2]		Re-analysis (2/20/02)	
	%TRR	ppm	%TRR	ppm
Extractahle	96.9	0.051	96.9	0.060
Nonextractablc	3.1	0.002	3.1	0.002
HPLC Separation				
P1	1.4	<0.001	2.9	0.002
P2	7.3	0.004	4.4	0.003
P4	2.2	0.001	3.4	0.002
P5	11.1	0.006	8.7	0.005
P6	65.3	0.034	59.4	0.037
P7	1.1	<0.001	6.1	0.004
P8	0.5	<0.001	2.2	0.001
P9	1.2	<0.001	1.3	<0.001
P10	1.2	<0.001	1.2	<0.001
P11	0.6	<0.001	0.6	<0.001
R1	1.0	<0.001	1.9	0.001
R2	4.1	0.002	4.2	0.003
R3			0.8	<0.001
Accountability	97.0	0.047	97.1	0.058

[1] Refer to Table C.2.2.3 for identification of peaks (P) and regions (R).
[2] These data are identical to those presented below in Table C.2.2.3.

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

TABLE C.2.1. Total Radioactive Residues (TRR) in Corn Matrices.

Matrix	Timing and Applic. No.	PHI (days)	TRR, ppm[1]	
			0.103 lb ai/A	0.181 lb ai/A
Immature plant	One broadcast foliar application to corn plants at the *BBCH 12-14 growth* stage.	0	16.389	53.747
Immature plant		14	1.516	3.785
Immature plant		49	0.013	0.053
Forage		84	0.023	0.066
Stover (including cobs)		124	0.046	0.124
Grain		124	0.011	0.029

[1] Determined by summing the radioactivity in rinses (0- and 14-DAT immature plants) and extractable and nonextractable fractions.

TABLE C.2.2.1. *Distribution of the Parent and the Metabolites* in Immature Corn Plants After Application of [Phenyl-U-^{14}C]Tembotrione at 0.103 lb ai/A.

Metabolite Fraction[1]	Whole Plant, 0 DAT		Whole Plant, 14 DAT		Whole Plant, 49 DAT	
	TRR = 16.389 ppm		TRR = 1.516 ppm		TRR = 0.013 ppm	
	%TRR	ppm	%TRR	Ppm	%TRR	ppm
ACN/water surface wash (S2)	11.9	1.949	4.5	0.069		
ACN/water extract (S5)	88.1	14.440	90.3	1.368	92.9	0.012
Total Extractable (wash + extract)[2]	100	16.389	94.8	1.436	92.9	0.012
P1, unknown, very polar	--	--	0.2	0.003	2.5	<0.001
P2, AE 1392936 (M2)	--	--	1.5	0.022	7.7	0.001
P3, unknown, polar	--	--	1.4	0.021	--	--
P4, unknown, polar	0.5	0.084	3.0	0.046	1.7	<0.001
P5, AE 1417268 (M5)	24.0	3.925	65.9	0.999	14.0	0.002
P6, AE 0456148 (M6)	7.0	1.150	7.9	0.119	59.8	0.008
P7, unknown, med polar	1.7	0.287	2.0	0.031	1.0	<0.001
P8, unknown, med polar	4.1	0.667	1.3	0.020	--	--
P9, unknown, med polar	6.2	1.010	0.1	0.001	1.1	<0.001
P10, AE 1444744 (M10)	27.7	4.545	0.1	0.002	--	--
P11, Tembotrione (parent)	27.3	4.480	0.3	0.005	--	--
R1, very polar region	0.7	0.113	8.6	0.130	1.7	<0.001
R2, polar region	0.6	0.101	2.5	0.037	1.5	<0.001
R3, medium polar region	0.2	0.026	--	--	1.8	<0.001
Nonextractable (S8)	<0.1	<0.001	5.2	0.079	7.1	0.001

[1] Shading indicates that the extraction step and/or characterization analysis was not conducted for the matrix in question. P = peak; R = region. R1 – R4 = chromatographic regions with several unidentified components.
[2] The surface wash and extract (after SPE cleanup and concentration) were separately analyzed by HPLC; however, the petitioner reported the combined residues.

TABLE C.2.2.2. Distribution of the Parent and the Metabolites in Corn Forage, Stover, and Grain After Application of [Phenyl-U-^{14}C]Tembotrione at 0.103 lb ai/A.

Metabolite Fraction[1]	Forage, 84 DAT		Stover, 124 DAT		Grain, 124 DAT	
	TRR = 0.023 ppm		TRR = 0.046 ppm		TRR = 0.011 ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm
ACN/water extract (S5)	91.1	0.021	78.0	0.036	81.9[2]	0.009
P1, unknown, very polar	1.8	<0.001	1.2	0.001	--	--
P2, AE 1392936 (M2)	10.3	0.002	11.6	0.005	--	--
P4, unknown, polar	7.2	0.002	6.0	0.003	--	--
P5, AE 1417268 (M5)	9.3	0.002	6.2	0.003	1.0	<0.001
P6, AE 0456148 (M6)	38.8	0.009	33.1	0.015	47.1	0.005
P7, unknown, med polar	3.3	0.001	3.9	0.002	--	--
P8, unknown, med polar	2.0	<0.001	0.9	<0.001	--	--
P9, unknown, med polar	--	--	1.3	0.001	--	--
R1, very polar region	14.0	0.003	11.5	0.005	5.3	0.001
R2, polar region	4.5	0.001	2.2	0.001	9.5	0.001
R3, medium polar region	--	--	--	--	0.3	<0.001
Nonextractable (S8)	8.9	0.002	22.0	0.010	18.1	0.002
1. Acid hydrolysis			2.5	0.001		
Organosoluble			1.2	<0.001		
Water soluble			1.1	<0.001		
Nonextractable			19.9	0.009		
2. Base hydrolysis			13.4	0.006		
Organosoluble			4.9	0.002		
Water soluble			8.4	0.004		
Nonextractable			8.6	0.004		

[1] Shading indicates that the extraction step and/or characterization analysis was not conducted for the matrix in question.
P = peak; R = region. R1 – R4 = chromatographic regions with several unidentified components.
[2] The petitioner reported that there was a loss of 18.6% TRR during HPLC analysis of the extract.

TABLE C.2.2.3. Distribution of the Parent and the Metabolites in Immature Corn Plants After Application of [Phenyl-U-^{14}C]Tembotrione at 0.181 lb ai/A.

Metabolite Fraction[1]	Whole Plant, 0 DAT		Whole Plant, 14 DAT		Whole Plant, 49 DAT	
	TRR = 53.747 ppm		TRR = 3.785 ppm		TRR = 0.053 ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm
ACN/water surface wash (S2)	13.3	7.162	3.5	0.131		
ACN/water extract (S5)	84.7	45.519	88.6	3.353	96.9	0.051
Total Extractable (wash + extract)[2]	98.0	52.681	92.1	3.484	96.9	0.051
P1, unknown, very polar	--	--	0.2	0.006	1.4	<0.001
P2, AE 1392936 (M2)	--	--	0.8	0.028	7.3	0.004
P3, unknown, polar	--	--	1.3	0.049	--	--
P4, unknown, polar	0.5	0.275	2.9	0.111	2.2	0.001
P5, AE 1417268 (M5)	12.1	6.474	64.4	2.438	11.1	0.006
P6, AE 0456148 (M6)	4.4	2.350	7.6	0.289	65.3	0.034
P7, unknown, med polar	0.7	0.400	2.1	0.081	1.1	<0.001
P8, unknown, med polar	1.6	0.882	1.6	0.059	0.5	<0.001
P9, unknown, med polar	2.6	1.378	1.2	0.044	1.2	<0.001
P10, AE 1444744 (M10)	30.1	16.199	0.2	0.009	1.2	<0.001

TABLE C.2.2.3. *Distribution of the Parent and the Metabolites in Immature Corn Plants After Application of [Phenyl-U-^{14}C]Tembotrione at 0.181 lb ai/A.*

Metabolite Fraction[1]	Whole Plant, 0 DAT		Whole Plant, 14 DAT		Whole Plant, 49 DAT	
	TRR = 53.747 ppm		TRR = 3.785 ppm		TRR = 0.053 ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm
P11, Tembotrione (parent)	42.8	23.025	0.7	0.027	0.6	<0.001
R1, very polar region	1.3	0.715	7.7	0.293	1.0	<0.001
R2, polar region	1.0	0.547	1.3	0.050	4.1	0.002
R3, medium polar region	0.8	0.435	--	--	--	--
Nonextractable (S8)	2.0	1.066	7.9	0.300	3.1	0.002

[1] Shading indicates that the extraction step and/or characterization analysis was not conducted for the matrix in question.
P = peak; R = region. R1 – R4 = chromatographic regions with several unidentified components.
[2] The surface wash and extract (after SPE cleanup and concentration) were separately analyzed by HPLC; however, the petitioner reported the combined residues.

TABLE C.2.2.4. Distribution of the Parent and the Metabolites in Corn Forage, Stover, and Grain After Application of [Phenyl-U-^{14}C]Tembotrione at 0.181 lb ai/A.

Metabolite Fraction[1]	Forage, 84 DAT		Stover, 124 DAT		Grain, 124 DAT	
	TRR = 0.066 ppm		TRR = 0.124 ppm		TRR = 0.029 ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm
ACN/water extract (S5)	92.5	0.061	78.7	0.098	87.7	0.025
P1, unknown, very polar	1.7	0.001	--	--	--	--
P2, AE 1392936 (M2)	10.2	0.007	11.6	0.014	0.3	<0.001
P4, unknown, polar	6.8	0.004	4.3	0.005	--	--
P5, AE 1417268 (M5)	9.8	0.006	5.5	0.007	0.9	<0.001
P6, AE 0456148 (M6)	40.9	0.027	39.6	0.049	59.5	0.017
P7, unknown, med polar	3.9	0.003	2.8	0.003	--	--
P8, unknown, med polar	1.8	0.001	--	--	--	--
P9, unknown, med polar	1.8	0.001	1.8	0.002	--	--
R1, very polar region	12.5	0.008	11.0	0.014	3.7	0.001
R2, polar region	3.1	0.002	2.1	0.003	5.8	0.002
Nonextractable (S8)	7.5	0.005	21.3	0.026	12.3	0.004
1. Acid hydrolysis			2.2	0.003		
Organosoluble			0.9	0.001		
Water soluble			1.1	0.001		
Nonextractable			18.1	0.022		
2. Base hydrolysis			13.0	0.016		
Organosoluble			4.5	0.006		
Water soluble			8.8	0.011		
Nonextractable			7.6	0.009		

[1] Shading indicates that the extraction step and/or characterization analysis was not conducted for the matrix in question.
P = peak; R = region. R1 – R4 = chromatographic regions with several unidentified components.
[2] Loss of 17.5% TRR during workup of extract.

TABLE C.2.3.1. Summary of Characterization and Identification of Radioactive Residues in Immature Corn Plants Following Application of [Phenyl-U-^{14}C]Tembotrione at 0.103 lb ai/A.

Compound	Whole Plant, 0 DAT		Whole Plant, 14 DAT		Whole Plant, 49 DAT	
	TRR = 16.389 ppm		TRR = 1.516 ppm		TRR = 0.013 ppm	
	% TRR	ppm	% TRR	ppm	% TRR	ppm
Tembotrione	27.3	4.480	0.3	0.005	--	--
AE 1444744 (M10)	27.7	4.545	0.1	0.002	--	--
AE 1417268 (M5)	24.0	3.925	65.9	0.999	14.0	0.002
AE 0456148 (M6)	7.0	1.150	7.9	0.119	59.8	0.008
AE 1392936 (M2)	--	--	1.5	0.022	7.7	0.001
Very polar fraction (peaks + region)	0.7	0.113	8.8	0.133	4.2	<0.001
Polar fraction (peaks + region)	1.1	0.185	6.9	0.104	3.2	<0.001
Medium polar fraction (peaks + region)	12.2	1.990	3.4	0.052	3.9	<0.001
Total identified	86.0	14.100	75.7	1.147	81.5	0.011
Total characterized	13.9	2.288	19.1	0.289	11.3	0.001
Total extractable	100.0	16.389	94.8	1.436	92.9	0.012
Unextractable[1]	<0.1	<0.001	5.2	0.079	7.1	0.001
Accountability[2]	100		100		100	

[1] Residues remaining after exhaustive extractions.
[2] Accountability = (Total extractable + Total unextractable); TRR determined by summing extractable and nonextractable fractions.

TABLE C.2.3.2. Summary of Characterization and Identification of Radioactive Residues in Corn Forage, Stover, and Grain Following Application of [Phenyl-U-^{14}C]Tembotrione at 0.103 lb ai/A.

Compound	Forage, 84 DAT		Stover, 124 DAT		Grain, 124 DAT	
	TRR = 0.023 ppm		TRR = 0.046 ppm		TRR = 0.011 ppm	
	% TRR	ppm	% TRR	ppm	% TRR	ppm
AE 1417268 (M5)	9.3	0.002	6.2	0.003	1.0	<0.001
AE 0456148 (M6)	38.8	0.009	33.1	0.015	47.1	0.005
AE 1392936 (M2)	10.3	0.002	11.6	0.005	--	--
Very polar fractions (peaks + regions)	15.8	<0.004	12.7	0.006	5.3	0.001
Polar fractions (peaks + regions)	11.7	0.003	8.2	0.004	9.5	0.001
Medium polar fractions (peaks + regions)	5.3	<0.002	6.1	<0.004	0.3	<0.001
Base hydrolysate	--	--	13.4	0.006	--	--
Total identified	58.4	0.013	50.9	0.023	48.1	<0.006
Total characterized	32.8	<0.008	40.4	<0.020	15.1	<0.003
Total extractable	91.1	0.021	91.4	0.042	81.9	0.009
Unextractable[1]	8.9	0.002	8.6	0.004	18.1	0.002
Accountability[2]	100		100		100	

[1] Residues remaining after exhaustive extractions (including base hydrolysis of stover).
[2] Accountability = (Total extractable + Total unextractable); TRR determined by summing extractable and nonextractable fractions.

TABLE C.2.3.3. Summary of Characterization and Identification of Radioactive Residues in Immature Corn Plants Following Application of [Phenyl-U-^{14}C]Tembotrione at 0.181 lb ai/A.

Compound	Whole Plant, 0 DAT		Whole Plant, 14 DAT		Whole Plant, 49 DAT	
	TRR = 53.747 ppm		TRR = 3.785 ppm		TRR = 0.053 ppm	
	% TRR	*ppm*	% TRR	*ppm*	% TRR	ppm
Tembotrione	42.8	23.025	0.7	0.027	0.6	<0.001
AE 1444744 (M10)	30.1	16.199	0.2	0.009	1.2	<0.001
AE 1417268 (M5)	12.1	6.474	64.4	2.438	11.1	0.006
AE 0456148 (M6)	4.4	2.350	7.6	0.289	65.3	0.034
AE 1392936 (M2)	--	--	0.8	0.028	7.3	0.004
Very polar fraction (peaks + region)	1.3	0.715	7.9	0.299	2.4	<0.002
Polar fraction (peaks + region)	1.5	0.822	5.5	0.210	6.3	0.003
Medium polar fraction (peaks + region)	5.7	3.095	4.9	0.184	2.8	<0.002
Total identified	89.4	48.048	73.7	2.791	85.5	<0.045
Total characterized	8.5	4.632	18.3	0.693	11.5	<0.007
Total extractable	98.0	52.681	92.1	3.484	96.9	0.051
Unextractable[1]	2.0	1.066	7.9	0.300	3.1	0.002
Accountability[2]	100		100		100	

[1] Residues remaining after exhaustive extractions.
[2] Accountability = (Total extractable + Total unextractable); TRR determined by summing extractable and nonextractable fractions.

TABLE C.2.3.4. Summary of Characterization and Identification of Radioactive Residues in Corn Forage, Stover, and Grain Following Application of [Phenyl-U-^{14}C]Tembotrione at 0.181 lb ai/A.

Compound	Forage, 84 DAT		Stover, 124 DAT		Grain, 124 DAT	
	TRR = 0.066 ppm		TRR = 0.124 ppm		TRR = 0.029 ppm	
	% TRR	ppm	% TRR	ppm	% TRR	ppm
AE 1417268 (M5)	9.8	0.006	5.5	0.007	0.9	*<0.001*
AE 0456148 (M6)	40.9	0.027	39.6	0.049	59.5	0.017
AE 1392936 (M2)	10.2	0.007	11.6	0.014	0.3	<0.001
Very polar fractions (peaks + regions)	14.2	0.009	11.0	0.014	3.7	0.001
Polar fractions (peaks + regions)	9.9	0.006	6.4	0.008	5.8	0.002
Medium polar fractions (peaks + regions)	7.5	0.005	4.6	0.005	--	--
Base hydrolysate	--	--	13.0	0.016	--	--
Total identified	60.9	0.040	56.7	0.070	60.7	<0.018
Total characterized	31.6	0.020	35.0	0.043	9.5	0.003
Total extractable	92.5	0.061	91.7	0.114	87.7	0.025
Unextractable[1]	7.5	0.005	7.6	0.009	12.3	0.004
Accountability[2]	100		99.3		100	

[1] Residues remaining after exhaustive extractions (including base hydrolysis of stover).
[2] Accountability = (Total extractable + Total unextractable); TRR determined by summing extractable and nonextractable fractions.

C.3. Proposed Metabolic Profile

Based on the PH-labeled corn metabolism study, tembotrione is metabolized in corn by hydroxylation of the cyclohexyl moiety to form the monohydroxy (AE 1444744) and dihydroxy

(AE 1417268) metabolite, followed by cleavage to the benzoic acid derivative (AE 0456148). Formation of metabolite AE 0456148 directly from the parent herbicide could not be ruled out. The metabolite AE 1392936 is formed by the subsequent cleavage of the trifluoroethoxy ether bond of AE 0456148.

FIGURE C.3.1. Proposed Metabolic Profile of Tembotrione in Corn

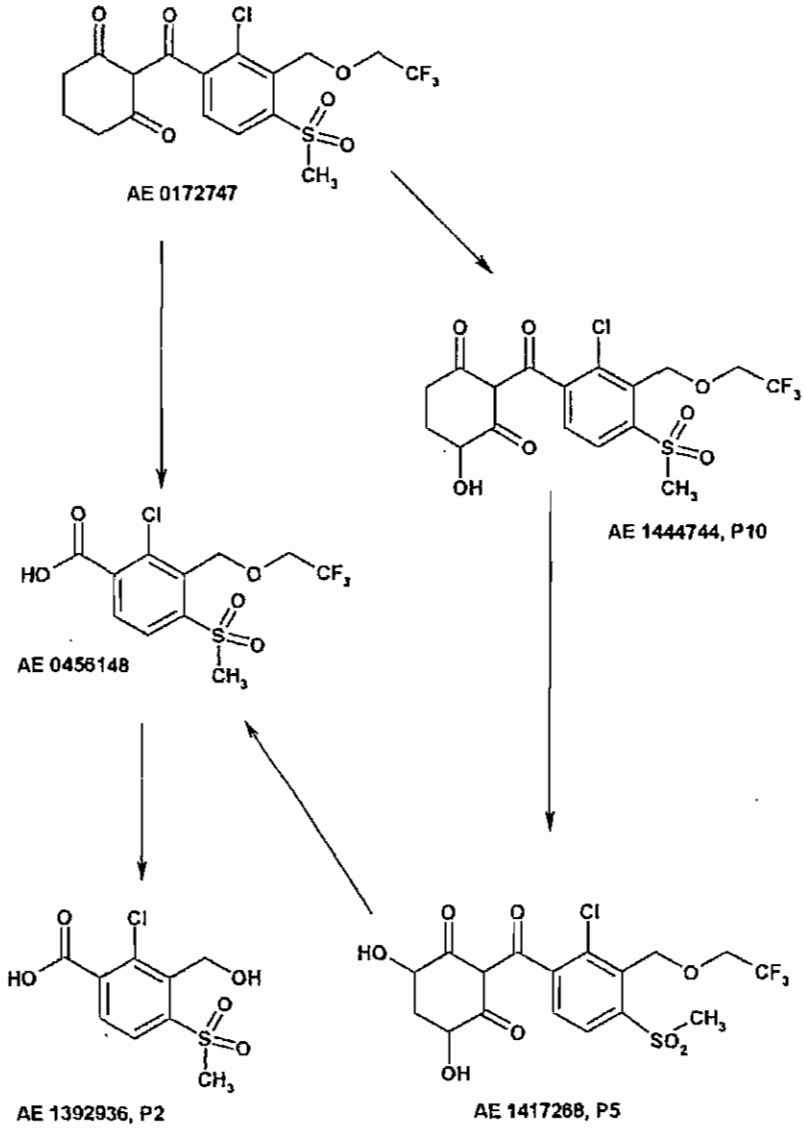
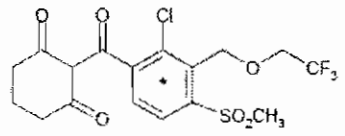
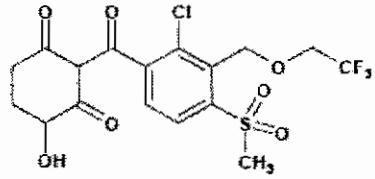
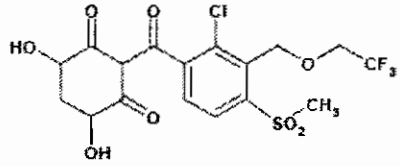
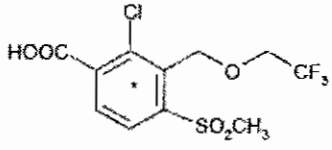
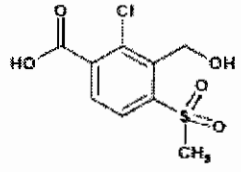


TABLE C.3.1. Identification of Compounds from Metabolism Study

Common name/code	Chemical name	Chemical structure
Tembotrione[1] (parent)	2-[2-Chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione	
AE 1444744 (M10)[1]	2-[2-Chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-4-hydroxy-1,3-cyclohexanedione	
AE 1417268 (M5)	2-[2-Chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-4,6-dihydroxy-1,3-cyclohexanedione	
AE 0456148 (M6)	2-Chloro-4-mesyl-3-[(2,2,2-trifluoroethoxy)methyl]benzoic acid	
AE 1392936 (M2)	2-Chloro-3-hydroxymethyl-4-mesyl-benzoic acid	

[1] Only identified in early immature corn plants.

D. CONCLUSION

Following foliar application of PH-labeled tembotrione at 0.103 lb ai/A, TRR were 16.389, 1.516, and 0.013 ppm in immature corn plants harvested 0, 14, and 49 DAT, respectively, and TRR were 0.023 ppm in forage, 0.046 ppm in stover, and 0.011 ppm in grain. Following foliar application of PH-labeled tembotrione at 0.181 lb ai/A, TRR were 53.747, 3.785, and 0.053 ppm in immature corn plants harvested 0, 14, and 49 DAT, respectively, and TRR were 0.066 ppm in forage, 0.124 ppm in stover, and 0.029 ppm in grain.

Plants collected at 0 and 14 DAT were rinsed with ACN/water before homogenization. Rinsed plants and remaining matrices were extracted with ACN/water. Nonextractable residues in stover were subjected to acid or base hydrolysis to release additional residues.

These procedures adequately extracted the majority of the residues from corn matrices. Because TRR were determined by summing extractable and nonextractable radioactivity, accountabilities were ~100%.

Residues were identified and quantitated by HPLC and confirmed by TLC. HPLC/MS, HPLC/MS/MS, and NMR analyses were also used for structure elucidation and identification/confirmation of metabolites. Adequate storage stability data were submitted to support the storage intervals and conditions of samples of immature plants and forage from the study. No additional storage stability data are required because all samples were stored for <6 months prior to initial analysis.

No residues of the parent, tembotrione, were found in corn forage, stover, or grain samples. Metabolite AE 0456148 was identified as the major residue in forage, stover, and grain, at 33.1-59.5% TRR. Other identified residues included AE 1392936 at ~10% TRR in forage, and 126% TRR in stover; and AE 1417268 at ~9-10% TRR in forage, and 6% TRR in stover. Residues of AE 1392936 and AE 1417268 were identified at ≤1.0 % TRR in corn grain. The remaining solvent-extractable residues in forage, stover, and grain, accounting for ~10-40% TRR, were characterized by the polarity of the residue according to its behavior on HPLC.

The parent herbicide, tembotrione, was identified in early immature plants, decreasing from ~27-43% TRR in 0-DAT samples to <0.6% TRR in 49-DAT samples. The metabolite AE 1444744 was also only identified in immature corn plants, decreasing from ~28-30% TRR in 0-DAT samples to ≤1.2% TRR in 49-DAT samples. Metabolite AE 1417268 was the major residue identified in 14-DAT plants at 64-66% TRR, and was also a significant residue in 0-DAT plants (12-24% TRR) and 49-DAT plants (11-14% TRR). Metabolite AE 0456148 (the major residue in forage and mature matrices) increased in immature plants with later sampling intervals (≤7% TRR at 0 DAT to 60-65% TRR at 49 DAT). Residues of AE 1392936 also increased in immature plants with later sampling intervals (<0.1% TRR at 0 DAT to <8% TRR at 49 DAT).

Based on the PH-labeled corn metabolism study, tembotrione is metabolized in corn by hydroxylation of the cyclohexyl moiety to form the monohydroxy (AE1444744) and dihydroxy (AE 1417268) metabolite, followed by cleavage to the benzoic acid derivative (AE 0456148). Formation of AE 0456148 directly from the parent herbicide could not be ruled out. The metabolite AE 1392936 is formed by the subsequent cleavage of the trifluoroethoxy ether bond of AE 0456148.

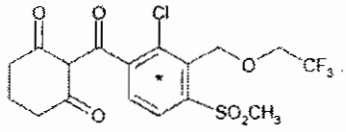
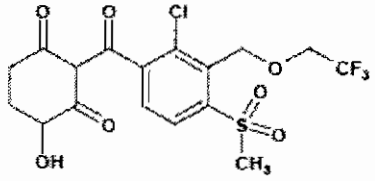
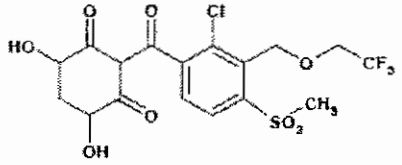
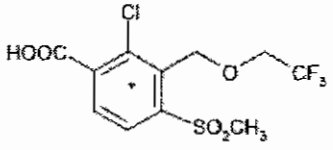
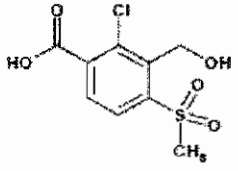
The submitted study is acceptable and successfully delineates the amount and distribution of TRR in corn tissues.

E. REFERENCES

None.

F. DOCUMENT TRACKING

RDI: RAB1 Chemists (12/6/06)
Petition Number: PP#5F7009
DP#s: 325349, 325663, and 331222
PC Code: 012801
Template Version June 2005

APPENDIX I. Chemical Names and Structures of Reference Standards Used in Corn Metabolism Study.		
Common name; Company code	Chemical name	Chemical structure
Tembotrione (P11)[1] (parent)	2-[2-Chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione	
AE 1444744 (P10) (M10) [2]	2-[2-Chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-4-hydroxy-1,3-cyclohexanedione	
AE 1417268 (P5) (M5)	2-[2-Chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-4,6-dihydroxy-1,3-cyclohexanedione	
AE 0456148 (P6) (M6) [1]	2-Chloro-4-mesyl-3-[(2,2,2-trifluoroethoxy)methyl]benzoic acid	
AE 1392936 (P2) (M2)	2-Chloro-3-hydroxymethyl-4-mesyl-benzoic acid	

[1] Radiolabeled and non-labeled standards were used.
[2] Isolated from cell culture experiment.

Tembotrione/AE 0172747/PC Code 012801/Bayer CropScience/264
DACO 6.2/OPPTS 860.1300/OECD II 6.2.2, 6.2.3 & IIIA 8.2, 8.4.1, 8.4.2
Nature of the Residues in Livestock - Poultry

Primary Evaluator	George F. Kramer, Ph.D., Senior Chemist Registration Action Branch (RAB1) Health Effects Division (HED) (7509P)	Date: 18-JUL-2007
Approved by	P.V. Shah P.V. Shah, Ph.D., Branch Senior Scientist RAB1/HED (7509P)	Date: 18-JUL-2007

This DER was originally prepared under contract by Dynamac Corporation (2275 Research Boulevard, Suite 300; Rockville, MD 20850; submitted 11/10/2006). The DER has been reviewed by HED and revised to reflect current Office of Pesticide Programs (OPP) policies.

STUDY REPORT:

46695534 Needham, D.; Swalwell, L.; Fisher, P. (2003) [Phenyl-U-(Carbon 14)]-AE 0172747: Absorption, Distribution, Metabolism and Excretion Following Repeated Oral Administration to the Laying Hen: Final Report. Project Number: 2014/061, 2014/061/D1145, 36663. Unpublished study prepared by Bayer Cropscience. 186 p.

The petitioner has submitted an evaluation template for the study (Bayer CropScience DER to Study 2014-061), which was used to generate this DER; selected sections were copied without alteration or were modified to more specifically reflect the Agency's data evaluation requirements.

EXECUTIVE SUMMARY:

Bayer CropScience has submitted a study investigating the metabolism of [phenyl-U-^{14}C]tembotrione (PH label; specific activity 5.625 MBq/mg) in laying hens. The test substance was administered orally to groups of five hens at 1 ppm and 10 ppm in the diet. The actual doses, based on the average feed consumption during the experiment, were 1.31 and 11.33 ppm. The hens were dosed once daily for 14 consecutive days. Eggs were collected twice daily throughout the study, and tissues (muscle, fat, liver, and skin with attached fat) were collected at sacrifice, within ~24 hours of the final dose.

Total radioactive residues (TRR) following dosing at 1.31 ppm in the diet were below the limit of quantitation (<LOQ) to 0.0003 ppm in egg whites, <LOQ-0.013 ppm in egg yolks, 0.011 ppm in muscle, 0.005 ppm in fat, 1.556 ppm in liver, and 0.065 ppm in skin with attached fat. TRR in hen matrices following dosing at 11.33 ppm were 0.001-0.003 ppm in egg whites, 0.001-0.106 ppm in egg yolks, 0.061 ppm in muscle, 0.043 ppm in fat, 2.099 ppm in liver, and 0.371 ppm in skin with attached fat. At both dose levels, TRR were highest in liver. TRR in egg whites were low at all time points, while TRR in egg yolks appeared to plateau after ~7 days of dosing (both dosing levels). The majority of the radioactivity (~89-92% of the administered dose) was excreted.

Metabolic profiling was conducted on tissues and egg yolk (Day 8) from the high-dose (11.33 ppm) hens. A second subsample of liver was also extracted using the same procedures to further investigate a metabolite. Solvent extraction with hexane, ethyl acetate, acetonitrile (ACN) and acidified ACN released ~82-104% of the TRR in muscle, fat, skin and egg yolk, and 54% and

95% TRR in the first and second liver subsamples, respectively. Hexane extracted only minor residues in all matrices except fat (3.7% TRR), ethyl acetate extracted the majority of residues in fat, skin, and egg yolk, and acetonitrile extracted the majority of residues for liver. Nonextractable residues following solvent extraction were 2.1-5.7% TRR (0.002-0.008 ppm) in muscle, fat, skin and egg yolk. Nonextractable residues in liver (both subsamples) were subjected to protease hydrolysis which released an additional 35% and 4% TRR from the first and second subsamples, respectively. Nonextractable residues of the first extraction sample were also subjected to acid hydrolysis which released an additional 1.5% TRR. Nonextractable residues in liver after exhaustive extractions were 2.6% TRR (0.055 ppm) and 0.4% TRR (0.008 ppm) in first and second subsamples, respectively.

The extraction procedures were adequate; and the accountabilities were 89-107%. Residues were identified and quantitated by high-performance liquid chromatography (HPLC) equipped with a flow-through radiodetector and confirmed by liquid chromatography/mass spectroscopy (LC/MS). Acceptable storage stability data, submitted in support of a hen metabolism study with cyclohexyl-labeled tembotrione (refer to 46695533.der.doc), are available to support the storage intervals and conditions of samples of liver from the current study. No additional storage stability data are required because all samples were stored frozen for <6 months prior to analysis.

The major and only residue identified was the parent, tembotrione, identified at 74.6% TRR (0.046 ppm) in muscle, 62.6% TRR (0.027 ppm) in fat, 82.6% TRR (1.730 ppm) in liver (first extraction), 97.1% TRR (2.037 ppm) in liver (second extraction), 81.7% TRR (0.303 ppm) in skin with attached fat, and 72.9% TRR (0.077 ppm) in egg yolk. The identity of the parent was confirmed by LC/MS analysis of the ethyl acetate extract (ACN/water phase) of skin and liver, the combined ACN extract of liver, and the ethyl acetate phase following protease hydrolysis of liver. Unknowns accounted for 0.7-5.3% TRR in egg yolk and tissues; no single unknown was present in any matrix at >2.6% TRR (0.043 ppm).

Based on the PH-labeled hen metabolism, tembotrione was not extensively metabolized by hens, with the major component in all tissues being parent compound. The similarity in the residue concentrations in liver at the two dose levels suggested that accumulation of tembotrione in liver was close to saturation at the low-dose level. The 10-fold increase in the dose level produced an increase of 5.7-8.9x in the radioactivity in all other matrices, and only a 1.3x increase in liver.

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the livestock metabolism data are classified as scientifically acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document [DP# 325349].

COMPLIANCE:

Signed and dated Good Laboratory Practice (GLP), Quality Assurance and Data Confidentiality statements were provided. No GLP deviations were reported which would impact the study results or their interpretation.

A. BACKGROUND INFORMATION

Tembotrione, a new herbicide with broad use against mono- and dicotyledons in selected crops such as corn, is a 4-hydroxyphenylpyruvate deoxygenase (HPPD) inhibitor (bleacher). The test compound nomenclature and physiochemical properties of the test compound are presented in Tables A.1 and A.2, respectively.

TABLE A.1. Test Compound Nomenclature for Tembotrione.

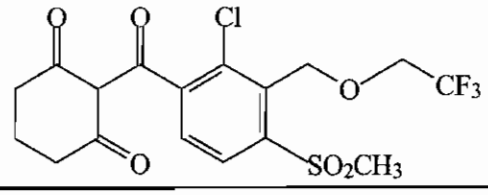
Compound: Tembotrione	Chemieal Structure 
Proposed common name	Tembotrione
Company experimental name	AE 0172747
IUPAC name	2-{2-chloro-4-mesyl-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl}cyclohexane-1,3-dione
CAS name	2-[2-chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione
CAS #	335104-84-2
End-use product/EP	AE 0172747 Herbicide, EPA Reg No. 264-xxx

TABLE A.2. Physicochemical Properties of Technical Grade Tembotrione.

Parameter	Value	Reference (MRID#)
Melting point	117 °C	46695402
pH @ 24 °C	3.63	
Density (g/mL @ 20 °C)	1.56	
Water solubility (mg/L @ 20 °C)	0.22 at pH4 28.3 at pH 7 29.7 at pH 9	
Solvent solubility (g/L at 20 °C) DMSO Methylene Chloride Acetone Ethyl Aeetate Toluene Hexane Ethanol	 >600 >600 300-600 180.2 75.7 47.6 8.2	
Vapor pressure (Torr, 20 °C)	8.25×10^{-11}	
Dissociation constant (pK_a)	3.2	
Octanol/water partition coefficient (P_{ow} @ 23 °C) (P_{ow} @ 24 °C) (P_{ow} @ 23 °C)	 0.0430 at pH 9.0 0.0807 at pH 7.0 144.9 at pH 2.0	
UV/visible absorption spectrum (nm)	Primary: 205 Secondary: 284 Tertiary: 240	

B. EXPERIMENTAL DESIGN

Two groups of five hens were orally dosed with PH-labeled tembotrione for 14 consecutive days. One group was dosed at a nominal rate of 1 ppm in the diet, and the other group was dosed at a nominal rate of 10 ppm in the diet. Upon receipt, hens were group housed for acclimatization. Hens were then placed in individual cages and acclimatized for 4 days prior to dosing. Hens were fed a commercial feed concentrate and grit, and feed consumption was recorded daily. Hens were dosed once daily in the morning. Information pertaining to the test animals and dietary and dosing regimes is presented in Tables B.1.1 - B.1.3.

B.1. Livestock

TABLE B.1.1. General Test Animal Information.

Animal Numbers	Species	Breed	Age weeks	Weight at study initiation (kg)	Health Status	Description of housing/holding area
Group A 101F 102F 103F 104F 105F	Laying hens (*Gallus gallus*)	Lohmann	19-22	1.561-1.772	Good	Individual metabolism cages in unit controlled at 19-24 °C, 56-88% RH, 16-hr fluorescent light/day, 10 air exchanges/hr.
Group B 201F 202F 203F 204F 205F				1.521-1.823		

TABLE B.1.2. Test Animal Dietary Regime.

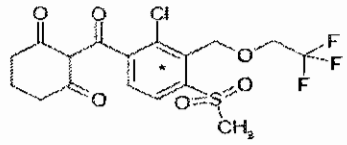
Animal Number	Composition of Diet	Feed consumption (kg/day), average	Water	Acclimation period	Predosing
Group A	Ground concentrate (507 P.H.L. Meal) plus grit at 0.15 kg/day (target)	0.131 kg/day	*Ad libitum*	15 days	None
Group B		0.133 kg/day			

TABLE B.1.3. Test Animal Dosing Regime.

Animal Number	Treatment Type	Feeding Level (ppm test material in food)	Vehicle	Timing/Duration
Low dose (Group A)	Oral	1 ppm nominal (1.31 ppm actual)	Gelatin capsule containing cellulose	Once a day in the morning for 14 days
High Dose (Group B)		10 ppm nominal (11.33 ppm actual)		

B.2. Test Materials

The radiolabeled test substance was dissolved in ACN and isotopically diluted with nonlabeled tembotrione, then prepared in gelatin capsules for dosing. The test material characteristics are presented in Table B.2.1.

TABLE B.2.1. Test Material Characteristics, Radiolabeled.	
Chemical structure	
Radiolabel position	[phenyl-U-^{14}C]AE 0172474
Lot No.	Z 32034-0
Purity	99.94% (by HPLC)
Specific activity (Bq)[1]	5.625 MBq/mg

[1] Bq = disintegrations per second

B.3. Sampling Information

Excreta and cage debris were collected daily, and eggs were collected twice daily. At 23-24 hours after the last dose, the hens were sacrificed, and samples of blood and tissues were collected.

TABLE B.3.1. Sample Collection Information.			
Eggs collected	Excreta and cage wash collected	Interval from last dose to sacrifice	Tissues harvested and analyzed
Twice daily, predosing in the a.m., and in the afternoon following dose administration; average egg production was 85-90% during the acclimation period and 100-103% during the dosing phase.[1]	Once daily	23-24 hours	Muscle (breast and thigh), fat (perirenal and peritoneal), liver, and skin with subcutaneous fat

[1] 100% = one egg produced within a 24-hour interval.

B.4. Identification/Characterization of Residues

B.4.1. Sample Handling and Preparation

Eggs were pooled daily for each hen; afternoon eggs were stored at 1-10 °C until pooled with the following morning sample. Daily pooled eggs were separated into egg whites and yolks. All samples were homogenized and subsampled on the day of collection prior to storage. All egg (whites and yolks) and tissue samples were stored at <-10 °C. The in-life and analytical phases of the study were conducted at the same facility (Covance Laboratories, Ltd., Harrogate, England); therefore, samples were not shipped.

Egg whites were not extracted because of the very low TRR. Pooled tissues and Day 8 egg yolk from high-dose hens were subjected to sequential solvent extraction with hexane, ethyl acetate, ACN, and acidified ACN (1% formic acid). Each fraction was collected following centrifugation. The ethyl acetate extracts were concentrated to near dryness, re-suspended in ACN:water (1:1, v:v), and centrifuged, and the residual pellet was resuspended in methanol. The resulting ACN/water and methanol phases were reserved for HPLC analysis. The ACN and acidified ACN phases were not further investigated for muscle and fat, and the acidified ACN phase was not further investigated for skin. For liver and egg yolk, these phases were combined. The resulting combined ACN or ACN phases were concentrated and transferred for

centrifugation; the flask was rinsed with hexane. The resulting ACN extracts were diluted with water and reserved for HPLC analysis. A second subsample of liver was extracted to generate a sufficient quantity of a metabolite (Rt = 21.8 min) for HPLC/MS analysis.

The nonextractable residues of liver (both subsamples) were subjected to enzyme hydrolysis with protease (in 0.1 M phosphate buffer, pH 7.5, for ~20.5 hours at 37 °C). Residues were then extracted sequentially with ethyl acetate and ACN. The resulting ethyl acetate and ACN extracts were concentrated, rinsed with methanol, and re-suspended in ACN. The re-suspended extracts were reduced, diluted with water, and filtered for HPLC analysis.

The nonextractable residues in liver (first subsample) remaining after protease hydrolysis were subjected to acid hydrolysis (0.1 N HCl at reflux for 1 hour), and then extracted with ethyl acetate. After centrifugation, the ethyl acetate and aqueous phases of the supernatant were collected. The ethyl acetate phase was reduced to near dryness, re-suspended in ACN, reduced again, and diluted with ACN/water for HPLC analysis.

The extraction scheme for liver, which is representative for all tissues, is presented in Figure B.4.1.1, and the protease hydrolysis procedures for liver is presented in Figure B.4.1.2. These figures were copied without alteration from MRID 46695534.

FIGURE B.4.1.1. Extraction Scheme for Liver.

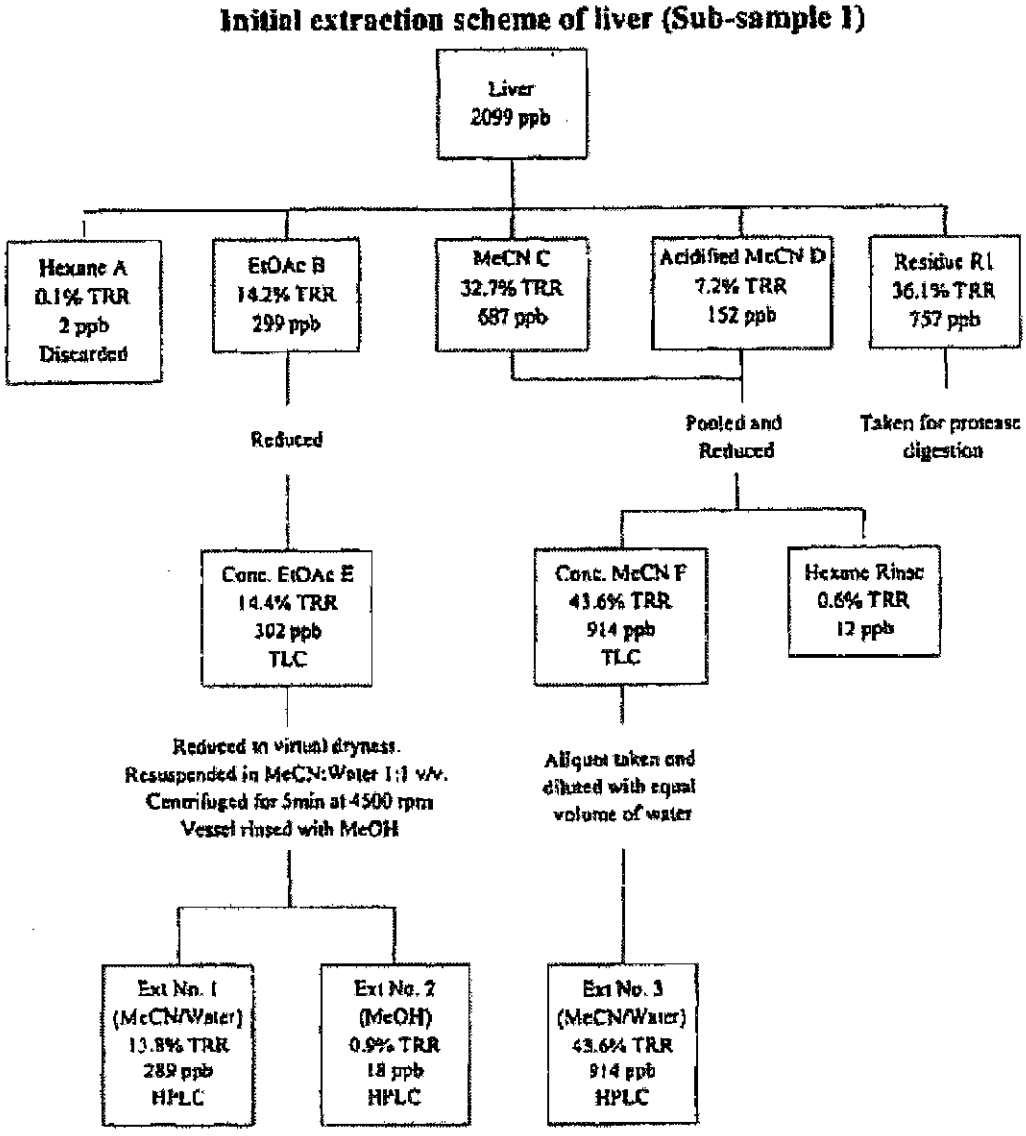
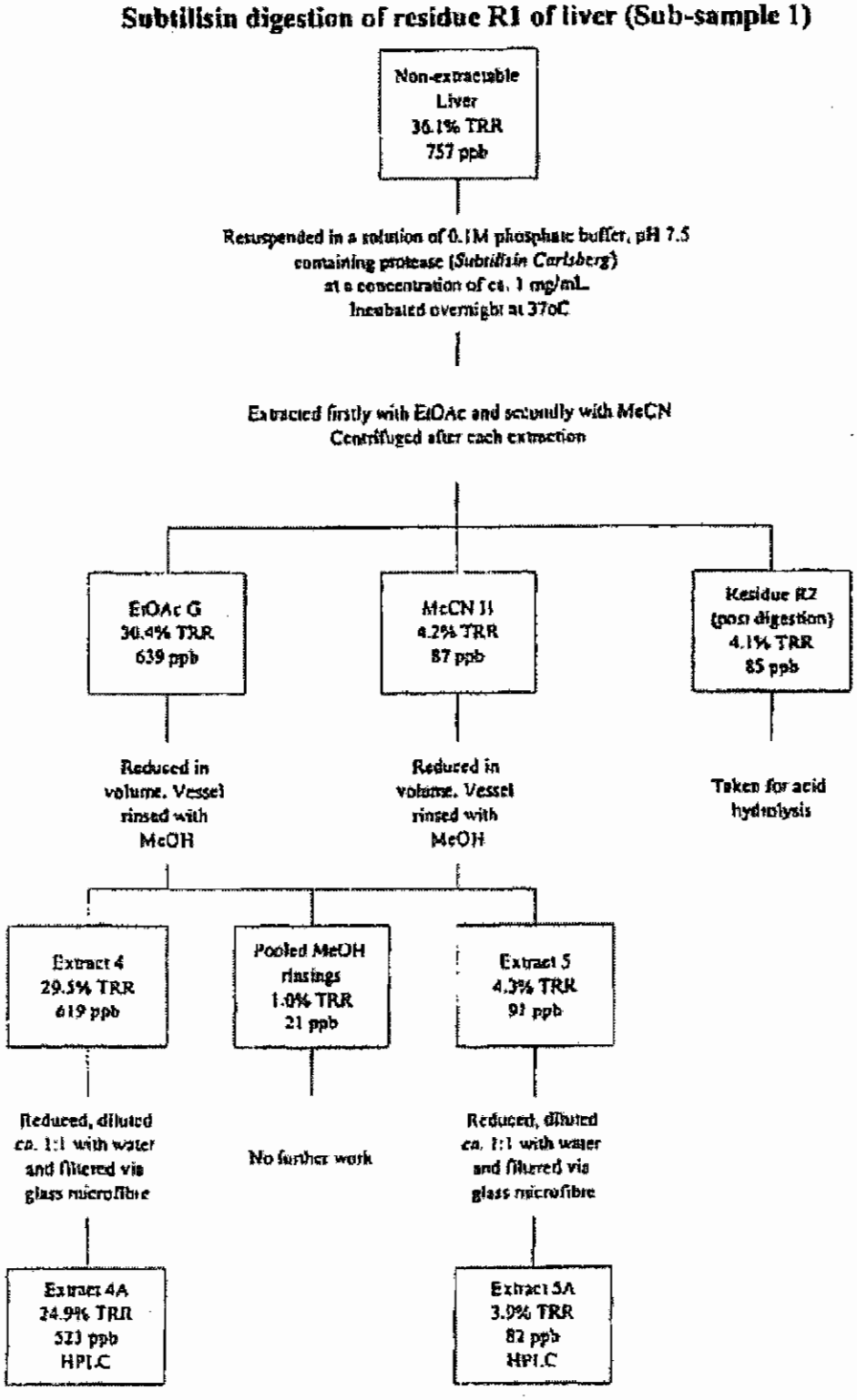


FIGURE B.4.1.2. Protease Hydrolysis of Nonextractable Residues of Liver.



B.4.2. Analytical Methodology

TRR were determined by liquid-scintillation counting (LSC), either directly or following solubilization or combustion. Radioactivity in extracts and hydrolysates was determined by direct LSC, and nonextractable radioactivity was determined by combustion/LSC. Extracts containing sufficient radioactivity were processed further for chromatographic analysis. The LOQ for TRR determinations was defined as 2x background.

Extracts of egg yolk and tissues were analyzed by reverse-phase HPLC, using a system equipped with a C18 column, a UV detector at 254 nm, and a flow-through radiodetector. A gradient mobile phase of water adjusted to pH 2 with trifluoroacetic acid:ACN was used. Residues were identified by retention time comparison with a non-labeled reference standard of tembotrione.

Residue identification was confirmed by HPLC/MS. A quadrupole ion-trap mass spectrometer with electrospray LC/MS interface was coupled to a gradient HPLC system with conditions as defined above. Positive/negative-ion electrospray mass-spectrometric analysis was carried out with a capillary temperature of 140 °C, a capillary voltage of 33/-18 V and a spray voltage of 2.5/2 kV. The scan range was *m/z* 120 to 700.

C. RESULTS AND DISCUSSION

The storage conditions and intervals for hen matrices are presented in Table C.1. The petitioner did not provide the dates of sample extraction and analysis but stated that profiling of tissues, with the exception of liver, was completed within 6 months of animal necropsy. Dated chromatograms and spectra reflecting confirmatory analysis for identification of tembotrione were included in the submission indicating that HPLC/MS analyses for liver and skin were conducted within 5.6 months of sacrifice. In support of the storage intervals and conditions of the submitted study, the petitioner referenced a hen metabolism study with cyclohexyl-labeled tembotrione (46695533.der.doc) in which residues in liver were found to be relatively stable for up to 7.8 months. No additional storage stability data are required because it appears that all samples were stored frozen for <6 months prior to analysis. The petitioner should note for future submissions that the critical study dates are required for each sample.

TRR in laying hen eggs and tissues are presented in Table C.2.1. Following oral dosing with PH-labeled tembotrione for 14 days at 1.31 ppm in the diet, TRR were <LOQ-0.0003 ppm in egg whites, <LOQ-0.013 ppm in egg yolks, 0.011 ppm in muscle, 0.005 ppm in fat, 1.556 ppm in liver, and 0.065 ppm in skin with attached fat. TRR in hen matrices following dosing at 11.33 ppm were 0.001-0.003 ppm in egg whites, 0.001-0.106 ppm in egg yolks, 0.061 ppm in muscle, 0.043 ppm in fat, 2.099 ppm in liver, and 0.371 ppm in skin with attached fat. At both dose levels, TRR were highest in liver. TRR in egg whites were low at all time points, while TRR in egg yolks appeared to plateau after ~7 days of dosing (both dosing levels). The majority of the radioactivity (~89-92% of the administered dose) was excreted. The pharmacokinetics of tembotrione in excreta and eggs are presented graphically in Figures C.2.1-C.2.3.

Metabolic profiling was conducted on tissues and egg yolk (Day 8) from the high-dose (11.33 ppm) hens. The distribution of the radioactivity in laying hen matrices is presented in Table C.2.2. Solvent extraction with hexane, ethyl acetate, ACN and acidified ACN released ~82-104% of the TRR in muscle, fat, skin and egg yolk, and 54% and 95% TRR in the first and second liver subsamples, respectively. Hexane extracted only minor residues in all matrices except fat (3.7% TRR), ethyl acetate extracted the majority of residues in fat, skin, and egg yolk, and acetonitrile extracted the majority of residues for liver. Nonextractable residues following solvent extraction were 2.1-5.7% TRR (0.002-0.008 ppm) in muscle, fat, skin and egg yolk. Nonextractable residues in liver (both subsamples) were subjected to protease hydrolysis which released an additional 35% and 4% TRR from the first and second subsamples, respectively. Nonextractable residues of the first extraction sample were also subjected to acid hydrolysis which released an additional 1.5% TRR. Nonextractable residues in liver after exhaustive extractions were 2.6% TRR (0.055 ppm) and 0.4% TRR (0.008 ppm) in first and second subsamples, respectively. The extraction procedures were adequate; and the accountabilities were 89-107%. Residues were identified and quantitated by HPLC, and confirmed by LC/MS.

The characterization and identification of residues in hen egg yolk and tissues is summarized in Table C.2.3. The major and only residue identified was the parent, tembotrione. Tembotrione was identified at 74.6% TRR (0.046 ppm) in muscle, 62.6% TRR (0.027 ppm) in fat, 82.6% TRR (1.730 ppm) in liver (first extraction), 97.1% TRR (2.037 ppm) in liver (second extraction), 81.7% TRR (0.303 ppm) in skin with attached fat, and 72.9% TRR (0.077 ppm) in egg yolk. The identity of the parent was confirmed by LC/MS analysis of the ethyl acetate extract (ACN/water phase) of skin and liver, the combined ACN extract of liver, and the ethyl acetate phase following protease hydrolysis of liver.

Unknowns accounted for to 0.7-5.3% TRR in egg yolk and tissues; no single unknown was present in any matrix at >2.6% TRR (0.043 ppm). Based on retention time comparisons, at least seven discrete unknowns were observed in hen tissues and egg yolk. All seven were observed in the first liver subsample, two each were common to muscle and liver and fat and liver, and one was common to fat and liver.

Although the petitioner attempted further investigation of a liver metabolite (Rt = 21.8 min) via the second subsample extraction, unknowns were present at much lower levels in the second subsample, and the metabolite in question was not detected in the organic extracts or protease hydrolysate. In general, significantly higher levels of radioactivity were released from the second extraction of liver. The concentration of tembotrione increased in this subsample with a concomitant decrease in minor metabolites. The petitioner attributed the difference between the two liver extractions to the fact that the second extraction was carried out in a more continuous manner, whereas during the first extraction, the recovery during each stage was determined before proceeding to the next stage. It was also suggested that some of the minor analytes seen during the workup of the first extraction may have been artifacts of that methodology.

C.1. Storage Stability

All samples were homogenized and subsampled on the day of collection prior to storage; processed samples were stored at <-10 °C. The petitioner did not provide the dates of sample extraction and analysis, but stated that profiling of tissues was completed within 6 months of animal necropsy. Dated chromatograms and spectra reflecting confirmatory analysis for identification of tembotrione the organic extract and protease hydrolysate of liver (first subsample) and the organic extract of skin were included in the submission indicating that HPLC/MS analyses were conducted within ~170 days (5.6 months) of sacrifice.

In support of the storage intervals and conditions of the submitted study, the petitioner also referenced a hen metabolism study with cyclohexyl-labeled tembotrione (46695533.der.doc) in which residues in liver were found to be relatively stable for up to ~8 months.

TABLE C.1. Summary of Storage Conditions.

Matrix	Storage Temperature (°C)	Actual Storage Duration	Interval of Demonstrated Storage Stability
Liver and skin	<-10	170 days (5.6 months): HPLC/MS.	Metabolic profile unchanged in liver extracted and analyzed 237 days (7.8 months) after collection.
Muscle, fat, and egg yolk		No dates provided.	

Storage stability data from the cyclohexyl-labeled hen metabolism study (refer to 46695533.der.doc).

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

TABLE C.2.1. TRR in Egg, Tissue and Excreta.[1]

Matrix	Collection Timing	Low-dose hens (1.31 ppm)		High-dose hens (11.33 ppm)	
		% AD	ppm	% AD	ppm
Excreta	Daily; study duration	91.30	--	88.20	--
Cage wash	Daily; study duration	0.881	--	0.725	--
Total excreta		92.181	--	88.925	--
Egg, whites	Day 1	<0.001	<LOQ	<0.001	0.001
	Day 2	<0.001	<LOQ	<0.001	0.002
	Day 3	<0.001	0.0003	<0.001	0.003
	Day 4	<0.001	<LOQ	0.001	0.003
	Day 5	<0.001	<LOQ	<0.001	0.003
	Day 6	<0.001	<LOQ	<0.001	0.003
	Day 7	<0.001	<LOQ	<0.001	0.003
	Day 8	<0.001	<LOQ	<0.001	0.003
	Day 9	<0.001	<LOQ	<0.001	0.003
	Day 10	<0.001	<LOQ	<0.001	0.003
	Day 11	<0.001	<LOQ	<0.001	0.003
	Day 12	<0.001	<LOQ	<0.001	0.003
	Day 13	<0.001	0.0003	<0.001	0.003
	Day 14	<0.001	<LOQ	<0.001	0.003
	Total; duration of study	0.005	--	0.006	--
Egg, yolks	Day 1	<0.001	<LOQ	<0.001	0.001
	Day 2	<0.001	<LOQ	<0.001	0.007
	Day 3	0.001	0.002	0.001	0.022
	Day 4	0.002	0.003	0.003	0.050
	Day 5	0.003	0.007	0.005	0.076
	Day 6	0.004	0.009	0.004	0.082
	Day 7	0.007	0.010	0.006	0.083
	Day 8	0.003	0.010	0.006	0.105
	Day 9	0.011	0.012	0.006	0.104
	Day 10	0.007	0.013	0.008	0.106
	Day 11	0.005	0.012	0.006	0.093
	Day 12	0.007	0.013	0.005	0.089
	Day 13	0.007	0.013	0.007	0.100
	Day 14	0.007	0.013	0.005	0.083
	Total; duration of study	0.068	--	0.066	--
Muscle	Sacrifice	0.099	0.011	0.053	0.061
Fat		0.003	0.005	0.002	0.043
Liver		2.683	1.556	0.411	2.099
Skin with attached fat		0.032	0.065	0.026	0.371
Blood		0.001	0.078	<0.001	0.501
Sum of Administered Dose (%)		95.07	--	89.49	--

[1] Mean of the five hens in the group. The LOQ for LSC determinations was defined as 2x background.

FIGURES C.2.1-C.2.3. Pharmacokinetics of Tembotrione4 in Excreta and Egg of Laying Hens.

Figure C.2.1. Excreta: Cumulative Recovery of Radioactivity in the Excreta of Laying Hens Following 14 Daily Doses of AE 0172747-[phenyl-UL-^{14}C].

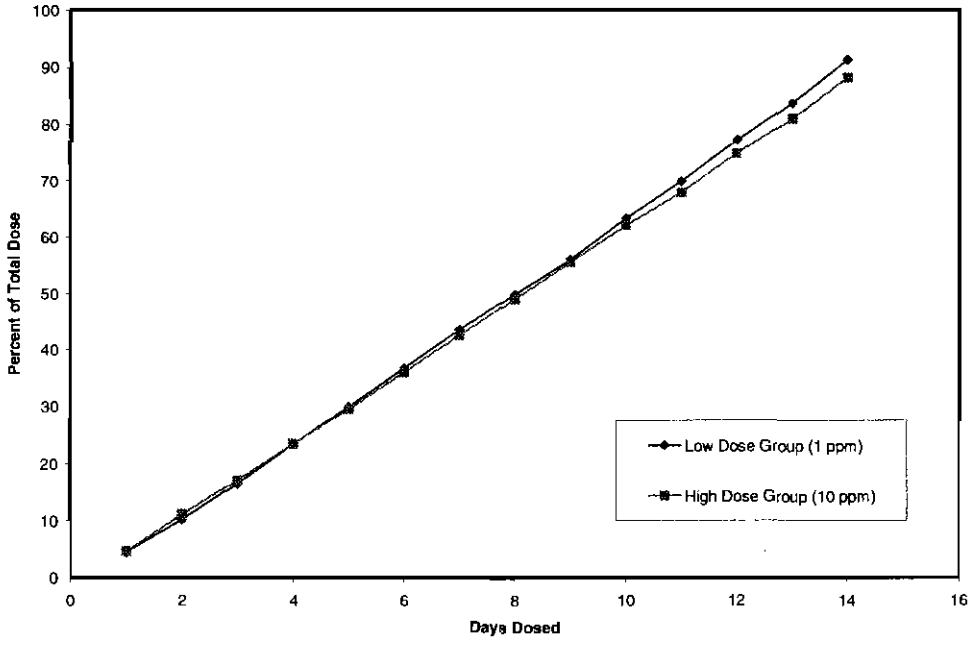


Figure C.2.2. Mean Concentrations of Radioactive Residues in Eggs of Laying Hens Following 14 Daily Oral Doses of AE 0172747-[phenyl-UL-^{14}C] at a Nominal Rate of 1 ppm in Diet

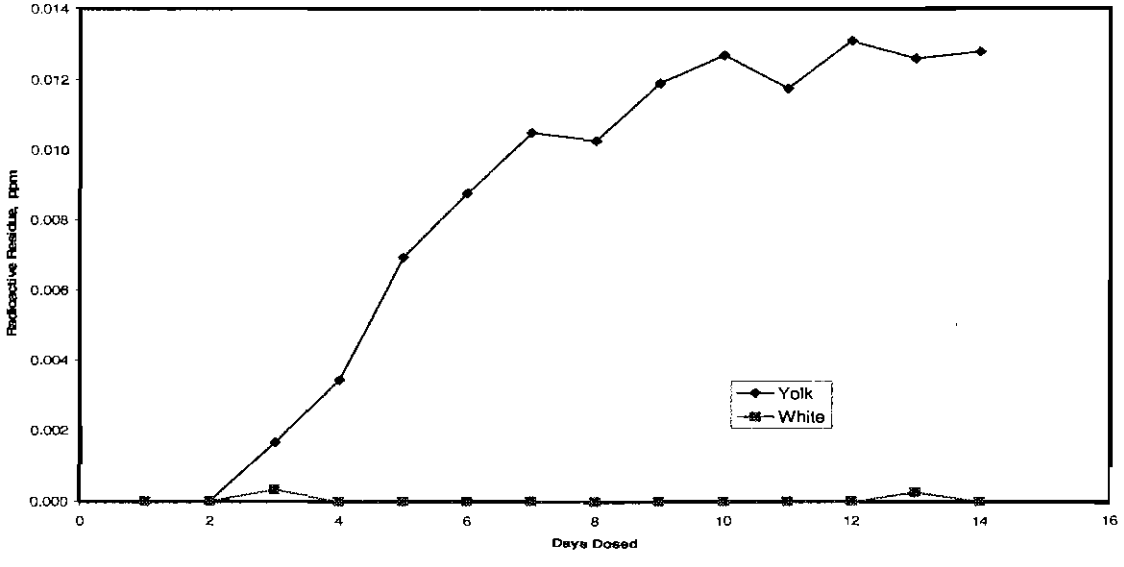


Figure C.2.3. Mean Concentrations of Radioactive Residues in Eggs of Laying Hens Following 14 Daily Oral Doses of AE 0172747-[phenyl-UL-^{14}C] at a Nominal Rate of 10 ppm in Diet

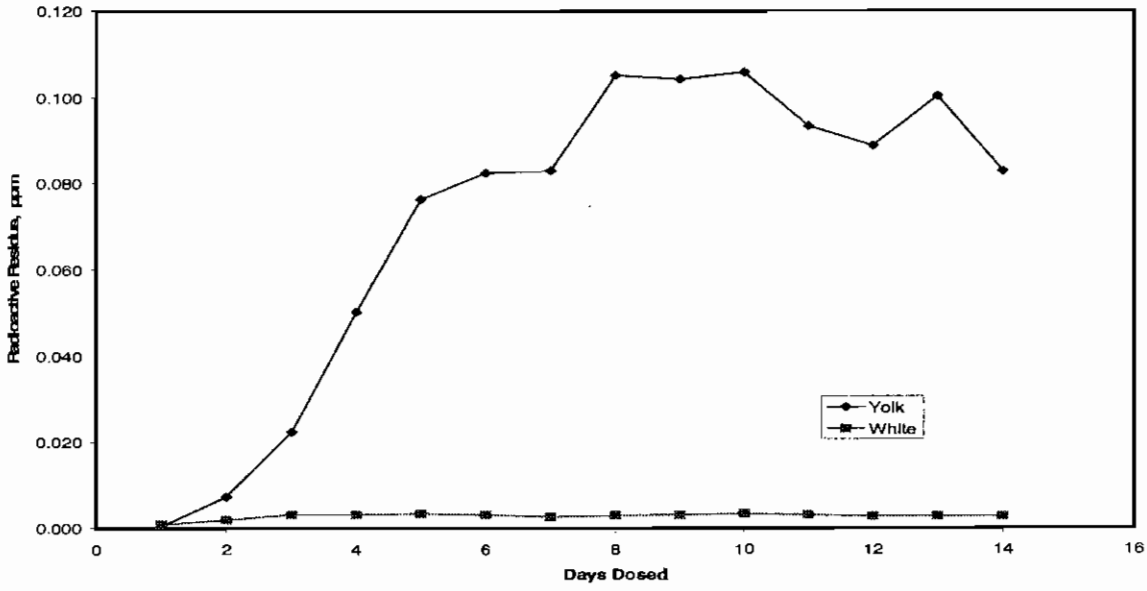


TABLE C.2.2. Distribution of the Parent and the Metabolites in Hen Matrices Following Administration of [phenyl-U-^{14}C]Tembotrione Once a Day for 14 Days at 11.33 ppm.[1]

Metabolite Fraction[2]	Muscle		Fat		Liver (first)		Liver (second)		Skin		Egg Yolk, Day 8	
	TRR=0.061 ppm		TRR=0.043 ppm		TRR=2.099 ppm		TRR=2.099 ppm		TRR=0.371 ppm		TRR=0.105 ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Hexane extract	0.6	<0.001	3.7	0.002	0.1	0.002	0.1	0.003	1.7	0.006	0.6	0.001
EtOAc extract	83.9	0.051	79.0	0.034	14.2	0.299	6.3	0.131	64.0	0.237	41.9	0.044
ACN/water phase	78.4	0.048	65.2	0.028	13.8	0.289	7.8	0.165	59.0	0.219	28.3	0.030
Tembotrione	74.6	0.046	62.6	0.027	13.6	0.285	7.8	0.163	59.0	0.219	27.7	0.029
Unknowns	3.8	0.002	2.6	0.001	0.2	0.004	<0.5	<0.001	--	--	0.6	0.001
Methanol rinse	2.7	0.002	3.3	0.001	0.9	0.018			2.1	0.008	10.1	0.011
Tembotrione					0.9	0.018					10.0	0.011
Unknowns					--	--					0.1	<0.001
ACN extract	15.3	0.009	3.4	0.001	32.7	0.687	68.3	1.434	22.2	0.082	29.5	0.031
Acidified ACN extraet	3.7	0.002	0.9	<0.001	7.2	0.152	20.2	0.425	2.3	0.008	10.0	0.011
Combined ACN [3]					NR	NR	NR	NR	NR	NR	NR	NR
ACN phase					43.6	0.914	86.7	1.820	22.7	0.084	35.2	0.037
Tembotrione					42.2	0.885	86.0	1.805	22.7	0.084	35.2	0.037
Unknowns					1.3	0.028	0.7	0.014	--	--	--	--
Hexane rinse					0.6	0.012			0.2	0.001	0.4	<0.001
Nonextractable	2.5	0.002	4.2	0.002	36.1	0.757	4.6	0.098	2.1	0.008	5.7	0.006
Protease EtOAc					30.4	0.639	3.3	0.070				
Conc. EtOAc					29.5	0.619	3.5	0.073				
Tembotrione					22.4	0.470	3.3	0.069				
Unknowns					2.6	0.053	<0.5	0.004				
Protease ACN					4.2	0.087	0.7	0.014				
Conc. ACN					4.3	0.091						
Tembotrione					3.2	0.067						
3 Unknowns					0.7	0.014						
Pooled MeOH[4]					1.0	0.021						
Protease Aqueous							0.2	0.003				
Nonextractable					4.1	0.085	0.4	0.008				
Acid EtOAc					1.0	0.021						
Tembotrione					0.25	0.005						
2 Unknowns					0.48	0.010						
Acid aqueous					0.5	0.010						
Nonextractable					2.6	0.055						

[1] Shading indicates that the extraction step and/or characterization analysis was not conducted (or is not applicable) for the matrix in question. NR = Not reported.

[2] The distribution of unknowns (based on Rt) by tissue follows: in muscle, 2 discrete unknowns, each ≤2.6% TRR (0.002 ppm); in fat, 1 unknown; in liver (first subsample), ≥7 discrete unknowns, each ≤2.6% TRR (0.043 ppm); in liver (second subsample), ≥4 discrete unknowns, each ≤0.5% TRR (0.011 ppm); and in egg yolk 1 unknown.

[3] Combined ACN + acidified ACN for all matrices except skin, where acidified ACN was not further investigated.

[4] Pooled methanol rinses of the concentrated ethyl acetate and ACN extracts.

TABLE C.2.3. Summary of Characterization and Identification of Radioactive Residues in Laying Hen Matrices Following Administration of [phenyl-U-^{14}C]Tembotrione Once a Day for 14 Days at 10 ppm.

Metabolite Fraction	Muscle		Fat		Liver (first)		Liver (second)		Skin		Egg Yolk, Day 8	
	TRR=0.061 ppm		TRR=0.043 ppm		TRR=2.099 ppm		TRR=2.099 ppm		TRR=0.371 ppm		TRR=0.105 ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Tembotrione	74.6	0.046	62.6	0.027	82.6	1.730	97.1	2.037	81.7	0.303	72.9	0.077
Unknowns[1]	3.8	0.002	2.6	0.001	5.3	0.109	0.9	0.018	--	--	0.7	0.001
Hexane soluble	0.6	<0.001	3.7	0.002	0.7	0.014	0.1	0.003	1.7	0.006	0.6	0.001
EtOAc: MeOH rinsate	2.7	0.002	3.3	0.001	--	--	--	--	2.1	0.008	--	--
ACN/acidified ACN	19.0	0.011	4.3	<0.002	--	--	--	--	--	--	--	--
Protease ACN	--	--	--	--	--	--	0.7	0.014	--	--	--	--
Protease MeOH	--	--	--	--	1.0	0.021	--	--	--	--	--	--
Protease aqueous	--	--	--	--	--	--	0.2	0.003	--	--	--	--
Acid aqueous	--	--	--	--	0.5	0.010	--	--	--	--	--	--
Total identified	74.6	0.046	62.6	0.027	82.6	1.730	97.1	2.037	81.7	0.303	72.9	0.077
Total characterized	26.1	<0.016	13.9	<0.006	7.5	0.154	1.9	0.038	4.0	0.015	1.7	0.002
Total extractable	103.5	0.063	87.0	0.037	90.3	1.897	99.1	2.080	90.2	0.333	82.0	0.087
Unextractable[2]	2.5	0.002	4.2	0.002	2.6	0.055	0.4	0.008	2.1	0.008	5.7	0.006
Accountability[3]	107		90.7		93.0		99.5		91.9		88.6	

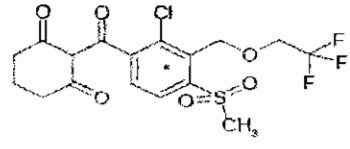
[1] Refer to Table C.2.4 for distribution of unknowns.
[2] Residues remaining after exhaustive extraetions.
[3] Accountability = (Total extractable + Total unextractable)/(TRR from eombustion analysis; see TABLE C.2.1) * 100.

C.3. Proposed Metabolic Profile

Based on the PH-labeled hen metabolism study, tembotrione was not extensively metabolized by hens, with the major component in all tissues being parent compound. The similarity in the residue concentrations in liver at the two dose levels suggested that accumulation of tembotrione in liver was close to saturation at the low-dose level. The 10-fold increase in the dose level produced an increase of 5.7-8.9x in the radioactivity in all other matrices, and only a 1.3x increase in liver.

Because the parent was the only analyte identified during this study, a metabolic scheme was not proposed.

TABLE C.3.1. Identification of Compounds from Metabolism Study

Common name/code	Chemical name (CAS)	Chemieal structure
Tembotrione (parent)	2-[2-Chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione	

D. CONCLUSION

Following oral dosing with PH-labeled tembotrione for 14 days at 1.31 ppm in the diet, were <LOQ-0.0003 ppm in egg whites, <LOQ-0.013 ppm in egg yolks, 0.011 ppm in muscle, 0.005 ppm in fat, 1.556 ppm in liver, and 0.065 ppm in skin with attached fat. TRR in hen matrices following dosing at 11.33 ppm were 0.001-0.003 ppm in egg whites, 0.001-0.106 ppm in egg yolks, 0.061 ppm in muscle, 0.043 ppm in fat, 2.099 ppm in liver, and 0.371 ppm in skin with attached fat. At both dose levels, radioactivity was highest in liver. Radioactivity in egg whites was low at all time points, while radioactivity in egg yolks appeared to plateau after ~6 days of dosing. The majority of the radioactivity (~89-92% of the administered dose) was excreted.

Metabolic profiling was conducted on tissues and egg yolk (Day 8) from the high-dose hens. Samples were subjected to sequential solvent extraction with hexane, ethyl acetate, ACN and acidified ACN. The nonextractable residues of liver were subjected to protease hydrolysis and acid hydrolysis, which released additional residues. These procedures adequately extracted the majority of residues from all hen matrices

The major and only residue identified was the parent, tembotrione. Tembotrione was identified at 74.6% TRR in muscle, 62.6% TRR in fat, 82.6% TRR in liver (first subsample), 97.1% TRR in liver (second subsample), 81.7% TRR in skin with attached fat, and 72.9% TRR in egg yolk. Unknowns accounted for to 0.7-5.3% TRR in egg yolk and tissues.

Based on the PH-labeled hen metabolism study, tembotrione was not extensively metabolized by hens. The submitted study is acceptable and successfully delineates the amount and distribution of TRR in poultry matrices following dosing with PH-labeled tembotrione.

E. REFERENCES

46695533 Hardwick, T.; Fisher, P. (2003) [Cyclohexyl-U-(Carbon 14)]-AE 0172747: Absorption, Distribution, Metabolism and Excretion Following. Project Number: 2014/060, 2014/060/D1145, 33420. Unpublished study prepared by Covance Laboratories, Ltd. 198 p.

F. DOCUMENT TRACKING

RDI: RAB1 Chemists (12/13/06)
Petition Number: PP#5F7009
DP#s: 325349, 325663, and 331222
PC Code: 012801

Template Version June 2005

Tembotrione/AE 0172747/PC Code 012801/Bayer CropScience/264
DACO 6.2/OPPTS 860.1300/OECD II 6.2.2, 6.2.3 & IIIA 8.2, 8.4.1, 8.4.2
Nature of the Residues in Livestock - Ruminant

Primary Evaluator	George F. Kramer, Ph.D., Senior Chemist Registration Action Branch (RAB1) Health Effects Division (HED) (7509P)	Date: 18-JUL-2007
Approved by	P.V. Shah, Ph.D., Branch Senior Scientist RAB1/HED (7509P)	Date: 18-JUL-2007

This DER was originally prepared under contract by Dynamac Corporation (2275 Research Boulevard, Suite 300; Rockville, MD 20850; submitted 11/10/2006). The DER has been reviewed by HED and revised to reflect current Office of Pesticide Programs (OPP) policies.

STUDY REPORT:

46695531 Hardwick, T.; Fisher, P. (2003) [Cyclohexyl-U-(Carbon 14)] - AE 0172747: Absorption, Distribution, Metabolism and Excretion Following Repeated Oral Administration to the Lactating Cow: Final Report. Project Number: 2014/059, 2014/059/D1145, 33421. Unpublished study prepared by Covance Laboratories, Ltd. 112 p.

The petitioner has submitted an evaluation template for the study (Bayer CropScience DER to Study 2014-059), which was used to generate this DER; selected sections were copied without alteration or were copied and modified to more specifically reflect the Agency's data evaluation requirements.

EXECUTIVE SUMMARY:

Bayer CropScience has submitted a study investigating the metabolism of [cyclohexyl-U-^{14}C]tembotrione (CY label; specific activity 6.279 MBq/mg) in lactating cows. The test substance was administered orally to two cows, one at 1 ppm and one at 10 ppm in the diet. The actual doses, based on feed consumption during the study, were 0.98 and 9.67 ppm. The cows were dosed two times daily for 7 consecutive days. Milk was collected twice daily throughout the study, and tissues (muscle, fat, liver, and kidney) were collected at sacrifice, 23.3 hours after the final dose.

Total radioactive residues (TRR) following dosing at 1 ppm were less than the limit of quantitation (<LOQ)-0.002 ppm in milk, <LOQ in muscle (fore and hindquarter) and omental fat, 0.011 ppm in renal fat, 0.550 ppm in kidney, and 2.730 ppm in liver. TRR following dosing at 10 ppm were 0.008-0.018 ppm in milk, <LOQ in forequarter muscle, 0.011 ppm in hindquarter muscle, 0.094 ppm in renal fat, 0.076 ppm in omental fat, 0.829 ppm in kidney, and 3.082 ppm in liver. Radioactivity was highest in liver and appeared to plateau in milk following 3 days of dosing. The majority of the radioactivity (~76-87% of the administered dose) was excreted.

Metabolic profiling was conducted on milk and tissues from the high-dose (10 ppm) cow. Solvent extraction with hexane, ethyl acetate, acetonitrile (ACN), and acidified ACN released ~41-47% of the TRR in milk (Day 5) and hindquarter muscle, and ~90-94% TRR in fat, kidney, and liver. Nonextractable residues following solvent extraction were 58.4% TRR (0.010 ppm) in

milk, 25.8% TRR (0.003 ppm) in muscle, 5.4% TRR (0.005 ppm) in fat, and 1.5% TRR (0.012 ppm) in kidney. Nonextractable residues in liver were subjected to protease digestion, which released an additional 2.3% TRR. A separate sample of kidney was subjected to protease digestion without prior solvent extraction, which released ~97% TRR. Nonextractable residues after exhaustive extractions were 0.7% and 1.8% TRR (≤0.02 ppm) in liver and kidney, respectively.

The extraction procedures were adequate; and the accountabilities were 82-106%. Residues were identified and quantitated by high-performance liquid chromatography (HPLC) and confirmed by liquid chromatography/mass spectroscopy (LC/MS). Adequate storage stability data were submitted to support the storage intervals and conditions of samples of liver from the study. No additional storage stability data are required because it appears that all samples were stored frozen for <6 months prior to initial analysis.

The major and only residue identified in milk and all tissues was the parent, tembotrione. Tembotrione was identified at 21.2% TRR (0.003 ppm) in milk, 45.4% TRR (0.005 ppm) in muscle, 82.5% TRR (0.070 ppm) in fat, 92.3% TRR (0.765 ppm) in kidney, and 92.8% TRR (2.859 ppm) in liver. A second metabolite, accounting for 3.4% TRR (0.106 ppm) in liver, was characterized by LC/MS, but no structure was elucidated. An unknown in milk, accounting for 13.8% TRR (0.002 ppm) and with a retention time similar to that of the liver unknown, was not further investigated.

Based on the CY-labeled cow metabolism study, tembotrione is not extensively metabolized in ruminants, with the major component in all tissues being parent compound.

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the livestock metabolism data are classified as scientifically acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document [DP# 325349].

COMPLIANCE:

Signed and dated Good Laboratory Practice (GLP), Quality Assurance and Data Confidentiality statements were provided. No GLP deviations were reported which would impact the study results or their interpretation.

A. BACKGROUND INFORMATION

Tembotrione, a new herbicide with broad use against mono- and dicotyledons in selected crops such as corn, is a 4-hydroxyphenylpyruvate deoxygenase (HPPD) inhibitor (bleacher). The test compound nomenclature and physiochemical properties of the test compound are presented in Tables A.1 and A.2, respectively.

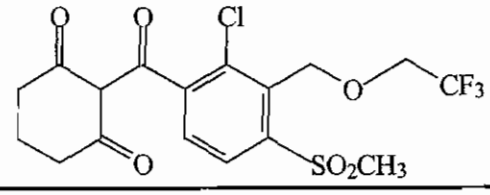
TABLE A.1. Test Compound Nomenclature for Tembotrione.	
Compound: Tembotrione	Chemical Structure 
Proposed common name	Tembotrione
Company experimental *name*	AE 0172747
IUPAC name	2-{2-chloro-4-mesyl-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl}cyclohexane-1,3-dione
CAS name	2-[2-chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione
CAS #	335104-84-2
End-use product/EP	AE 0172747 Herbicide, EPA Reg No. 264-xxx

***TABLE A.2. Physicochemical Properties* of Technical Grade Tembotrione.**		
Parameter	Value	Reference (MRID#)
Melting point	117 °C	46695402
pH @ 24 °C	3.63	
Density (g/mL @ 20 °C)	1.56	
Water solubility (mg/L @ 20 °C)	0.22 at pH4 28.3 at pH 7 29.7 at pH 9	
Solvent solubility (g/L at 20 °C) DMSO Methylene Chloride Acetone Ethyl Acetate Toluene Hexane Ethanol	 >600 >600 300-600 180.2 75.7 47.6 8.2	
Vapor pressure (Torr, 20 °C)	8.25×10^{-11}	
Dissociation constant (pK_a)	3.2	
Octanol/water partition coefficient (P_{ow} @ 23 °C) (P_{ow} @ 24 °C) (P_{ow} @ 23 °C)	 0.0430 at pH 9.0 0.0807 at pH 7.0 144.9 at pH 2.0	
UV/visible absorption spectrum (nm)	Primary: 205 Secondary: 284 Tertiary: 240	

B. EXPERIMENTAL DESIGN

Two lactating cows were dosed orally with CY-labeled tembotrione for 7 consecutive days. One cow was dosed at a nominal rate of 1 ppm in the diet, and the other was dosed at a nominal rate of 10 ppm in the diet. The cows were maintained in individual metabolism cages and were fed a commercial feed concentrate and hay twice daily at milking. The cows were dosed two times

daily following morning and afternoon milkings. Information pertaining to the test animals and the dietary and dosing regimes is presented in Tables B.1.1 - B.1.3.

B.1. Livestock

TABLE B.1.1. General Test Animal Information

Animal Number	Species	Breed	Age years	Weight at study initiation (kg)	Health Status	Description of housing/holding area
101F	Lactating cow (*Bos taurus*)	Holstein Friesian	3.5+	571	Good	Individual metabolism cages in unit controlled at 19-21°C, 56-83% RH, 16-hr fluorescent light/day, 10 air exchanges/hr.
201F				535		

TABLE B.1.2. Test Animal Dietary Regime

Animal Number	Composition of Diet	Feed consumption (kg/day), average	Water	Acclimation period	Predosing
101F	3 kg/2x/day 261-Kestrel Concentratc Hay twice a day Consumption measured	22.0	*Ad libitum*	7 days	None
201F		22.1			

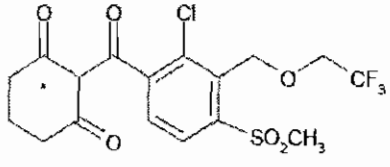
TABLE B.1.3. Test Animal Dosing Regime

Animal Number	Treatment Type	Feeding Level (ppm test material in food)	Vehicle	Timing/Duration
101F	Oral	1 ppm nominal (0.976 ppm actual)	gelatin capsule, using balling gun	Twice/day for 7 days; following morning and afternoon milkings
201F		10 ppm nominal (9.672 ppm actual)		

B.2. Test Materials

The radiolabeled test substance was dissolved in ACN, isotopically diluted with nonlabeled tembotrione, and prepared in gelatin capsules for dosing. The test material characteristics are presented in Table B.2.1.

TABLE B.2.1. Test Material Characteristics.

Chemical structure	
Radiolabel position	[cyclohexyl-U-^{14}C]tembotrione
Lot No.	Z 32015-1
Purity	97.4% (by HPLC)
Specific activity (Bq)[1]	6.279 MBq/mg

[1] Bq = disintegrations per second

B.3. Sampling Information

Cows were milked twice daily, and excreta were collected once daily. Cows were sacrificed ~23 hours after the last dosing, and tissues and blood were collected.

TABLE B.3.1. Sample Collection Information

Milk collected	Urine, feces and cage wash collected	Interval from last dose to sacrifice	Tissues harvested and analyzed
Twice daily prior to dose administration; average milk production was 16.9-17.8 kg/day during the acclimation period and 17.0-17.2 kg/day during the dosing period.	Once daily	23.3 hours	Muscle (hind and forequarter), fat (renal and omental), liver, and kidneys

B.4. Identification/Characterization of Residues

B.4.1. Sample Handling and Preparation

All samples were homogenized and subsampled on the day of collection prior to storage. All milk and tissue samples were stored at <-10 °C. The in-life and analytical phases of the study were conducted at the same facility (Covance Laboratories, Ltd., Harrogate, England); therefore, samples were not shipped. The following samples from the high-dose cows were subjected to extraction for characterization/identification of residues: Day 5 milk (combined a.m. and p.m. subsamples), hindquarter muscle, pooled omental and renal fat, kidney, and liver.

Milk and tissue samples were subjected to sequential solvent extraction with hexane, ACN, acidified ACN (1% formic acid), and/or ethyl acetate; the order of the solvent extractions varied slightly between tissues. Each fraction was collected following centrifugation. For fat and milk, the hexane extract was partitioned with ACN. In fat, three phases (hexane, ACN, and emulsion) resulted, while in milk the radioactivity remained in the hexane phase. For all tissues, the ACN and acidified ACN phases were combined and concentrated, and the ethyl acetate extracts were combined, if applicable, and concentrated. The concentrated ACN and ethyl acetate extracts for each tissue were then combined, concentrated to aqueous, and freeze-dried. The residues were reconstituted in ACN:water (1:1, v:v) and centrifuged to remove particulate matter prior to HPLC analysis.

The nonextractable residues of liver were subjected to enzyme hydrolysis with protease (in 0.1 M phosphate buffer, pH 7.5, overnight at 37 °C). Residues were then extracted sequentially with ethyl acetate and ACN. The ethyl acetate extract was reduced to dryness, rinsed with methanol, concentrated again, and diluted with water, then filtered for HPLC analysis.

A separate sample of the kidney homogenate was subjected to protease hydrolysis, as described above for liver nonextractable residues, without prior extraction. The ethyl acetate and ACN extracts were concentrated, rinsed with methanol, concentrated again, diluted with water, filtered and combined for HPLC analysis.

The extraction scheme for liver, which is representative of the procedures performed for milk and tissues, is presented in Figure B.4.1.1, and the protease hydrolysis procedures for liver and

kidney are presented in Figures B.4.1.2 and B.4.1.3, respectively. These figures were copied without alteration from MRID 46695531.

FIGURE B.4.1.1. Extraction Scheme for Milk and Tissues.

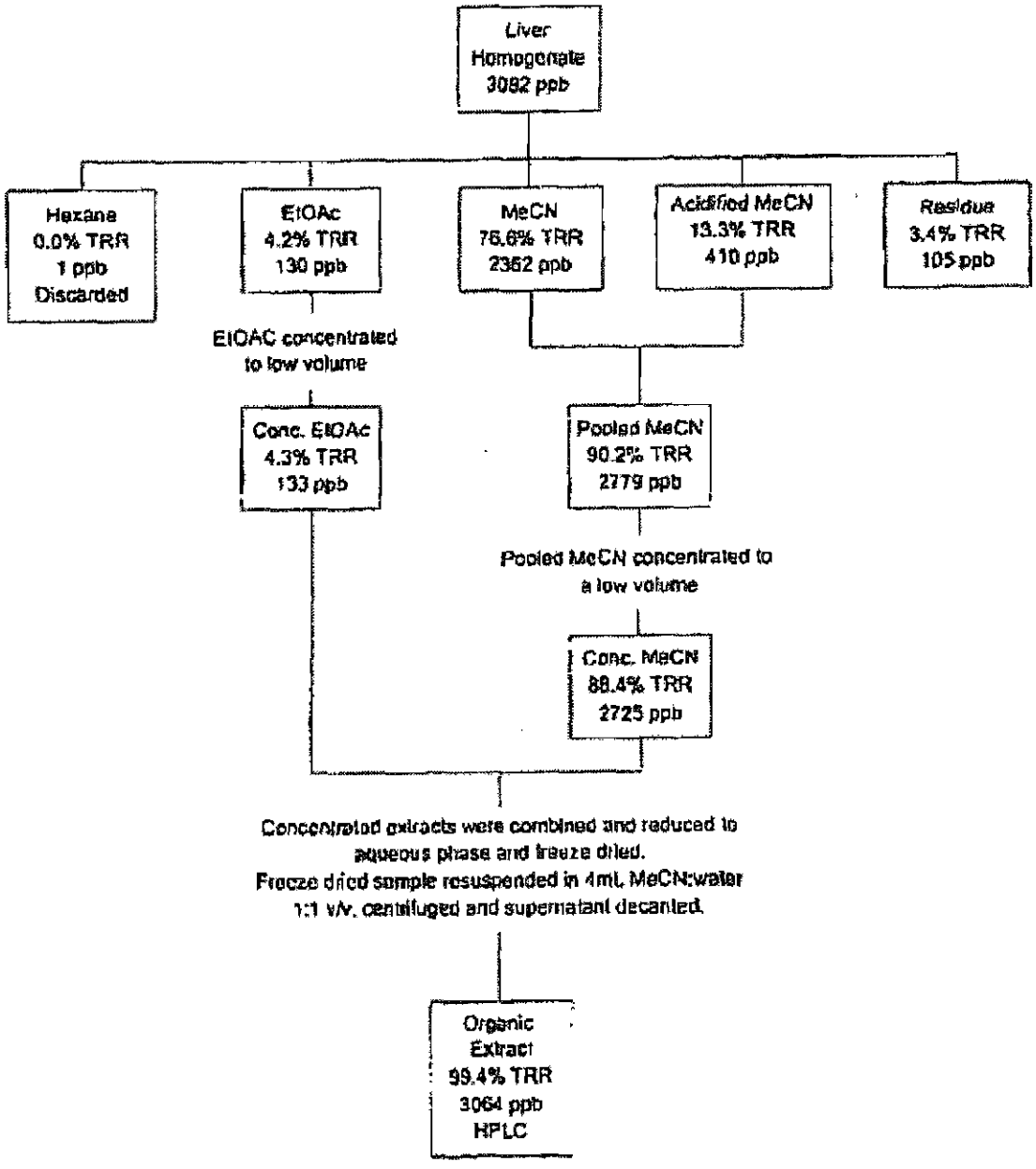


FIGURE B.4.1.2. Protease Hydrolysis of Nonextractable Residues of Liver.

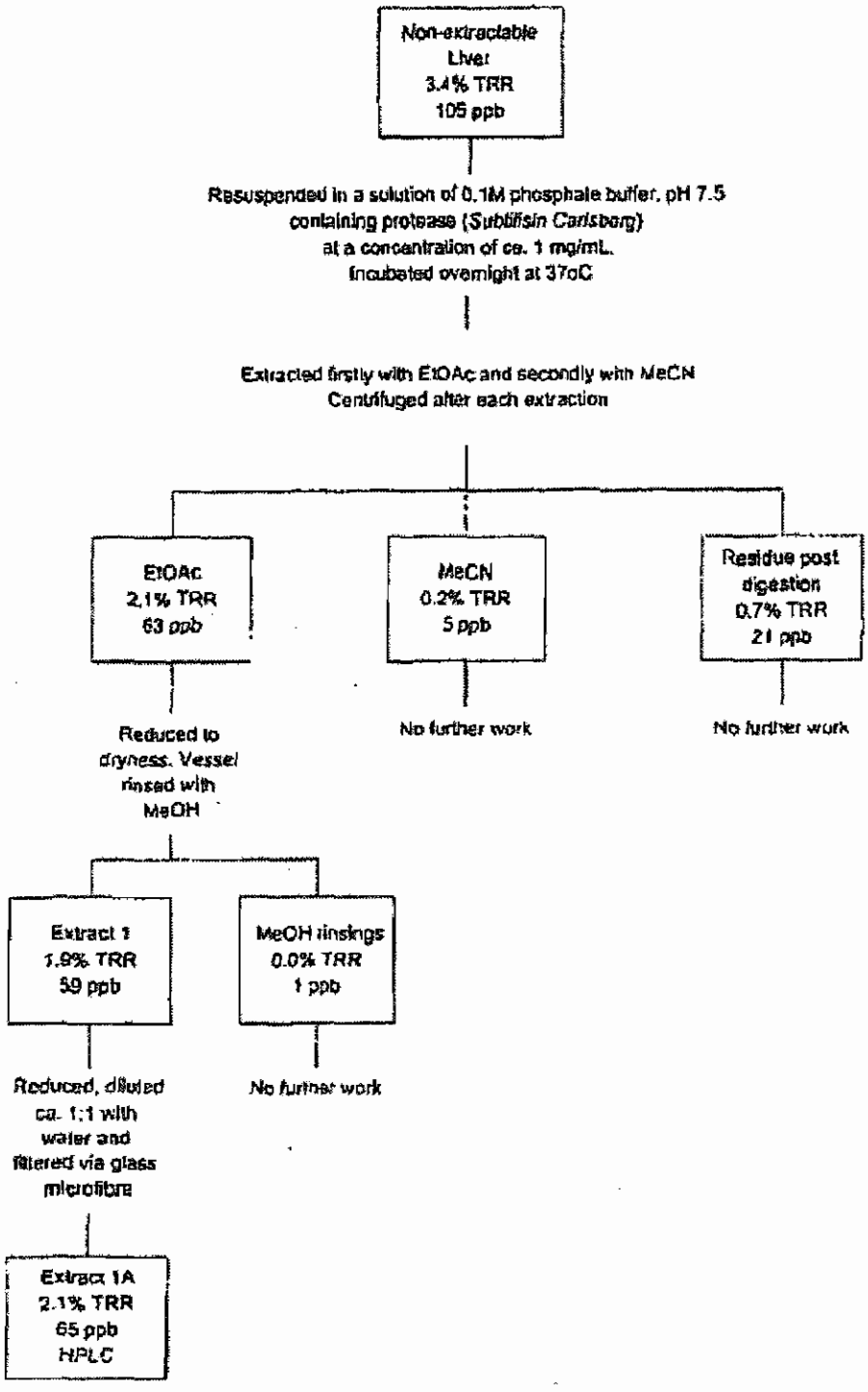
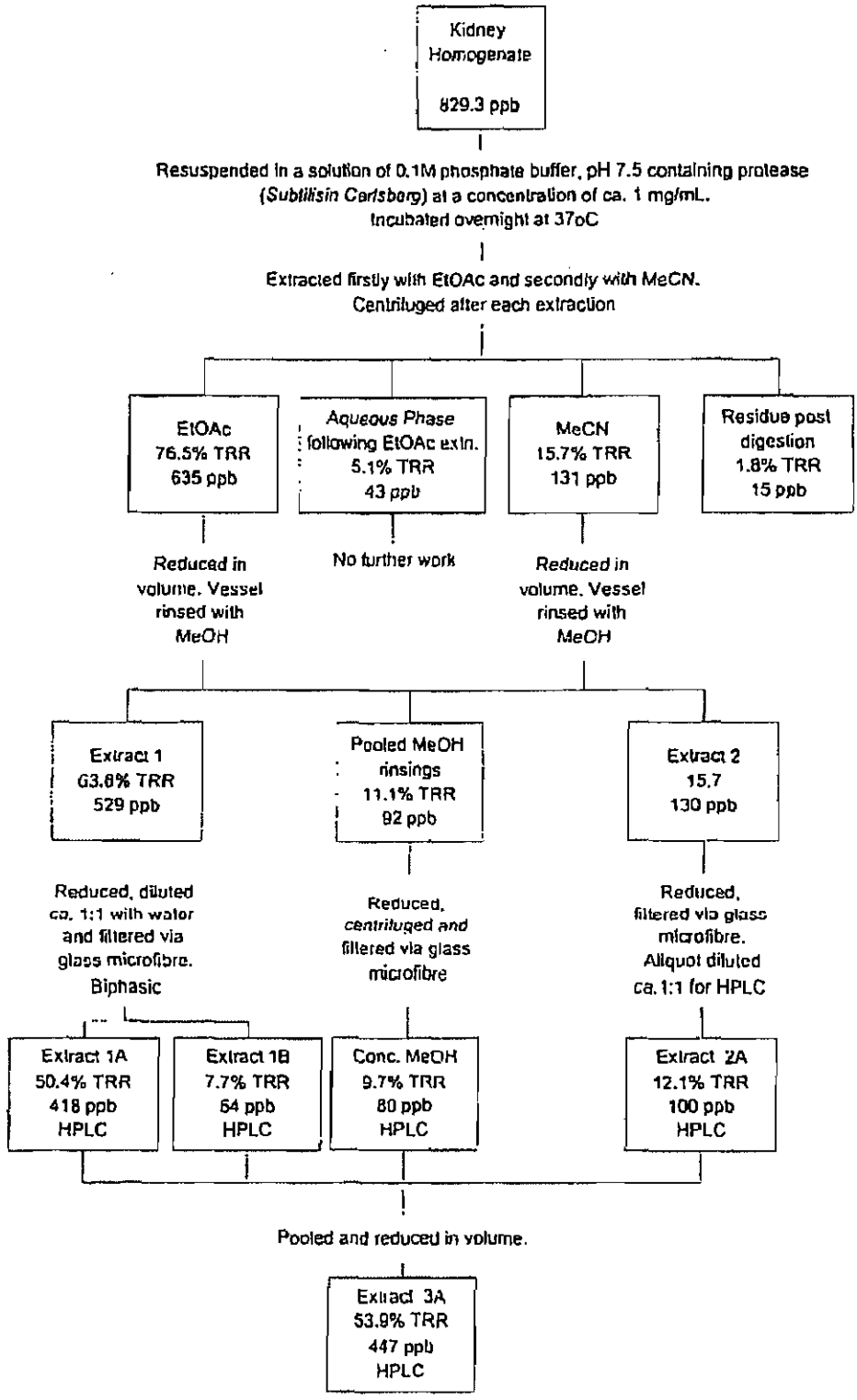


FIGURE B.4.1.3. Protease Hydrolysis of Kidney.



B.4.2. Analytical Methodology

The total radioactive residues were determined by liquid-scintillation counting (LSC), either directly or following solubilization or combustion. Radioactivity in extracts and hydrolysates was determined by direct LSC, and nonextractable radioactivity was determined by combustion/LSC. Extracts containing sufficient radioactivity were processed further for chromatographic analysis. The LOQ for TRR determinations was defined as 2x background.

Extracts of milk and tissues were analyzed by reverse-phase HPLC using a system equipped with a C18 column, a UV detector at 254 nm, and a flow-through radiodetector. A gradient mobile phase of water adjusted to pH 2 with trifluoroacetic acid:ACN was used. Residues were identified by retention time comparison with a non-labeled reference standard of tembotrione.

Residue identification was confirmed by HPLC/MS. A quadrupole ion-trap mass spectrometer with electrospray LC/MS interface was coupled to a gradient HPLC system with conditions as described above. Positive/negative-ion electrospray MS analysis was carried out with a capillary temperature of 150°C, a capillary voltage of 3/-47 V and a spray voltage of 4.5 kV. The scan range was *m/z* 100 to 700.

C. RESULTS AND DISCUSSION

The storage conditions and intervals for cow matrices are presented in Table C.1. The petitioner did not provide the dates of sample extraction and analysis for all matrices, but stated that profiling of tissues, with the exception of liver, was completed within 6 months of animal necropsy; liver was subjected to extra processing to generate a metabolite for identification purposes. Based on dated chromatograms and spectra included in the submission, liver was stored for ~2.2 months prior to initial analysis and was re-extracted for metabolite characterization ~9.1 months after sacrifice; HPLC/MS analyses for liver, kidney, and muscle were conducted within ~6.8 months of sacrifice. No significant differences were observed on comparison of the metabolite profiles for liver analyzed 2.2 and 9.1 months after sacrifice. These data are adequate to support the storage interval for liver. No additional storage stability data are required because it appears that all samples were stored for <6 months prior to initial analysis. The petitioner should note for future submissions that the critical study dates are required for each sample.

TRR in milk and tissues are presented in Table C.2.1. Following oral dosing of CY-labeled tembotrione for 7 days at 1 ppm in the diet, TRR were <LOQ-0.002 ppm in milk, <LOQ in muscle (fore and hindquarter) and omental fat, 0.011 ppm in renal fat, 0.550 ppm in kidney, and 2.730 ppm in liver. TRR following dosing at 10 ppm were 0.008-0.018 ppm in milk, <LOQ in forequarter muscle, 0.011 ppm in hindquarter muscle, 0.094 ppm in renal fat, 0.076 ppm in omental fat, 0.829 ppm in kidney, and 3.082 ppm in liver. Radioactivity was highest in liver and appeared to plateau in milk following 3 days of dosing. The majority of the radioactivity (~76-87% of the administered dose) was excreted. The pharmacokinetics of tembotrione in excreta and milk are presented graphically in Figures C.2.1 - C.2.4.

Metabolic profiling was conducted on milk and tissues from the high-dose (10 ppm) cow. The distribution of the radioactivity in cow matrices is presented in Table C.2.2. Solvent extraction with hexane, ethyl acetate, acetonitrile, and acidified ACN released ~41-47% of the TRR in milk (Day 5) and hindquarter muscle, and ~90-94% TRR in fat, kidney, and liver. Nonextractable residues following solvent extraction were 58.4% TRR (0.010 ppm) in milk, 25.8% TRR (0.003 ppm) in muscle, 5.4% TRR (0.005 ppm) in fat, and 1.5% TRR (0.012 ppm) in kidney. Nonextractable residues in liver were subjected to protease digestion, which released an additional 2.3% TRR. A separate sample of kidney was subjected to protease digestion without prior solvent extraction, which released ~97% TRR. Nonextractable residues after exhaustive extractions were 0.7% and 1.8% TRR (≤0.02 ppm) in liver and kidney, respectively.

The extraction procedures were adequate; and the accountabilities were 82-106%. Residues were identified and quantitated by HPLC and confirmed by LC/MS.

The characterization and identification of residues in cow matrices are summarized in Table C.2.3. The major and only residue identified in milk and all tissues was the parent, tembotrione. Tembotrione was identified at 21.2% TRR (0.003 ppm) in milk, 45.4% TRR (0.005 ppm) in muscle, 82.5% TRR (0.070 ppm) in fat, 92.3% TRR (0.765 ppm) in kidney, and 92.8% TRR (2.859 ppm) in liver. The identity of the parent was confirmed by LC/MS analysis of the organic extract of fat, kidney and liver, and the protease hydrolysates of kidney and liver.

A second metabolite, accounting for 3.4% TRR (0.106 ppm) in liver and consisting of a single polar peak on initial HPLC analysis (Rt = 3.8 min), was subjected to LC/MS analysis following dilution of the extract with water; radioactivity was resolved into two components. Although major ions were observed for both components, no structures could be proposed for these metabolites. An unknown in milk (Rt = 3.5 min), accounting for 13.8% TRR (0.002 ppm), was not further investigated.

C.1. Storage Stability

All samples were homogenized and subsampled on the day of collection prior to storage; processed samples were stored at <-10 °C. The petitioner did not provide the dates of sample extraction and analysis for all matrices, but stated that profiling of tissues, with the exception of liver, was completed within 6 months of animal necropsy; liver was subjected to extra processing to generate a metabolite for identification purposes. The petitioner included a dated HPLC chromatogram for liver indicating that initial profiling was completed within 2.2 months. Dated chromatograms and spectra were also included in the submission for liver, kidney, and muscle indicating that HPLC/MS analyses were conducted within 208 days (6.8 months) of sacrifice.

In support of the storage intervals and conditions of the submitted study, the petitioner presented a side-by-side comparison of the HPLC chromatogram for liver reflecting initial profiling and a chromatogram reflecting re-extraction to isolate the metabolite conducted 277 days (9.1 months) after sacrifice. No significant differences were observed on comparison of the metabolite profiles.

TABLE C.1. Summary of Storage Conditions.			
Matrix	Storage Temperature(°C)	Actual Storage Duration	Interval of Demonstrated Storage Stability
Milk and muscle	<-10	No dates provided	None provided.
Liver		68 days (2.2 months): initial profiling 208 days (6.8 months): HPLC/MS 277 days (9.1 months): re-extraction	Metabolic profile unchanged in liver extracted and analyzed 277 days (9.1 months) after collection.
Kidney and muscle		208 days (6.8 months): HPLC/MS	None provided

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

TABLE C.2.1. TRR in Milk, Tissue and Excreta.[1]					
Matrix	Collection Timing	Low-dose cow, 101F (1 ppm)		High-dose cow, 102F (10 ppm)	
		% AD	ppm	% AD	ppm
Urine	Daily; study duration	53.16	--	35.12	--
Feces	Daily; study duration	20.37	--	26.43	--
Cage wash	Daily; study duration	2.096	--	25.26	--
Total excreta		75.63	--	86.81	--
Milk	Day 1 a.m.	<LOQ	<LOQ	0.007	0.008127
	Day 1 p.m.	<LOQ	<LOQ	0.004	0.01198
	Day 2 a.m.	<LOQ	<LOQ	0.011	0.01519
	Day 2 p.m.	0.007	0.001703	0.007	0.01757
	Day 3 a.m.	<LOQ	<LOQ	0.011	0.01475
	Day 3 p.m.	<LOQ	<LOQ	0.007	0.01775
	Day 4 a.m.	<LOQ	<LOQ	0.012	0.01567
	Day 4 p.m.	<LOQ	<LOQ	0.006	0.01680
	Day 5 a.m.	<LOQ	<LOQ	0.012	0.01599
	Day 5 p.m.	<LOQ	<LOQ	0.006	0.01667
	Day 6 a.m.	<LOQ	<LOQ	0.011	0.01542
	Day 6 p.m.	<LOQ	<LOQ	0.007	0.01597
	Day 7 a.m.	<LOQ	<LOQ	0.010	0.01462
	Day 7 p.m.	<LOQ	<LOQ	0.007	0.01457
	Sacrifice	<LOQ	<LOQ	0.008	0.009447
	Total; study duration	0.095	--	0.125	--
Muscle, hind	Sacrifice	<LOQ	<LOQ	<0.001	0.01128
Muscle, forequarter		<LOQ	<LOQ	<LOQ	<LOQ
Fat, renal		<0.001	0.01112	<0.001	0.09395
Fat, omental		<LOQ	<LOQ	<0.001	0.07596
Kidney		0.579	0.5498	0.071	0.8293
Liver		15.85	2.730	1.541	3.082
Blood		<LOQ	<LOQ	<LOQ	0.01202
Sum of Administered Dose (%)		92.15	--	88.55	--

[1] The LOQ for LSC determinations was defined as 2x background.

FIGURES C.2.1-C.2.4. Pharmacokinetics of Tembotrione4 in Excreta and Milk of Lactating Cow.

Figure C.2.1. Cumulative Recovery of Radioactivity in Excreta from Cow 101F Following Twice Daily Oral Administration of [cyclohexyl-U-^{14}C]-AE 0172747 for Seven Days at a Nominal Dose of 1 ppm Based on Diet.

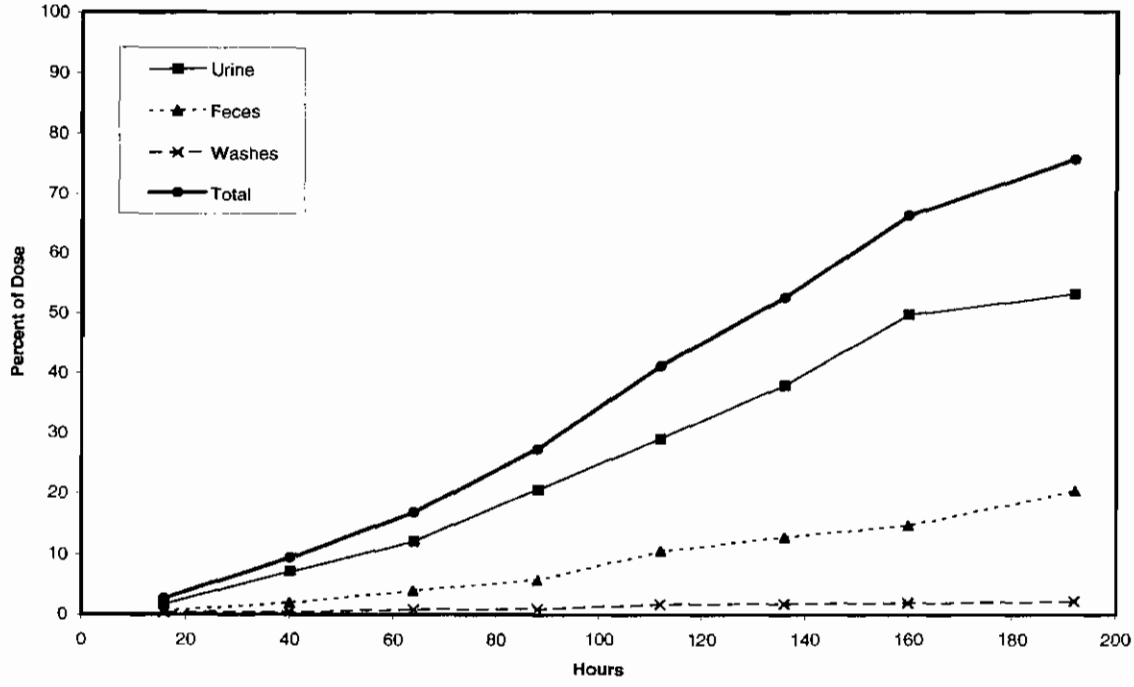


Figure C.2.2. Cumulative Recovery of Radioactivity in Excreta from Cow 201F Following Twice Daily Oral Administration of [cyclohexyl-U-14C]-AE 0172747 for Seven Days at a Nominal Dose of 10 ppm Based on Diet..

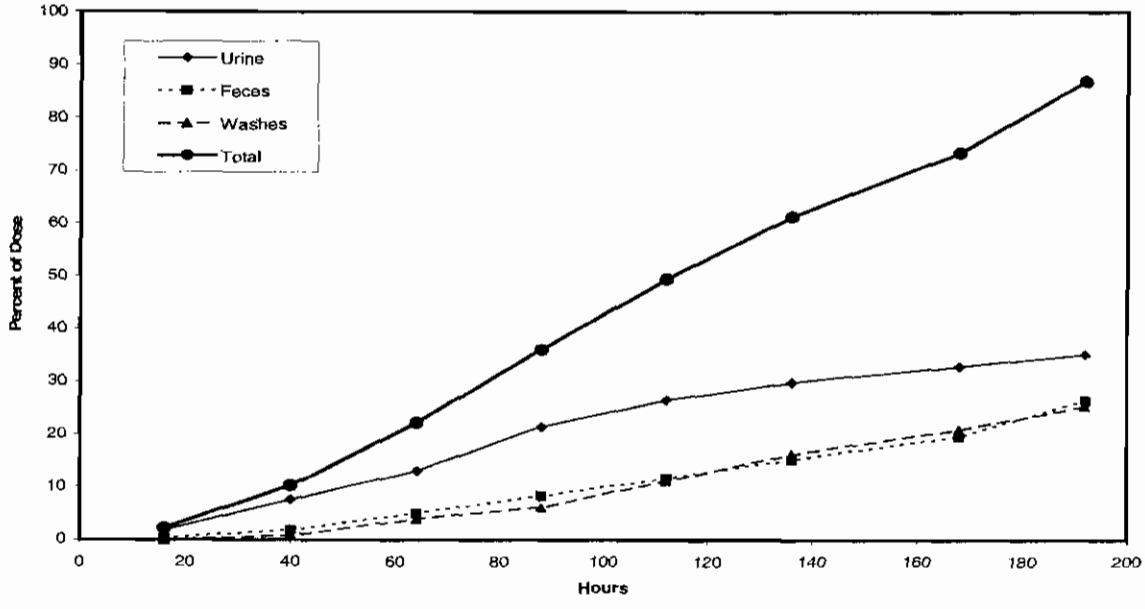


Figure C.2.3. Cumulative Recovery of Radioactivity in Milk from Cow 201F Following Twice Daily Oral Administration of [cyclohexyl-U-14C]-AE 0172747 for Seven Days at a Nominal Dose of 10 ppm Based on Diet.

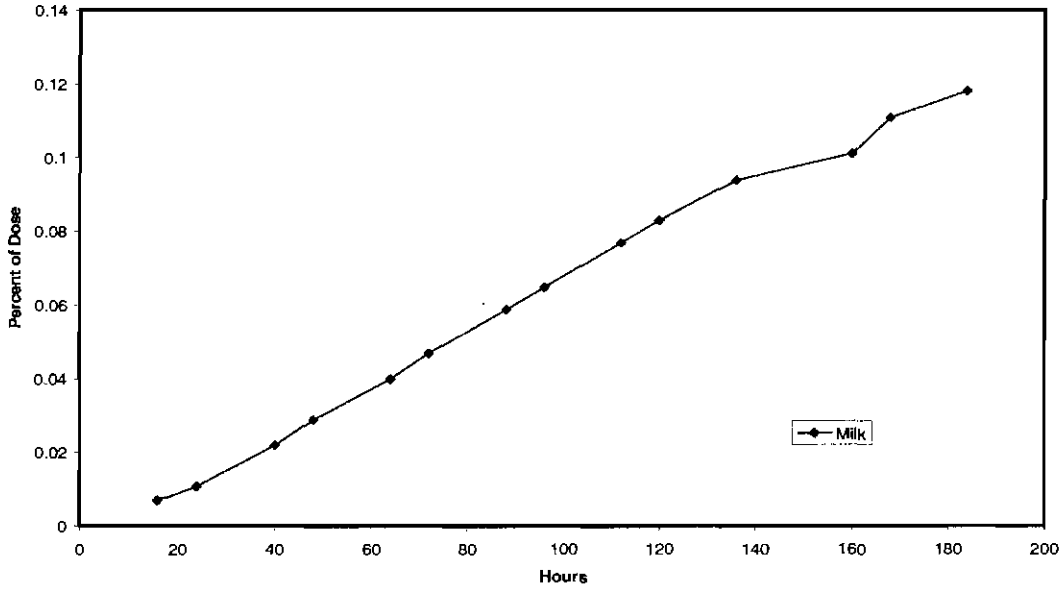


Figure C.2.4. Radioactivity Residues in Milk from Cow 201F Following Twice Daily Oral Administration of [cyclohexyl-U-14C]-AE 0172747 for Seven Days at a Nominal Dose of 10 ppm Based on Diet.

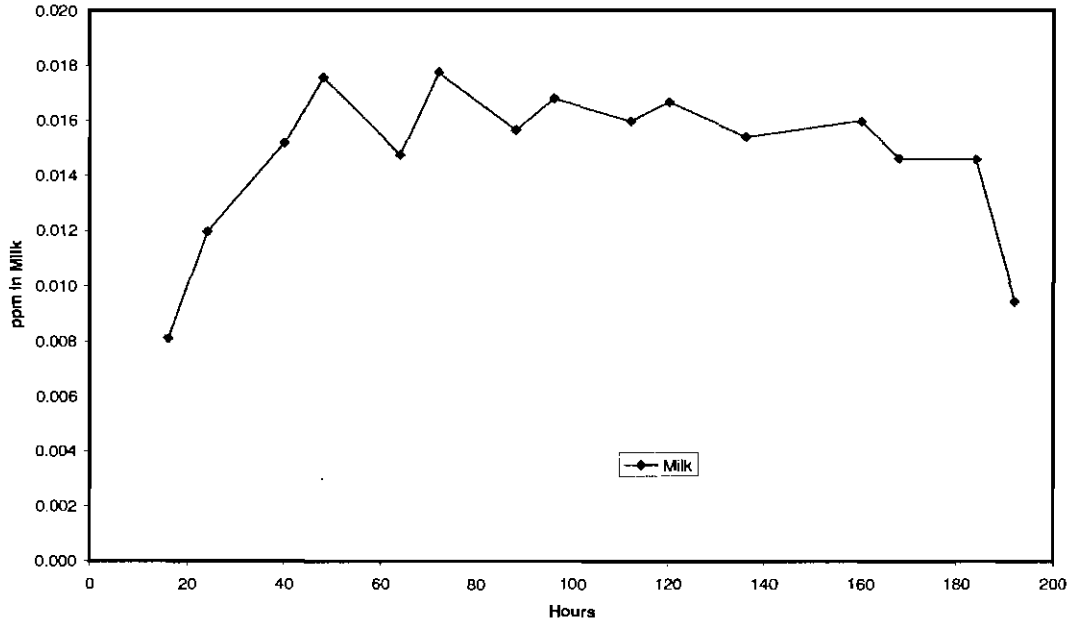


TABLE C.2.2. Distribution of the Parent and the Metabolites in Bovine Matrices Following Administration of [cyclohexyl-U-^{14}C]Tembotrione Twice a Day for 7 Days at 10 ppm.[1]

Metabolite Fraction	Muscle, hind		Fat, pooled		Kidney		Liver		Milk, Day 5	
	TRR=0.011 ppm		TRR=0.085 ppm		TRR=0.829 ppm		TRR=3.082 ppm		TRR=0.016 ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Subsample 1										
Hexane extract	1.5	<0.001	19.8	0.017	0.1	0.001	<0.1	0.001	6.4	0.001
Hexane phase			6.5	0.006					6.2	0.001
ACN phase			7.9	0.007					<0.1	<0.001
Emulsion			7.3	0.006					--	--
EtOAc extract(s)[2]	25.2	0.003	38.7	0.033	25.7	0.214	4.2	0.130	16.2	0.003
ACN extract	15.3	0.002	33.2	0.028	55.8	0.463	76.6	2.362	9.6	0.002
Acidified ACN extract	4.9	0.001	2.7	0.002	8.7	0.073	13.3	0.410	9.2	0.002
Combined extracts[3]	45.4	0.005	82.5	0.070	90.2	0.748	94.1	2.900	35.0	0.006
Tembotrione	45.4	0.005	82.5	0.070	90.2	0.748	90.6	2.794	21.2	0.003
Unknowns[4]	--	--	--	--	--	--	3.4	0.106	13.8	0.002
Nonextractable	25.8	0.003	5.4	0.005	1.5	0.012	3.4	0.105	58.4	0.010
Protease EtOAc							2.1	0.065		
Tembotrione							2.1	0.065		
Protease ACN							0.2	0.005		
Nonextractable							0.7	0.021		
Subsample 2										
Protease hydrolysis[5]					97.3	0.807				
EtOAc					76.5	0.635				
ACN					15.7	0.131				
Comb. EtOAc+ACN					92.2	0.764				
Tembotrione					92.3	0.765				
Aqueous					5.1	0.043				
Nonextractable					1.8	0.015				

[1] Shading indicates that the extraction step and/or characterization analysis was not conducted for the matrix in question.
[2] Sum of two extractions for kidney.
[3] Includes EtOAc, ACN, acidified ACN, and ACN phase of hexane extract for fat and milk, and EtOAc, ACN, and acidified ACN for muscle, kidney, and liver.
[4] Consisting of a single polar peak on initial HPLC analysis (Rt = 3.8 min in liver and 3.5 min in milk); in liver, resolved into two components on LC/MS analysis following dilution of the extract with water.
[5] Calculated by the study reviewer.

TABLE C.2.3. Summary of Characterization and Identification of Radioactive Residues in Bovine Matrices Following Administration of [cyclohexyl-U-^{14}C]Tembotrione Twice a Day for 7 Days at 10 ppm.

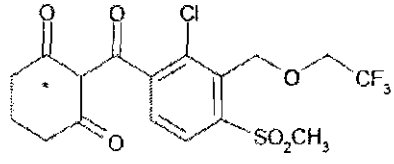
Compound	Muscle		Fat		Kidney		Liver		Milk (Day 5)	
	TRR=0.011 ppm		TRR=0.085 ppm		TRR=0.829 ppm		TRR=3.082 ppm		TRR=0.016 ppm	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	%TRR	ppm
Tembotrione	45.4	0.005	82.5	0.070	92.3	0.765	92.8	2.859	21.2	0.003
Unknown (Rt = 3.8/3.5 min)	--	--	--	--	--	--	3.4	0.106	13.8	0.002
Hexane soluble	1.5	<0.001	6.5	0.006	0.1	0.001	<0.1	0.001	6.4	0.001
Hexane emulsion	--	--	7.3	0.006	--	--	--	--	--	--
Protease aqueous	--	--	--	--	5.1	0.043	--	--	--	--
Protease ACN	--	--	--	--	--	--	0.2	0.005	--	--
Total identified	45.5	0.005	82.5	0.070	92.3	0.765	92.8	2.859	21	0.003
Total characterized	1.5	<0.001	13.8	0.012	5.2	0.044	3.4	0.107	6.4	0.001
Total extractable	46.9	0.006	94.4	0.080	97.3	0.809	96.5	2.973	41.4	0.007
Unextractable[1]	25.8	0.003	5.4	0.005	1.8	0.015	0.7	0.021	58.4	0.010
Accountability[2]	81.8		100		99.4		97.1		106	

[1] Residues remaining after exhaustive extractions.
[2] Accountability = (Total extractable + Total unextractable)/(TRR from combustion analysis; see TABLE C.2.1) * 100.

C.3. Proposed Metabolic Profile

Based on the cow metabolism study with CY-labeled tembotrione, tembotrione is not extensively metabolized in ruminants, with the major component in all tissues being parent compound. Because the parent was the only analyte identified during this study, a metabolic scheme was not proposed.

TABLE C.3.1. Identification of Compounds from Metabolism Study

Common name/code	Chemical name (CAS)	Chemical structure
Tembotrione (parent)	2-[2-Chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione	

D. CONCLUSION

Following oral dosing for 7 days with CY-labeled tembotrione at 1 ppm in the diet, TRR were <LOQ-0.002 ppm in milk, <LOQ in muscle (fore and hindquarter) and omental fat, 0.011 ppm in renal fat, 0.550 ppm in kidney, and 2.730 ppm in liver. TRR following dosing at 10 ppm were 0.008-0.018 ppm in milk, <LOQ in forequarter muscle, 0.011 ppm in hindquarter muscle, 0.094 ppm in renal fat, 0.076 ppm in omental fat, 0.829 ppm in kidney, and 3.082 ppm in liver. Radioactivity was highest in liver and appeared to plateau in milk following 3 days of dosing. The majority of the radioactivity (~76-87% of the administered dose) was excreted.

Metabolic profiling was conducted on milk and tissues from the high-dose (10 ppm) cow. Samples were subjected to sequential extraction with hexane, ethyl acetate, ACN, and acidified ACN. The nonextractable residues of liver were subjected to protease hydrolysis, which released additional residues, and a separate sample of kidney was subjected to protease digestion without prior solvent extraction. These procedures adequately extracted the majority of residues from cow matrices.

Residues were identified and quantitated by HPLC and confirmed by LC/MS. Adequate storage stability data were submitted to support the storage intervals and conditions of samples of liver from the study. No additional storage stability data are required because it appears that all samples were stored for <6 months prior to initial analysis.

The major and only residue identified in milk and all tissues was the parent, tembotrione, accounting for ~21% TRR in milk, ~45% TRR in muscle, and for 83-93% TRR in fat, liver, and kidney. Based on these results, tembotrione is not extensively metabolized in ruminants.

The submitted study is acceptable and successfully delineates the amount and distribution of TRR in ruminant matrices.

E. REFERENCES

None.

F. DOCUMENT TRACKING

RDI: RAB1 Chemists (12/6/06)
Petition Number: PP#5F7009
DP#s: 325349, 325663, and 331222
PC Code: 012801

Template Version June 2005

Tembotrione/AE 0172747/PC Code 012801/Bayer CropScience/264
DACO 6.2/OPPTS 860.1300/OECD II 6.2.2, 6.2.3 & IIIA 8.2, 8.4.1, 8.4.2
Nature of the Residues in Livestock - Ruminant

Primary Evaluator	George F. Kramer, Ph.D., Senior Chemist Registration Action Branch (RAB1) Health Effects Division (HED) (7509P)	Date: 18-JUL-2007
Approved by	P.V. Shah, Ph.D., Branch Senior Scientist RAB1/HED (7509P)	Date: 18-JUL-2007

This DER was originally prepared under contract by Dynamac Corporation (2275 Research Boulevard, Suite 300; Rockville, MD 20850; submitted 11/10/2006). The DER has been reviewed by HED and revised to reflect current Office of Pesticide Programs (OPP) policies.

STUDY REPORT:

46695532 Needham, D.; Swalwell, L. (2004) (Phenyl-U-(Carbon 14)] - AE 0172747: Absorption, Distribution, Metabolism and Excretion Following Repeated Oral Administration to the Lactating Cow: Final Report. Project Number: 2014/062, 2014/062/D1145, 37534. Unpublished study prepared by Covance Laboratories, Ltd. 109 p.

The petitioner has submitted an evaluation template for the study (Bayer CropScience DER to Study 2014-062), which was used to generate this DER; selected sections were copied without alteration or were copied and modified to more specifically reflect the Agency's data evaluation requirements.

EXECUTIVE SUMMARY:

Bayer CropScience has submitted a study investigating the metabolism of [phenyl-U-^{14}C]tembotrione (PH label; specific activity 5.625 MBq/mg) in lactating cows. The test substance was administered orally to two cows, one at 1 ppm and one at 10 ppm in the diet. The actual doses, based on feed consumption during the experiment, were 0.82 and 8.01 ppm. The cows were dosed two times daily for 7 consecutive days. Milk was collected twice daily throughout the study, and tissues (muscle, fat, liver, and kidney) were collected at sacrifice, ~23 hours after the final dose.

Total radioactive residues (TRR) following dosing at 0.82 ppm were less than the limit of quantitation (<LOQ) in milk, muscle (fore and hindquarter), and omental fat, 0.031 ppm in renal fat, 0.433 ppm in kidney, and 1.696 ppm in liver. TRR following dosing at 8.01 ppm were <LOQ in milk, muscle (fore and hindquarter), and fat (renal and omental), 0.550 ppm in kidney, and 2.128 ppm in liver. At both dose levels, radioactivity was highest in liver, and radioactivity in milk was below the LOQ at all time points. The majority of the radioactivity (~73-111% of the administered dose) was excreted.

Metabolic profiling was conducted on kidney and liver from the high-dose (8.01 ppm) cow. Solvent extraction with hexane, ethyl acetate, acetonitrile (ACN), and acidified ACN released ~87-103% of the TRR in kidney and liver. Polar organic solvents extracted more residues than nonpolar solvents; hexane dissolved little residue, ethyl acetate dissolved more, but ACN was the most efficient solvent. Nonextractable residues following solvent extraction were 6.3% TRR

(0.034 ppm) in kidney. Nonextractable residues in liver were subjected to protease hydrolysis, which released an additional 3.4% TRR. Nonextractable residues after exhaustive extractions were 0.7% TRR (<0.02 ppm) in liver.

The extraction procedures were adequate; and the accountabilities were ~93 and 107% in kidney and liver, respectively. Residues were identified and quantitated by high-performance liquid chromatography (HPLC) and confirmed by liquid chromatography/mass spectroscopy (LC/MS). Acceptable storage stability data from a cow metabolism study with cyclohexyl-labeled tembotrione (refer to 46695531.der.doc) are available to support the storage intervals and conditions of samples of liver from the current study. No additional storage stability data are required because it appears that all samples were stored frozen for <6 months prior to analysis.

The major and only residue identified was the parent, tembotrione. Tembotrione was identified at 70.1% TRR (0.386 ppm) in kidney, and 96.8% TRR (2.061 ppm) in liver. Two unknowns, accounting for 2.9% TRR (0.016 ppm) in kidney and 1.7% TRR (0.035 ppm) in liver were detected but were not further investigated.

Based on the cow metabolism study with PH-labeled tembotrione, tembotrione is not extensively metabolized in ruminants, with the major component in tissues being parent compound. The petitioner noted that although the dosing levels differed by 10x, the differences in TRR in kidney and liver from the different dosing levels did not approach this order of magnitude. These results suggest that accumulation of tembotrione in tissues was approaching saturation at the low-dose level and that comparable levels of residues would eventually be reached following any dose level, provided the duration of dosing was sufficiently prolonged.

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the livestock metabolism data are classified as scientifically acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document [DP# 325349].

COMPLIANCE:

Signed and dated Good Laboratory Practice (GLP), Quality Assurance and Data Confidentiality statements were provided. No GLP deviations were reported which would impact the study results or their interpretation.

A. BACKGROUND INFORMATION

Tembotrione, a new herbicide with broad use against mono- and dicotyledons in selected crops such as corn, is a 4-hydroxyphenylpyruvate deoxygenase (HPPD) inhibitor (bleacher). The test compound nomenclature and physiochemical properties of the test compound are presented in Tables A.1 and A.2, respectively.

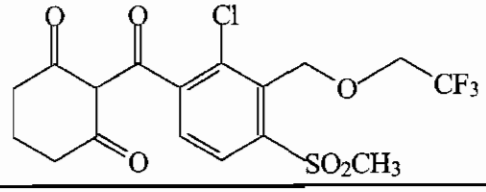
TABLE A.1. Test Compound Nomenclature for Tembotrione.	
Compound: Tembotrione	Chemical Structure 
Proposed common name	Tembotrione
Company experimental name	AE 0172747
IUPAC name	2-{2-chloro-4-mesyl-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl}cyclohexane-1,3-dione
CAS name	2-[2-chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione
CAS #	335104-84-2
End-use product/EP	AE 0172747 Herbicide, EPA Reg No. 264-xxx

TABLE A.2. Physicochemical Properties of Technical Grade Tembotrione.		
Parameter	Value	Reference (MRID#)
Melting point	117 °C	46695402
pH @ 24 °C	3.63	
Density (g/mL @ 20 °C)	1.56	
Water solubility (mg/L @ 20 °C)	0.22 at pH 4 28.3 at pH 7 29.7 at pH 9	
Solvent solubility (g/L at 20 °C) DMSO Methylene Chloride Acetone Ethyl Acetate Toluene Hexane Ethanol	 >600 >600 300-600 180.2 75.7 47.6 8.2	
Vapor pressure (Torr, 20 °C)	8.25×10^{-11}	
Dissociation constant (pK_a)	3.2	
Octanol/water partition coefficient (P_{ow} @ 23 °C) (P_{ow} @ 24 °C) (P_{ow} @ 23 °C)	 0.0430 at pH 9.0 0.0807 at pH 7.0 144.9 at pH 2.0	
UV/visible absorption spectrum (nm)	Primary: 205 Secondary: 284 Tertiary: 240	

B. EXPERIMENTAL DESIGN

Two lactating cows were dosed orally with PH-labeled tembotrione for 7 consecutive days. One cow was dosed at a nominal rate of 1 ppm in the diet, and the other was dosed at a nominal rate of 10 ppm in the diet. The cows were maintained in individual metabolism cages and were fed a commercial feed concentrate and hay twice daily at milking. The cows were dosed two times

daily following morning and afternoon milkings. Information pertaining to the test animals and the dietary and dosing regimes is presented in Tables B.1.1-B.1.3.

B.1. Livestock

TABLE B.1.1. General Test Animal Information

Animal Number	Species	Breed	Age years	Weight at study initiation (kg)	Health Status	Description of housing/holding area
101F	Lactating cow (*Bos taurus*)	Holstein Friesian	4-6	528	Good	Individual metabolism cages in unit controlled at 19-24 °C, 56-87% RH, 16-hr fluorescent light/day, 10 air exchanges/hr.
201F				561		

TABLE B.1.2. Test Animal Dietary Regime

Animal Number	Composition of Diet	Feed consumption (kg/day), average	Water	Acclimation period	Predosing
101F	3 kg/2x/day 261-Kestrel Concentrate Hay twice a day Consumption measured	16 expected; 19.6 actual	*Ad libitum*	7 days	None
201F		16 expected; 20.0 actual			

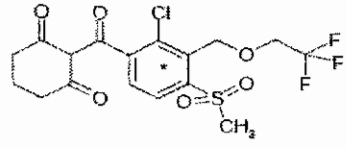
TABLE B.1.3. Test Animal Dosing Regime

Animal Number	Treatment Type	Feeding Level (ppm test material in food)	Vehicle	Timing/Duration
101F	Oral	1 ppm nominal (0.82 actual)	gelatin capsule, using balling gun	Twice/day for 7 days; following morning and afternoon milkings
201F		10 ppm nominal (8.01 actual)		

B.2. Test Materials

The radiolabeled test substance was dissolved in ACN, isotopically diluted with nonlabeled tembotrione, and prepared in gelatin capsules for dosing. The test material characteristics are presented in Table B.2.1.

TABLE B.2.1. Test Material Characteristics, Radiolabeled

Chemical structure	
Radiolabel position	[phenyl-U-^{14}C]AE 0172474
Lot No.	Z 32034-0
Purity	99.4%
Specific activity (Bq) [1]	5.625 MBq/mg

[1] Bq = disintegrations per second

B.3. Sampling Information

Cows were milked twice daily, and excreta were collected once daily. Cows were sacrificed ~23 hours after the last dosing, and tissues and blood were collected.

TABLE B.3.1. Sample Collection Information

Milk collected	Urine, feces and cage wash collected	Interval from last dose to sacrifice	Tissues harvested and analyzed
Twice daily prior to dose administration; average milk production was 11.6-16.9 kg/day during the acclimation period and 9.68-15.0 kg/day during the dosing period.	Once daily	23.0-23.25 hours	Muscle (hind and forequarter), fat (renal and omental), liver, and kidneys

B.4. Identification/Characterization of Residues

B.4.1. Sample Handling and Preparation

All samples were homogenized and subsampled on the day of collection prior to storage. All milk and tissue samples were stored at <-10 °C. The in-life and analytical phases of the study were conducted at the same facility (Covance Laboratories, Ltd., Harrogate, England); therefore, samples were not shipped.

The only tissues with sufficient radioactive residue for metabolic profiling were the liver and the kidneys. Samples of kidney and liver from the high-dose cow were subjected to sequential solvent extraction with hexane, ethyl acetate, ACN, and acidified ACN (1% formic acid). Each fraction was collected following centrifugation. The ethyl acetate extracts were concentrated to near dryness, resuspended in ACN:water (1:1, v:v), and centrifuged, and the residual pellet was resuspended in methanol. The resulting ACN/water and methanol phases were reserved for HPLC analysis. The ACN and acidified ACN extracts were combined and concentrated, then transferred for centrifugation; the flask was rinsed with hexane. The combined ACN extract of kidney was diluted with water and reserved for HPLC analysis. Following centrifugation, the combined ACN extract of liver separated into an upper ACN phase and a lower aqueous phase; on frozen storage the aqueous phase separated further into an upper and lower phase. All related phases were diluted with water and reserved for HPLC analysis.

The nonextractable residues of liver were subjected to enzyme hydrolysis with protease (in 0.1 M phosphate buffer, pH 7.5, overnight at 37 °C). Residues were then extracted sequentially with ethyl acetate and ACN. The ethyl acetate extract was reduced to dryness, rinsed with methanol, concentrated again, and diluted with water, then filtered for HPLC analysis.

Representative extraction procedures are presented below in Figure B.4.1.1, and the protease hydrolysis procedures for nonextractable residues in liver are presented in Figure B.4.1.2. These figures were copied without alteration from MRID 46695532.

FIGURE B.4.1.1. Extraction Scheme.

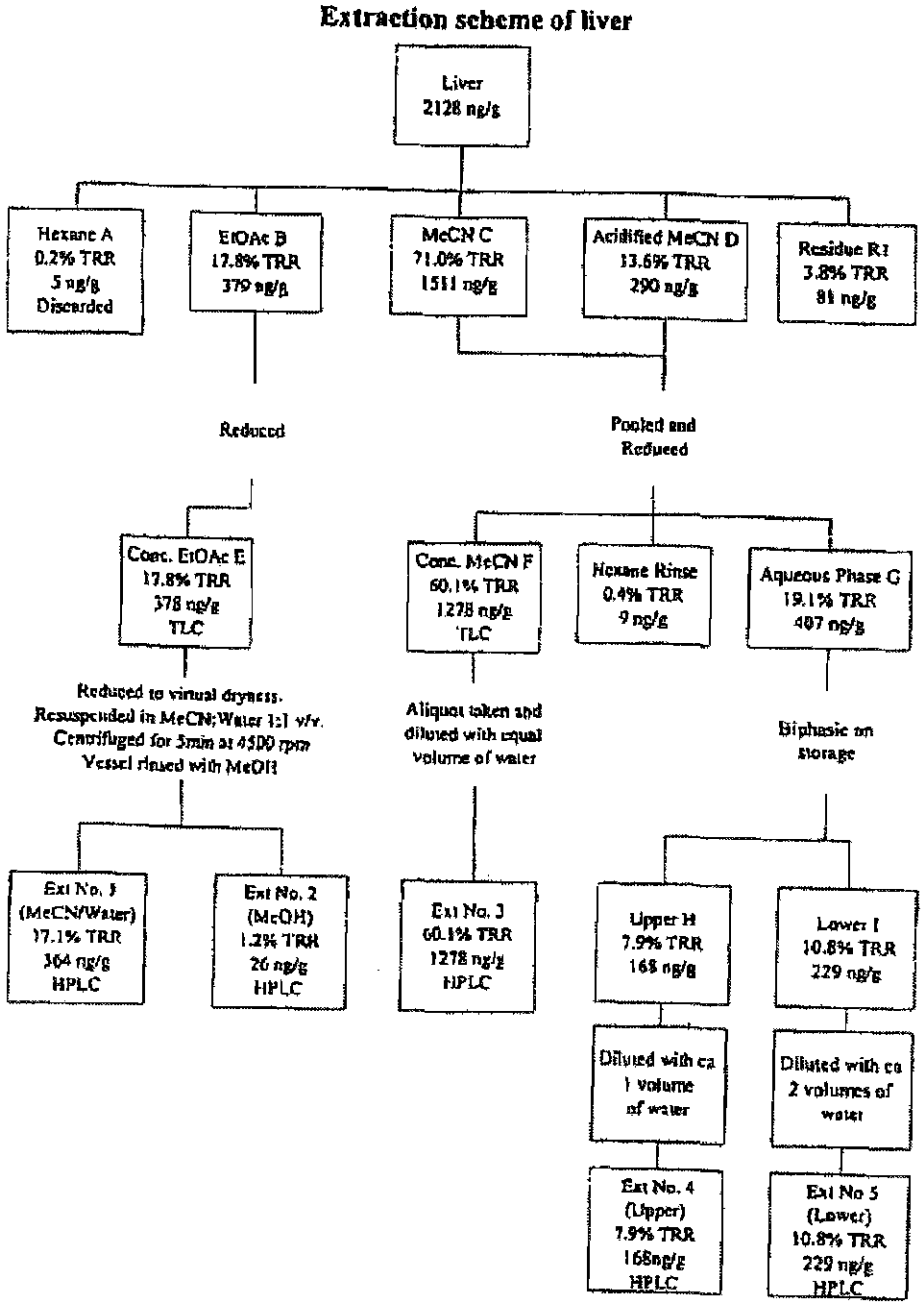
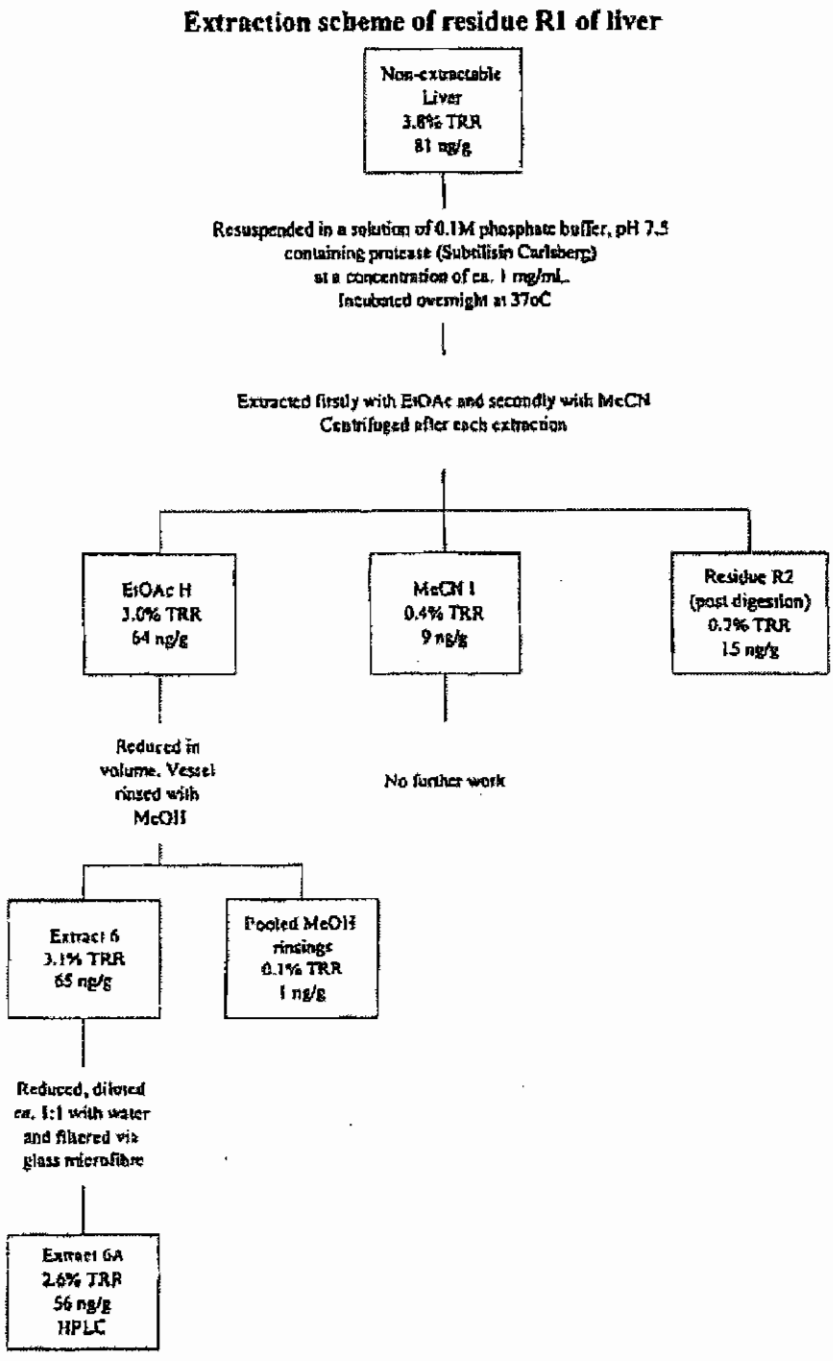


FIGURE B.4.1.2. Protease Hydrolysis of Nonextractable Residues of Liver.



B.4.2. Analytical Methodology

The TRR were determined by liquid-scintillation counting (LSC), either directly or following solubilization or combustion. Radioactivity in extracts and hydrolysates was determined by direct LSC, and nonextractable radioactivity was determined by combustion/LSC. Extracts

containing sufficient radioactivity were processed further for chromatographic analysis. The LOQs for TRR determinations were reported to be 0.003 ppm for milk and 2x background for tissues.

Extracts of kidney and liver were analyzed by reverse-phase HPLC using a system equipped with a C18 column, an ultraviolet (UV) detector at 254 nm, and a flow-through radiodetector. A gradient mobile phase of water adjusted to pH 2 with trifluoroacetic acid:ACN was used. Residues were identified by retention time comparison with a non-labeled reference standard of tembotrione.

Residue identification was confirmed by HPLC/MS. A quadrupole ion-trap mass spectrometer with an electrospray LC/MS interface was coupled to a gradient HPLC system with conditions as defined above. Positive/negative-ion electrospray MS analysis was carried out with a capillary temperature of 140 °C, a capillary voltage of 33/-18 V and a spray voltage of 2.5/2 kV. The scan range was *m/z* 120 to 700.

C. RESULTS AND DISCUSSION

The storage conditions and intervals for cow matrices are presented in Table C.1. The petitioner did not provide the dates of sample extraction and analysis; however, dated chromatograms and spectra reflecting confirmatory analysis for identification of tembotrione were included in the submission indicating that HPLC/MS analyses for liver and kidney were conducted within 5.6 months of sacrifice. In support of the storage intervals and conditions of the submitted study, the petitioner referenced a cow metabolism study with cyclohexyl-labeled tembotrione (46695531.der.doc) in which residues in liver were found to be relatively stable for up to 9.1 months. No additional storage stability data are required because it appears that all samples were stored for <6 months prior to analysis. The petitioner should note for future submissions that the critical study dates are required for each sample.

TRR in milk and tissues are presented in Table C.2.1. Following oral dosing of PH-labeled tembotrione for 7 days at 0.82 ppm, TRR were <LOQ in milk, muscle (fore and hindquarter), and omental fat, 0.031 ppm in renal fat, 0.433 ppm in kidney, and 1.696 ppm in liver. TRR following dosing at 8.01 ppm were <LOQ in milk, muscle (fore and hindquarter), and fat (renal and omental), 0.550 ppm in kidney, and 2.128 ppm in liver. At both dose levels, radioactivity was highest in liver, and radioactivity in milk was below the LOQ at all time points. The majority of the radioactivity (~73-111% of the administered dose) was excreted. The pharmacokinetics of tembotrione in excreta and milk are presented graphically in Figures C.2.1-C.2.3.

Metabolic profiling was conducted on kidney and liver from the high-dose (8.01 ppm) cow. The distribution of the radioactivity in cow matrices is presented in Table C.2.2. Solvent extraction with hexane, ethyl acetate, ACN and acidified ACN released ~87-103% of the TRR in kidney and liver. Polar organic solvents extracted more residues than nonpolar solvents; hexane dissolved little residue, ethyl acetate dissolved more, but ACN was the most efficient solvent. Nonextractable residues following solvent extraction were 6.3% TRR (0.034 ppm) in kidney.

Nonextractable residues in liver were subjected to protease hydrolysis, which released an additional 3.4% TRR. Nonextractable residues after exhaustive extractions were 0.7% TRR (<0.02 ppm) in liver.

The extraction procedures were adequate; and the accountabilities were 93-107%. Residues were identified and quantitated by HPLC and confirmed by LC/MS.

The characterization and identification of residues in cow kidney and liver are summarized in Table C.2.3. The major and only residue identified was the parent, tembotrione. Tembotrione was identified at 70.1% TRR (0.386 ppm) in kidney, and 96.8% TRR (2.061 ppm) in liver. The identity of the parent was confirmed by LC/MS analysis of the ACN extract of kidney and liver. Two unknowns (Rts = ~28 min in kidney and ~22 min in liver), accounting for 2.9% TRR (0.016 ppm) in kidney and 1.7% TRR (0.035 ppm) in liver were detected but were not further investigated.

C.1. Storage Stability

All samples were homogenized and subsampled on the day of collection prior to storage; processed samples were stored at <-10 °C. The petitioner did not provide the dates of sample extraction and analysis; however, dated chromatograms and spectra reflecting confirmatory analysis for identification of tembotrione were included in the submission indicating that HPLC/MS analyses were conducted within 169 days (5.6 months) of sacrifice.

In support of the storage intervals and conditions of the submitted study, the petitioner referenced a cow metabolism study with cyclohexyl-labeled tembotrione (46695531.der.doc) in which residues in liver were found to be relatively stable for up to 9.1 months.

TABLE C.1. Summary of Storage Conditions.

Matrix	Storage Temperature (°C)	Actual Storage Duration	Interval of Demonstrated Storage Stability
Kidney and Liver	<-10	169 days (5.6 months): HPLC/MS	Metabolic profile unchanged in liver extracted and analyzed 277 days (9.1 months) after collection.[1]

[1] *Refer to 46695531.der.doc.*

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

TABLE C.2.1. TRR in Milk, Tissue and Excreta.

Matrix	Collection Timing	Low-dose cow, 101F (0.82 ppm)		High-dose cow, 102F (8.01 ppm)	
		% AD	ppm	% AD	ppm
Urine	Daily; study duration	52.22	--	37.48	--
Feces	Daily; study duration	51.00	--	21.02	--
Cage wash	Daily; study duration	7.545	--	14.66	--
Total excreta		110.77	--	73.16	--
Milk	Day 1 a.m.	<LOQ [1]	<LOQ	<LOQ	<LOQ
	Day 1 p.m.	<LOQ	<LOQ	<LOQ	<LOQ
	Day 2 a.m.	<LOQ	<LOQ	<LOQ	<LOQ
	Day 2 p.m.	<LOQ	<LOQ	<LOQ	<LOQ
	Day 3 a.m.	<LOQ	<LOQ	<LOQ	<LOQ
	Day 3 p.m.	<LOQ	<LOQ	<LOQ	<LOQ
	Day 4 a.m.	<LOQ	<LOQ	<LOQ	<LOQ
	Day 4 p.m.	<LOQ	<LOQ	<LOQ	<LOQ
	Day 5 a.m.	<LOQ	<LOQ	<LOQ	<LOQ
	Day 5 p.m.	<LOQ	<LOQ	<LOQ	<LOQ
	Day 6 a.m.	<LOQ	<LOQ	<LOQ	<LOQ
	Day 6 p.m.	<LOQ	<LOQ	<LOQ	<LOQ
	Day 7 a.m.	<LOQ	<LOQ	<LOQ	<LOQ
	Day 7 p.m.	<LOQ	<LOQ	<LOQ	<LOQ
	Sacrifice	<LOQ	<LOQ	<LOQ	<LOQ
	Total; duration of study	0.025	--	0.007	--
Muscle, hind	Sacrifice	<LOQ	<LOQ	<LOQ	<LOQ
Muscle, fore		<LOQ	<LOQ	<LOQ	<LOQ
Fat, renal		<0.001	0.03123	<LOQ	<LOQ
Fat, omental		<LOQ	<LOQ	<LOQ	<LOQ
Kidney		0.659	0.4327	0.092	0.5499
Liver		11.68	1.696	1.563	2.128
Blood		<LOQ	<LOQ	<LOQ	<LOQ
Sum of Administered Dose (%)		123.1	--	74.82	--

[1] The LOQ was 0.003 ppm in milk and 2x background for tissues.

FIGURES C.2.1-C.2.3. Pharmacokinetics of Tembotrione in Excreta and Milk of Lactating Cow.

Figure C.2.1. Cumulative Recovery of Radioactivity in Excreta from Cow 101F Following Twice Daily Oral Administration of [phenyl-U-14C]-AE 0172747 for Seven Days at a Nominal Dose of 1 ppm Based on Diet.

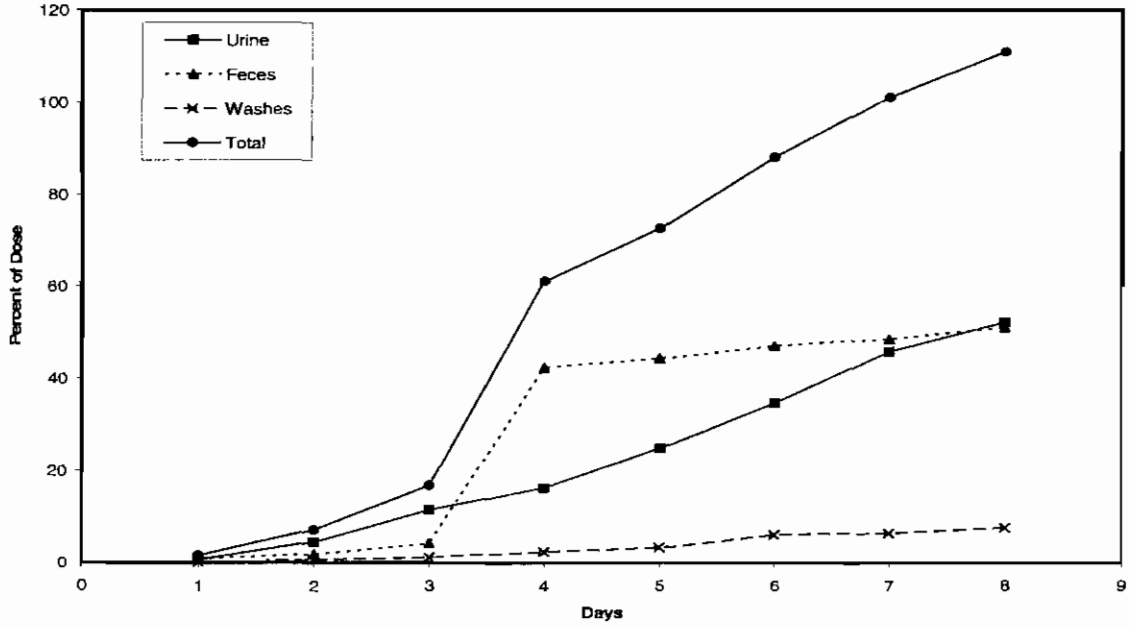


Figure C.2.2. Cumulative Recovery of Radioactivity in Excreta from Cow 201F Following Twice Daily Oral Administration of [phenyl-U-14C]-AE 0172747 for Seven Days at a Nominal Dose of 10 ppm Based on Diet.

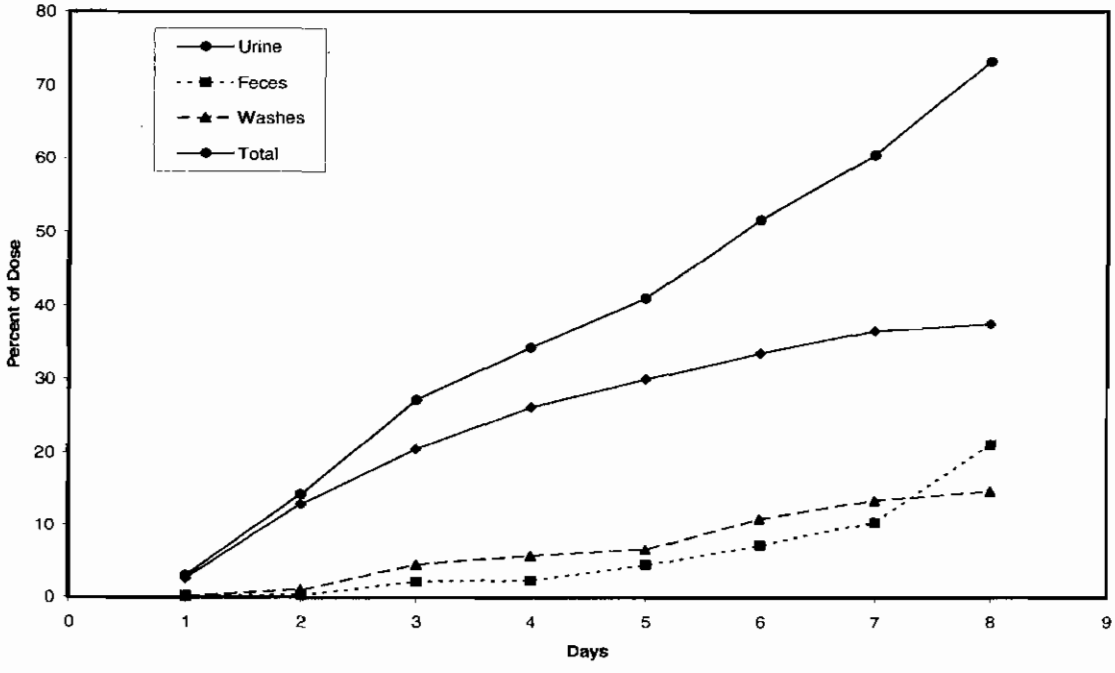


Figure C.2.3. Radioactivity Residues in Milk from Cow 201F Following Twice Daily Oral Administration of [phenyl-U-14C]-AE 0172747 for Seven Days at a Nominal Dose of 10 ppm Based on Diet.

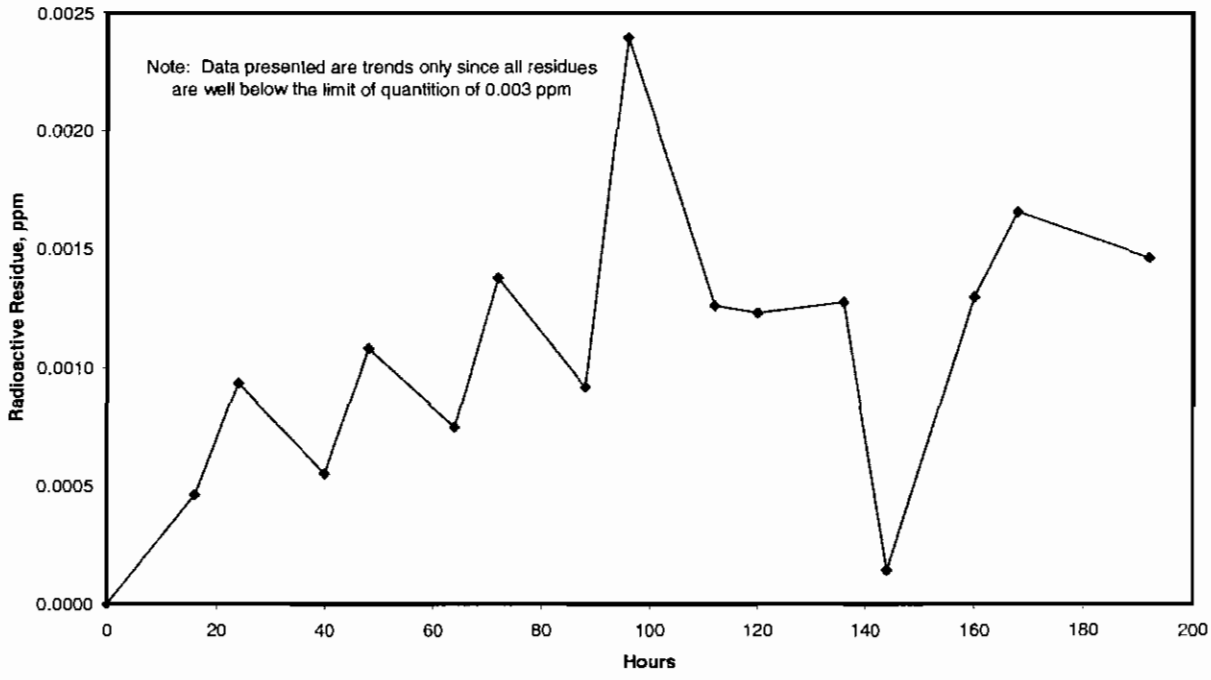


TABLE C.2.2. Distribution of the Parent and tbe Metabolites in Bovine Matrices Following Administration of [phenyl-U-^{14}C]Tembotrione Twice a Day for 7 Days at 8.01 ppm.[1]

Metabolite Fraetion	Kidney		Liver	
	TRR = 0.550 ppm		TRR = 2.128 ppm	
	%TRR	ppm	%TRR	ppm
Hexane extraet	0.1	<0.001	0.2	0.005
EtOAc extract	10.9	0.060	17.8	0.379
ACN/water	8.5	0.047	17.1	0.364
Tcmbotrione	8.2	0.045	17.1	0.364
Unknown (Rt = 27.9 min)	0.3	0.002	--	--
Methanol [2]	1.0	0.005	1.2	0.026
ACN extract	47.7	0.262	71.0	1.511
Acidified ACN extraet	28.2	0.155	13.6	0.290
Combincd ACN - Hexane rinse	0.1	0.001	0.4	0.009
Combined ACN - ACN phase (upper)	64.5	0.355	60.1	1.278
Tembotrione	61.9	0.341	58.7	1.249
Unknown (Rt = 28.0/22.2 min)	2.6	0.014	1.4	0.029
Combined ACN -- Aqueous phase (lower)			19.1	0.407
Upper aqueous phase			7.9	0.168
Tembotrione			7.8	0.166
Unknown (Rt = 22.3 min)			0.1	0.002
Lower aqueous phase			10.8	0.229
Tembotrione			10.6	0.226
Unknown (Rt = 21.7 min)			0.2	0.004
Nonextractable	6.3	0.034	3.8	0.081
Protease EtOAc			3.0	0.064
Tembotrione			2.6	0.056
Protease ACN			0.4	0.009
Nonextractable			0.7	0.015

[1] Shading indicates that the extraction step and/or characterization analysis was not conducted (or is not applicable) for the matrix in question.

[2] The petitioner stated that the main component of this fraction was unchanged tembotrione; no quantitative data or chromatograms were provided.

TABLE C.2.3. Summary of Characterization and Identification of Radioactive Residues in Bovine Matrices Following Administration of [phenyl-U-^{14}C]Tembotrione Twice a Day for 7 Days at 8.01 ppm.

Compound	Kidney		Liver	
	TRR = 0.550 ppm		TRR = 2.128 ppm	
	%TRR	ppm	%TRR	ppm
Tembotrione	70.1	0.386	96.8	2.061
Unknowns	2.9	0.016	1.7	0.035
Hexane soluble	0.2	<0.002	0.6	0.014
Methanol soluble	1.0	0.005	1.2	0.026
Protease ACN	--	--	0.4	0.009
Total identified	70.1	0.386	96.8	2.061
Total characterized	4.1	<0.023	3.9	0.084
Total extractable	86.9	<0.478	106.0	2.258
Unextractable)[1]	6.3	0.034	0.7	0.015
Accountability[2]	93.0		106.8	

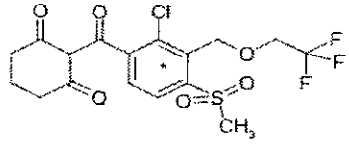
[1] Residues remaining after exhaustive extraetions.
[2] Accountability = (Total extractable + Total unextractable)/(TRR from combustion analysis; see TABLE C.2.1) * 100.

C.3. Proposed Metabolic Profile

Based on the PH-labeled cow metabolism study, tembotrione is not extensively metabolized in ruminants, with the major component in tissues being parent compound. The petitioner noted that although the dosing levels differed by 10x, the differences in TRR in kidney and liver from the different dosing levels did not approach this order of magnitude. These results suggest that accumulation of tembotrione in tissues was approaching saturation at the low-dose level and that comparable levels of residues would eventually be reached following any dose level, provided the duration of dosing was sufficiently prolonged.

Because the parent was the only analyte identified during this study, a metabolic scheme was not proposed.

TABLE C.3.1. Identification of Compounds from Metabolism Study

Common name/code	Chemical name (CAS)	Chemieal structure
Tembotrione (parent)	2-[2-Chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione	

D. CONCLUSION

Following 7 days of oral dosing with PH-labeled tembotrione at 0.82 ppm in the diet, TRR were <LOQ in milk, muscle (fore and hindquarter), and omental fat, 0.031 ppm in renal fat, 0.433 ppm in kidney, and 1.696 ppm in liver. TRR following dosing at 8.01 ppm were <LOQ in milk, muscle (fore and hindquarter), and fat (renal and omental), 0.550 ppm in kidney, and 2.128 ppm in liver. At both dose levels, radioactivity was highest in liver, and radioactivity in milk was below the limit of quantification at all time points. The majority of the radioactivity (~73-111% of the administered dose) was excreted.

Metabolic profiling was conducted on kidney and liver from the high-dose (8.01 ppm) cow. Samples were subjected to sequential extraction with hexane, ethyl acetate, ACN, and acidified ACN. The nonextractable residues of liver were subjected to protease hydrolysis, which released additional residues. These procedures adequately extracted the majority of residues from cow matrices.

Residues were identified and quantitated by HPLC and confirmed by LC/MS. The petitioner referenced storage stability data (refer to 46695531.der.doc) to support the storage intervals and conditions of liver samples analyzed in the current study. No additional storage stability data are required because it appears that all samples were stored for <6 months prior to analysis.

The major and only residue identified was the parent, tembotrione. Tembotrione was identified at 70.1% TRR (0.386 ppm) in kidney, and 96.8% TRR (2.061 ppm). Based on these results, tembotrione is not extensively metabolized in ruminants.

The submitted study is acceptable and successfully delineates the amount and distribution of TRR in ruminant matrices.

E. REFERENCES

46695531 Hardwick, T.; Fisher, P. (2003) [Cyclohexyl-U-(Carbon 14)] - AE 0172747: Absorption, Distribution, Metabolism and Excretion Following Repeated Oral Administration to the Lactating Cow: Final Report. Project Number: 2014/059, 2014/059/D1145, 33421. Unpublished study prepared by Covance Laboratories, Ltd. 112 p.

F. DOCUMENT TRACKING

RDI: RAB1 Chemists (12/6/06)
Petition Number: PP#5F7009
DP#s: 325349, 325663, and 331222
PC Code: 012801

Template Version June 2005

Tembotrione/AE 0172747/PC Code 012801/Bayer CropScience/264
DACO 6.2/OPPTS 860.1300/OECD II 6.2.2, 6.2.3 & IIIA 8.2, 8.4.1, 8.4.2
Nature of the Residues in Livestock - Poultry

Primary Evaluator	George F. Kramer, Ph.D., Senior Chemist Registration Action Branch (RAB1) Health Effects Division (HED) (7509P)	Date: 18-JUL-2007
Approved by	P.V. Shah, Ph.D., Branch Senior Scientist RAB1/HED (7509P)	Date: 18-JUL-2007

This DER was originally prepared under contract by Dynamac Corporation (2275 Research Boulevard, Suite 300; Rockville, MD 20850; submitted 11/10/2006). The DER has been reviewed by HED and revised to reflect current Office of Pesticide Programs (OPP) policies.

STUDY REPORT:

46695533 Hardwick, T.; Fisher, P. (2003) [Cyclohexyl-U-(Carbon 14)]-AE 0172747: Absorption, Distribution, Metabolism and Excretion Following. Project Number: 2014/060, 2014/060/D1145, 33420. Unpublished study prepared by Covance Laboratories, Ltd. 198 p.

The petitioner has submitted an evaluation template for the study (Bayer CropScience DER to Study 2014-060), which was used to generate this DER; selected sections were copied without alteration or were copied and modified to more specifically reflect the Agency's data evaluation requirements.

EXECUTIVE SUMMARY:

Bayer CropScience has submitted a study investigating the metabolism of [cyclohexyl-U-^{14}C]tembotrione (CY label; specific activity 6.279 MBq/mg) in laying hens. The test substance was administered orally to groups of five hens at 1 ppm and 10 ppm in the diet. The actual doses, based on the average feed consumption during the experiment, were 1.14 and 12.34 ppm. The hens were dosed once daily for 14 consecutive days. Eggs were collected twice daily throughout the study, and tissues (muscle, fat, liver, and skin with attached fat) were collected at sacrifice, ~24 hours after the final dose.

Total radioactive residues (TRR) following dosing at 1.14 ppm in the diet were 0.001 ppm in egg whites, <0.001-0.018 ppm in egg yolks, 0.011 ppm in muscle, 0.004 ppm in fat, 1.688 ppm in liver, and 0.053 ppm in skin with attached fat. TRR following dosing at 12.34 ppm were 0.002-0.017 ppm in egg whites, below the limit of quantitation (LOQ) to 0.196 ppm in egg yolks, 0.063 ppm in muscle, 0.030 ppm in fat, 1.712 ppm in liver, and 0.404 ppm in skin with attached fat. At both dose levels, TRR were highest in liver. TRR plateaued after 3 days of dosing in egg whites and after 6 days of dosing in egg yolk. The majority of the radioactivity (~92-96% of the administered dose) was excreted.

Metabolic profiling was conducted on tissues and egg whites and yolk (Day 13) from the high-dose (12.34 ppm) hens. Solvent extraction with hexane, ethyl acetate, acetonitrile (ACN), and acidified ACN released ~80-94% of the TRR in muscle, fat, liver, skin and egg yolk; and 41% TRR in egg whites. Hexane extracted only minor residues in all matrices except fat, where ~24% TRR were extracted. Nonextractable residues following solvent extraction were 1.9-8.1% TRR (0.002-0.008 ppm) in muscle, fat, and skin; nonextractable residues in egg whites were

51.4% TRR (0.005 ppm). Nonextractable residues in liver and egg yolk were subjected to protease hydrolysis which released an additional 5-6% TRR, and a separate subsample of skin was subjected to protease hydrolysis without previous solvent extraction which released ~90% of the TRR. Nonextractable residues after exhaustive extractions were 1.7% TRR (0.029 ppm) in liver, 12.2% TRR (0.018 ppm) in egg yolk, and 1.8% TRR (0.007 ppm) in skin.

The extraction procedures were adequate; and the accountabilities were 91-102%. Residues were identified and quantitated by high-performance liquid chromatography (HPLC) equipped with a flow-through radiodetector and confirmed by liquid chromatography/mass spectroscopy (LC/MS). Adequate storage stability data were submitted to support the liver storage intervals and conditions. No additional storage stability data are required because it appears that all samples were stored for <6 months prior to initial analysis.

The major and only residue identified was the parent, tembotrione, identified at 90.5% TRR (0.057 ppm) in muscle, 23.3% TRR (0.007 ppm) in fat, 89.8% TRR (1.536 ppm) in liver, 90.1% TRR (0.364 ppm) in skin with attached fat, 79.7% TRR (0.114 ppm) in egg yolk, and 18.2% TRR (0.002 ppm) in egg whites. Up to three unknowns were observed in muscle, liver, and egg white. In muscle and egg white, no single unknown was present at >0.001 ppm. In liver, one unknown, present at 3.6% TRR (0.061 ppm), was further investigated by LC/MS and was tentatively identified as a hydroxy product of the ammonium-adducted parent compound; the position of hydroxylation could not be determined. The two remaining liver unknowns were each present at ≤2.3% TRR (≤0.040 ppm) and were not further investigated.

Based on the results of the CY-labeled hen metabolism study, tembotrione was not extensively metabolized in hens, with the major component in all tissues being parent compound. Only one other minor residue was tentatively identified in liver, the hydroxy metabolite of the parent compound, and a structure was not proposed.

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the livestock metabolism data are classified as scientifically acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document [DP# 325349].

COMPLIANCE:

Signed and dated Good Laboratory Practice (GLP), Quality Assurance and Data Confidentiality statements were provided. No GLP deviations were reported which would impact the study results or their interpretation.

A. BACKGROUND INFORMATION

Tembotrione, a new herbicide with broad use against mono- and dicotyledons in selected crops such as corn, is a 4-hydroxyphenylpyruvate deoxygenase (HPPD) inhibitor (bleacher). The test compound nomenclature and physiochemical properties of the test compound are presented in Tables A.1 and A.2, respectively.

TABLE A.1. Test Compound Nomenclature for Tembotrione.

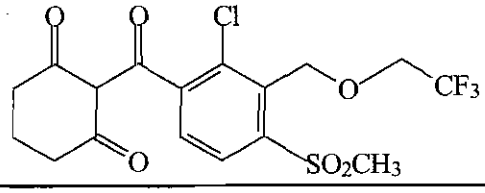
Compound: Tembotrione	Chemical Structure 
Proposed common name	Tembotrione
Company experimental name	AE 0172747
IUPAC name	2-{2-chloro-4-mesyl-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl}cyclohexane-1,3-dione
CAS name	2-[2-chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione
CAS #	335104-84-2
End-use product/EP	AE 0172747 Herbicide, EPA Reg No. 264-xxx

TABLE A.2. Physicochemical Properties of Technical Grade Tembotrione.

Parameter	Value	Reference (MRID#)
Melting point	117 °C	46695402
pH @ 24 °C	3.63	
Density (g/mL @ 20 °C)	1.56	
Water solubility (mg/L @ 20 °C)	0.22 at pH4 28.3 at pH 7 29.7 at pH 9	
Solvent solubility (g/L at 20 °C) DMSO Methylene Chloride Acetone Ethyl Acetate Toluene Hexane Ethanol	 >600 >600 300-600 180.2 75.7 47.6 8.2	
Vapor pressure (Torr, 20 °C)	8.25×10^{-11}	
Dissociation constant (pK_a)	3.2	
Octanol/water partition coefficient (P_{ow} @ 23 °C) (P_{ow} @ 24 °C) (P_{ow} @ 23 °C)	 0.0430 at pH 9.0 0.0807 at pH 7.0 144.9 at pH 2.0	
UV/visible absorption spectrum (nm)	Primary: 205 Secondary: 284 Tertiary: 240	

B. EXPERIMENTAL DESIGN

Two groups of five hens were orally dosed with CY-labeled tembotrione for 14 consecutive days. One group was dosed at a nominal rate of 1 ppm in the diet, and the other group was dosed at a nominal rate of 10 ppm in the diet. Upon receipt, hens were group housed for acclimatization. Hens were then placed in individual cages and acclimatized for 6 days prior to dosing. Hens were fed a commercial feed concentrate and grit, and feed consumption was recorded daily. Hens were dosed once daily in the morning. Information pertaining to the test animals and dietary and dosing regimes is presented in Tables B.1.1 - B.1.3.

B.1. Livestock

TABLE B.1.1. General Test Animal Information

Animal Numbers	Species	Breed	Age weeks	Weight at study initiation (kg)	Health Status	Description of housing/holding area
Group A 101F 102F 103F 104F 105F	Laying hens (*Gallus gallus*)	*Lohmann*	19-22	1.665-1.991	Good	Individual metabolism cages in unit controlled at 18-22 °C, 51-87% RH, 16-hr fluorescent light/day, 10 air exchanges/hr.
Group B 201F 202F 203F 204F 205F				1.505-1.985		

TABLE B.1.2. Test Animal Dietary Regime

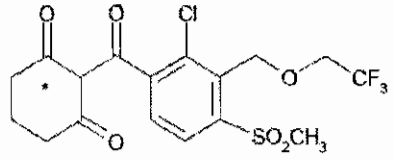
Animal Number	Composition of Diet	Feed consumption (kg/day), average	Water	Acelimation period	Predosing
Group A	Ground concentrate (507 P.H.L. Meal) plus grit at 0.15 kg/day (target)	0.132 kg/day	*Ad libitum*	24 days	None
Group B		0.125 kg/day			

TABLE B.1.3. Test Animal Dosing Regime

Animal Number	Treatment Type	Feeding Level (ppm test material in food)	Vehicle	Timing/Duration
Low dose (Group A)	Oral	1 ppm nominal (1.14 ppm actual)	Gelatin capsule containing cellulose	Once a day in the morning for 14 days
High Dose (Group B)		10 ppm nominal (12.34 ppm actual)		

B.2. Test Materials

The radiolabeled test substance was dissolved in ACN and isotopically diluted with nonlabeled tembotrione, then prepared in gelatin capsules for dosing. The test material characteristics are presented in Table B.2.1.

TABLE B.2.1. Test Material Characteristics, Radiolabeled	
Chemical structure	
Radiolabel position	[cyclohexyl ring UL-^{14}C]tembotrione
Lot No.	Z 32015-1
Purity	97.4% (by HPLC)
Specific activity (Bq)[1]	6.279 MBq/mg

[1] Bq = disintegrations per second

B.3. Sampling Information

Excreta and cage debris were collected daily, and eggs were collected twice daily. At 23-24 hours after the last dose, the hens were sacrificed, and samples of blood and tissues were collected.

TABLE B.3.1. Sample Collection Information			
Eggs collected	Excreta and cage wash collected	Interval from last dose to sacrifice	Tissues harvested and analyzed
Twice daily, predosing in the a.m. and in the afternoon following dose administration; average egg production was 80-87% during the acclimation period and 93-101% during the dosing phase.[1]	Once daily	23-24 hours	Muscle (breast and thigh), fat (perirenal and peritoneal), liver, and skin with subcutaneous fat

[1] 100% = one egg produced within a 24-hour interval.

B.4. Identification/Characterization of Residues

B.4.1. Sample Handling and Preparation

Eggs were pooled daily for each hen; afternoon eggs were stored at 1-10 °C until pooled with the following morning sample. Daily pooled eggs were separated into egg whites and yolks. All samples were homogenized and subsampled on the day of collection prior to storage. All egg (whites and yolks) and tissue samples were stored at <-10 °C. The in-life and analytical phases of the study were conducted at the same facility (Covance Laboratories, Ltd., Harrogate, England); therefore, samples were not shipped.

Pooled tissues and Day-13 egg yolks and whites from high-dose hens were subjected to sequential solvent extraction with hexane, ethyl acetate, ACN (1-2x), acidified ACN (1% formic acid; 1-2x), and ethyl acetate (skin only). For fat, the hexane extract was partitioned with ACN. For all tissues, the ACN and acidified ACN phases were combined and concentrated, and the ethyl acetate extracts were combined, if applicable, and concentrated. The concentrated ACN and ethyl acetate extracts for each tissue were then combined, concentrated to aqueous, and freeze-dried. The residues were reconstituted in ACN:water (1:1, v:v) and centrifuged to remove

particulate matter prior to HPLC analysis. The reconstituted residues of fat separated into upper and lower phases which were collected and centrifuged again to remove particulates which formed on storage. A second subsample of liver was extracted to generate a sufficient quantity of a metabolite (Rt = 23.3 min) for HPLC/MS analysis.

The nonextractable residues of liver were subjected to enzyme hydrolysis with protease (in 0.1 M phosphate buffer, pH 7.5, for ~18 hours at 37 °C). Residues were then extracted sequentially with ethyl acetate and ACN. The ethyl acetate extract was reduced to dryness, rinsed with methanol, concentrated again, and diluted with water, then filtered for HPLC analysis.

A separate subsample of skin was subjected to protease hydrolysis for ~21 hours, as described above for liver nonextractable residues, without prior extraction. The ethyl acetate and ACN extracts were concentrated, rinsed with methanol, concentrated again, diluted with water, filtered and combined for HPLC analysis.

The extraction scheme for liver, which is representative of all tissues, is presented in Figure B.4.1.1, and the protease hydrolysis procedures for liver and skin are presented in Figures B.4.1.2 and B.4.1.3, respectively. These figures were copied without alteration from MRID 46695533.

FIGURE B.4.1.1. Extraction Scheme for Liver.

Figure III: Extraction of liver with organic solvents

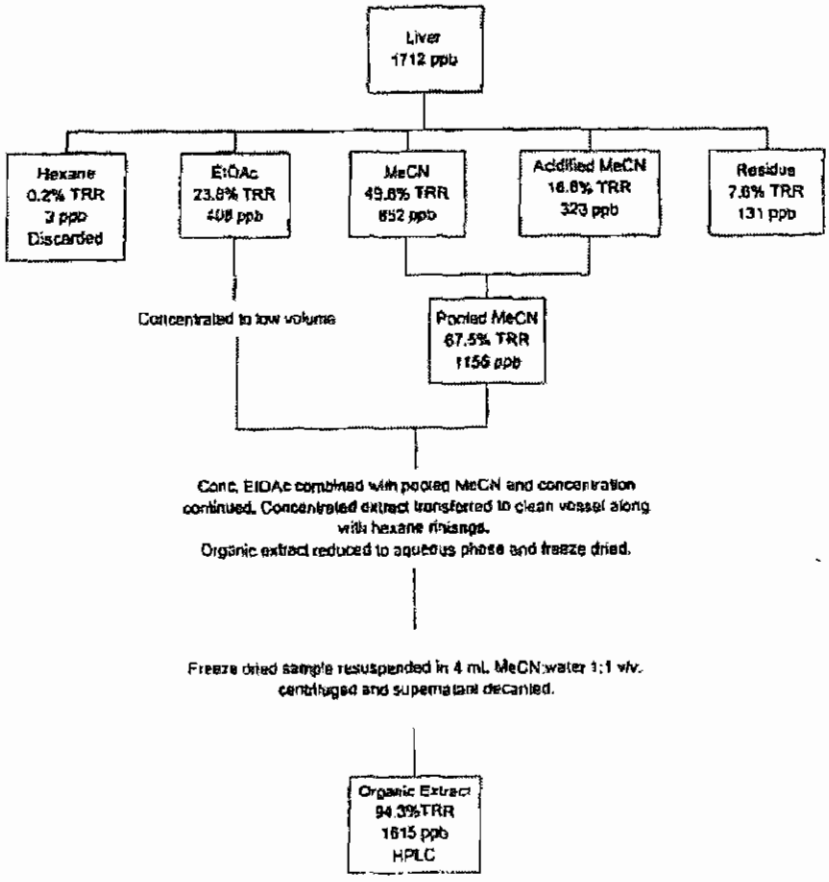


FIGURE B.4.1.2. Protease Hydrolysis of Nonextractable Residues of Liver.

Figure XI: The non-organically extractable residue of liver

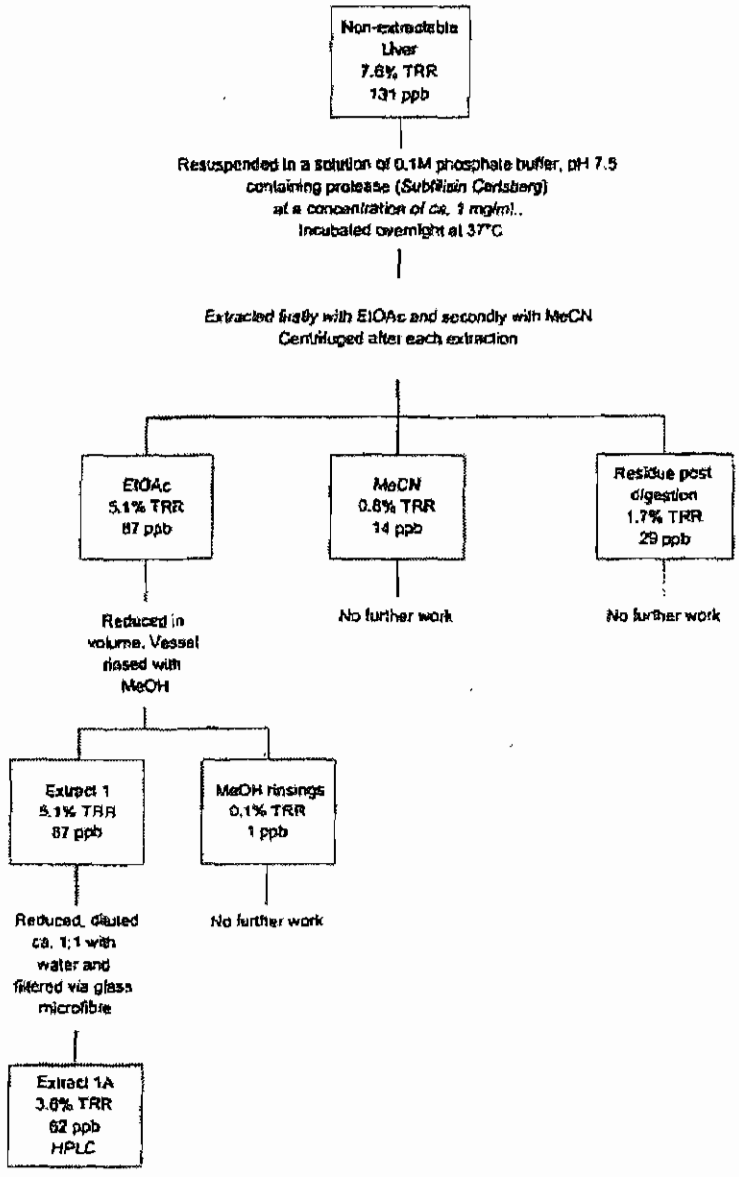
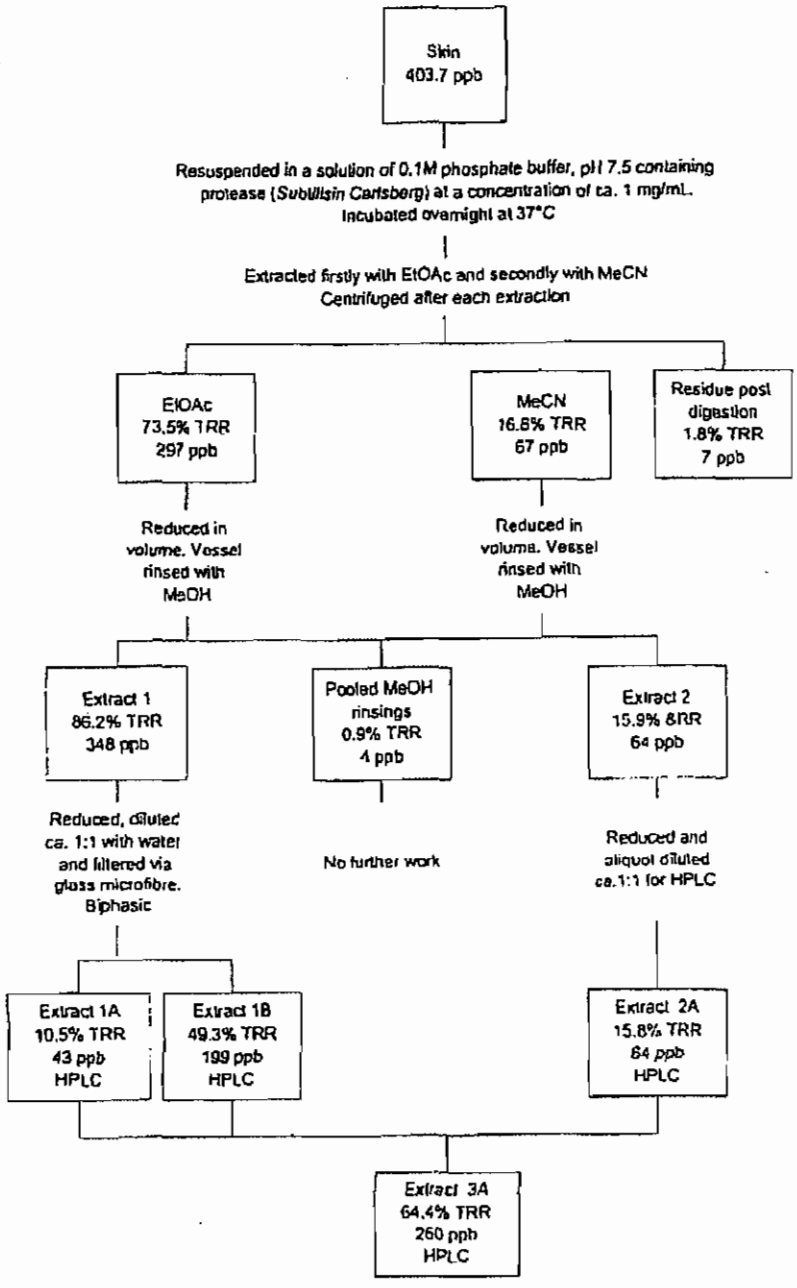


FIGURE B.4.1.3. Protease Hydrolysis of Skin.



B.4.2. Analytical Methodology

TRR were determined by liquid-scintillation counting (LSC), either directly or following solubilization or combustion. Radioactivity in extracts and hydrolysates was determined by direct LSC, and nonextractable radioactivity was determined by combustion/LSC. Extracts containing sufficient radioactivity were processed further for chromatographic analysis. The LOQ for TRR determinations was defined as 2x background.

Extracts of egg whites, yolks and tissues were analyzed by reverse-phase HPLC using a system equipped with a C18 column, a UV detector at 254 nm, and a flow-through radiodetector. A gradient mobile phase of water adjusted to pH 2 with trifluoroacetic acid:ACN was used. Residues were identified by retention time comparison with a non-labeled reference standard of tembotrione. Preparative HPLC was used to isolate the hydroxy metabolite in liver for LC/MS analysis.

Residue identification was confirmed by HPLC/MS. A quadrupole ion-trap mass spectrometer with electrospray LC/MS interface was coupled to a gradient HPLC system with conditions as defined above. Positive/negative-ion electrospray mass-spectrometric analysis was carried out with a capillary temperature of 140 °C, a capillary voltage of 33/-18 V and a spray voltage of 2.5/2 kV. The scan range was *m/z* 120 to 700. A second system utilizing a C8 column and a mobile phase of 10 mM aqueous ammonium acetate:methanol and the same MS parameters was used for investigation of the liver metabolite.

C. RESULTS AND DISCUSSION

The storage conditions and intervals for hen matrices are presented in Table C.1. The petitioner did not provide the dates of sample extraction and analysis for all matrices, but stated that profiling of tissues, with the exception of liver, was completed within 6 months of animal necropsy; liver was subjected to extra processing to generate a metabolite for identification purposes. Based on dated chromatograms and spectra included in the submission, liver was stored for ~2 months prior to initial analysis and was re-extracted for metabolite characterization ~9.8 months after sacrifice; HPLC/MS analysis of the organic extracts of liver, egg yolk, and skin were conducted within ~6.6 months of sacrifice. No significant differences were observed on comparison of the metabolite profiles for liver analyzed ~2 and 9.8 months after sacrifice. These data are adequate to support the storage interval for liver. No additional storage stability data are required because, based on the available dates, it appears that all samples were stored for ≤6 months prior to initial analysis. The petitioner should note for future submissions that the critical study dates are required for each sample.

TRR in laying hen eggs and tissues are presented in Table C.2.1. Following oral dosing with CY-labeled tembotrione for 14 days at 1.14 ppm in the diet, TRR were 0.001 ppm in egg whites, <0.001-0.018 ppm in egg yolks, 0.011 ppm in muscle, 0.004 ppm in fat, 1.688 ppm in liver, and 0.053 ppm in skin with attached fat. TRR following dosing at 12.34 ppm were 0.002-0.017 ppm in egg whites, <LOQ-0.196 ppm in egg yolks, 0.063 ppm in muscle, 0.030 ppm in fat, 1.712 ppm in liver, and 0.404 ppm in skin with attached fat. At both dose levels, TRR were highest in liver. TRR plateaued after 3 days of dosing in egg whites and after 6 days of dosing in egg yolk. The majority of the radioactivity (~92-96% of the administered dose) was excreted. The pharmacokinetics of tembotrione in excreta and eggs are presented graphically in Figures C.2.1 - C.2.3.

Metabolic profiling was conducted on tissues and egg whites and yolk (Day 13) from the high-dose (10 ppm) hens. The distribution of the radioactivity in laying hen matrices is presented in Table C.2.2. Solvent extraction with hexane, ethyl acetate, ACN, and acidified ACN released

~80-94% of the TRR in muscle, fat, liver, skin and egg yolk; and 41% TRR in egg whites. Hexane extracted only minor residues in all matrices except fat, where ~24% TRR was extracted. Nonextractable residues following solvent extraction were 1.9-8.1% TRR (0.002-0.008 ppm) in muscle, fat, and skin; nonextractable residues in egg whites were 51.4% TRR (0.005 ppm). Nonextractable residues in liver and egg yolk were subjected to protease hydrolysis which released an additional 5-6% TRR, and a separate subsample of skin was subjected to protease hydrolysis without previous solvent extraction which released ~90% of the TRR. Nonextractable residues after exhaustive extractions were 1.7% TRR (0.029 ppm) in liver, 12.2% TRR (0.018 ppm) in egg yolk, and 1.8% TRR (0.007 ppm) in skin. The extraction procedures were adequate; and the accountabilities were 91-102%. Residues were identified and quantitated by HPLC, and confirmed by LC/MS.

The characterization and identification of residues in hen egg yolk and tissues are summarized in Table C.2.3. The major and only residue identified was the parent, tembotrione, identified at 90.5% TRR (0.057 ppm) in muscle, 23.3% TRR (0.007 ppm) in fat, 89.8% TRR (1.536 ppm) in liver, 90.1% TRR (0.364 ppm) in skin with attached fat, 79.7% TRR (0.114 ppm) in egg yolk, and 18.2% TRR (0.002 ppm) in egg whites. Up to three unknowns were observed in muscle, liver, and egg white. In muscle and egg white, no single unknown was present at 0.001 ppm. In liver, one unknown, present at 3.6% TRR (0.061 ppm), was further investigated by LC/MS and was tentatively identified as a hydroxy product of the ammonium-adducted parent compound; the position of hydroxylation could not be determined. The two remaining liver unknowns were each present at ≤2.3% TRR (≤0.040 ppm) and were not further investigated.

The petitioner noted that higher levels of radioactivity were released with extraction of the second liver sample (used to obtain additional amounts of the metabolite for identification) and that with HPLC analysis the metabolite at Rt = 23.3 min was present at a lower level, 0.019 ppm versus 0.061 ppm in the initial sample. The petitioner did not investigate the differences between the two liver samples further.

C.1. Storage Stability

All samples were homogenized and subsampled on the day of collection prior to storage; processed samples were stored at <-10 °C. The petitioner did not provide the dates of sample extraction and analysis for all matrices, but stated that profiling of tissues, with the exception of liver, was completed within 6 months of animal necropsy; liver was subjected to extra processing to generate a metabolite for identification purposes. The petitioner included a dated HPLC chromatogram for liver indicating that initial profiling was completed within 2.0 months. Dated chromatograms and spectra were also included in the submission for liver, egg yolk, and skin indicating that HPLC/MS analysis of the organic extracts was conducted within 202 days (6.6 months) of sacrifice and that HPLC/MS analysis to identify the liver metabolite was completed within 10.1 months of sacrifice.

In support of the storage intervals and conditions of the submitted study, the petitioner presented a side-by-side comparison of the HPLC chromatogram for liver reflecting initial profiling and a chromatogram reflecting re-extraction to isolate the metabolite conducted 237 days (7.8 months) after sacrifice. No significant differences were observed on comparison of the metabolite

profiles.

TABLE C.1. Summary of Storage Conditions.

Matrix	Storage Temperature (°C)	Actual Storage Duration	Interval of Demonstrated Storage Stability
Liver	<-10	62 days (2.0 months): initial profiling. 202 days (6.6 months): HPLC/MS organic extract. 237 days (7.8 months): re-extraction. 306 days (10.1 months): HPLC/MS hydroxy metabolite.	Metabolic profile unchanged in liver re-extracted and analyzed 237 days (7.8 months) after collection.
Egg yolk and skin		202 days (6.6 months): HPLC/MS organic extract.	None provided.
Egg yolk, egg whites, fat, muscle, and skin		No dates provided.	None provided.

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

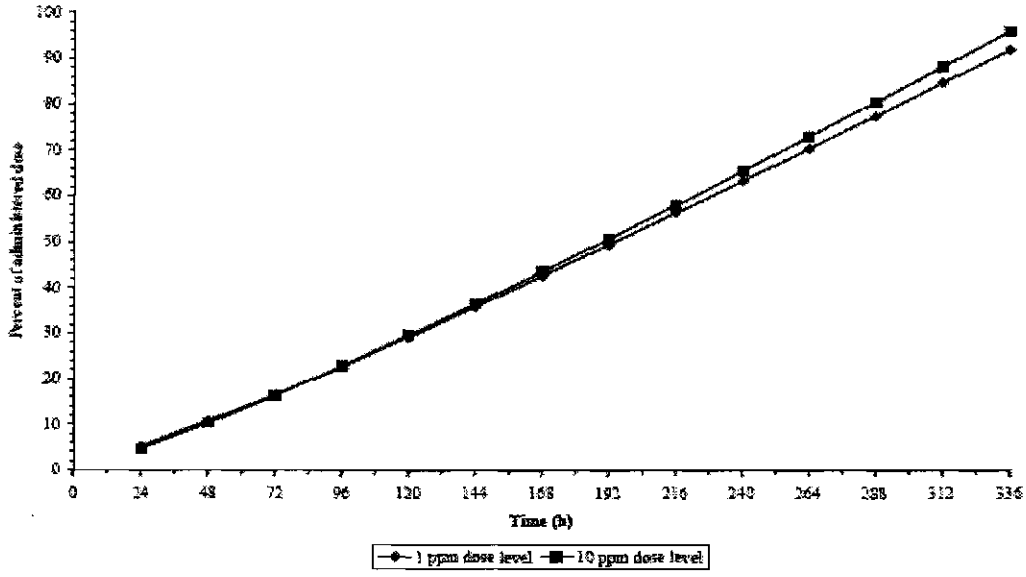
TABLE C.2.1. TRR in Egg, Tissue and Excreta.[1]

Matrix	Collection Timing	Low-dose hens (1 ppm)		High-dose hens (10 ppm)	
		% AD	ppm	% AD	ppm
Excreta	Daily; study duration	91.81	--	95.83	--
Cage wash	Daily; study duration	0.037	--	0.032	--
Total excreta		91.85	--	95.86	--
Egg, whites	Day 1	<0.001	0.0006	<0.001	0.0016
	Day 2	0.001	0.0009	<0.001	0.0109
	Day 3	0.001	0.0013	<0.001	0.0136
	Day 4	0.001	0.0013	0.001	0.0169
	Day 5	0.001	0.0010	0.001	0.0097
	Day 6	0.001	0.0009	0.001	0.0091
	Day 7	0.001	0.0006	0.001	0.0079
	Day 8	0.001	0.0009	0.001	0.0084
	Day 9	0.001	0.0011	0.001	0.0091
	Day 10	0.001	0.0008	0.001	0.0070
	Day 11	0.001	0.0008	0.001	0.0067
	Day 12	0.001	0.0007	0.001	0.0063
	Day 13	0.001	0.0013	0.001	0.0106
	Day 14	0.002	0.0008	0.001	0.0071
	Total; duration of study	0.015	--	0.012	--
Egg, yolks	Day 1	<0.001	0.0002	<LOQ	<LOQ
	Day 2	<0.001	0.0008	<0.001	0.0106
	Day 3	<0.001	0.0031	<0.001	0.0325
	Day 4	0.002	0.0074	0.001	0.0850
	Day 5	0.002	0.0138	0.001	0.1021
	Day 6	0.002	0.0161	0.002	0.1959
	Day 7	0.004	0.0170	0.003	0.1913
	Day 8	0.005	0.0183	0.004	0.1947
	Day 9	0.006	0.0172	0.004	0.1662
	Day 10	0.005	0.0160	0.005	0.1453
	Day 11	0.007	0.0161	0.005	0.1370
	Day 12	0.005	0.0184	0.004	0.1425
	Day 13	0.006	0.0176	0.006	0.1431
	Day 14	0.008	0.0175	0.006	0.1303
	Total; duration of study	0.052	--	0.041	--
Muscle	Sacrifice	0.006	0.011	0.003	0.063
Fat		<0.001	0.004	<0.001	0.030
Liver		0.219	1.688	0.022	1.712
Skin with attached fat		0.002	0.053	0.001	0.404
Blood		<0.001	0.171	<0.001	0.484
Sum of Administered Dose (%)		92.15	--	95.94	--

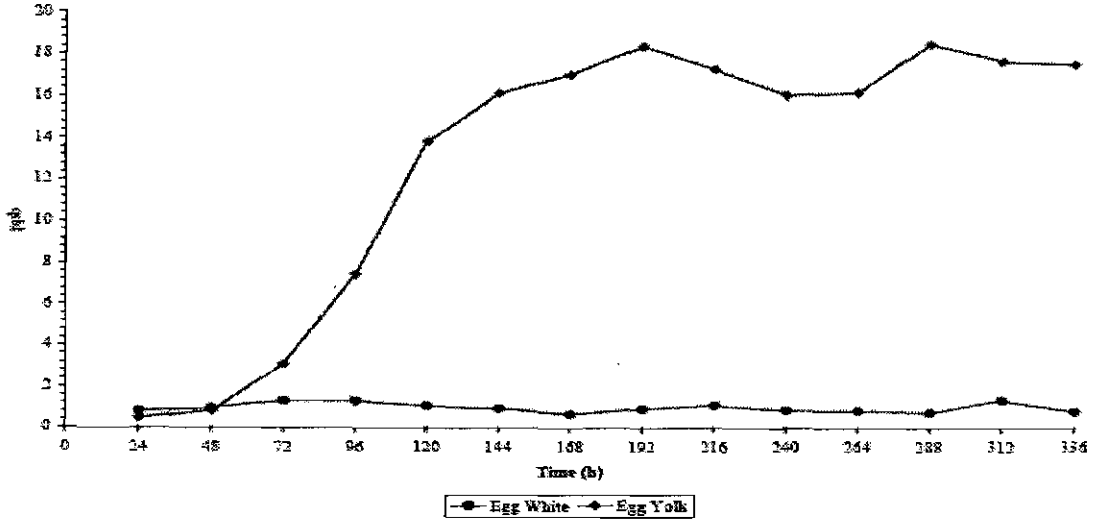
[1] Mean of the five hens in the group. The LOQ for LSC determinations was defined as 2x background.

FIGURES C.2.1-C.2.3. Pharmacokinetics of Tembotrione4 in Excreta and Egg of Laying Hens.

Excreta: Cumulative recovery of radioactivity in laying hens following 14 daily oral administrations of [cyclohexyl-U-^{14}C]-AE 0172747 at nominal dose levels of 1 *and* 10 ppm based on diet



Eggs: Mean concentrations of radioactivity in laying hens following 14 daily oral administrations of [cyclohexyl-U-^{14}C]-AE 0172747 at a nominal dose level of 1 ppm based on diet



Eggs: Mean concentrations of radioactivity in laying hens following 14 daily oral administrations of [cyclohexyl-U-^{14}C]-AE 0172747 at a nominal dose level of 10 ppm based on diet

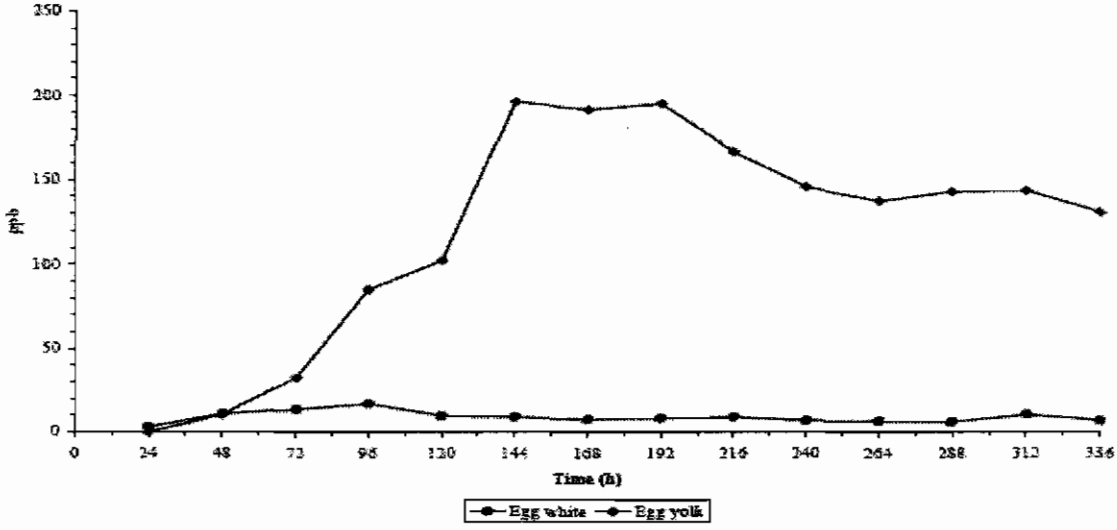


TABLE C.2.2. Distribution of the Parent and the Metabolites in Hen Matrices Following Administration of [cyclohexyl-U-^{14}C]Tembotrione Once a Day for 14 Days at 12.34 ppm.[1]

Metabolite Fraction	Muscle		Fat		Liver		Skin		Egg Yolk, Day 13		Egg White, Day 13	
	TRR=0.063 ppm		TRR=0.030 ppm		TRR=1.712 ppm		TRR=0.404 ppm		TRR=0.143 ppm		TRR=0.011 ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Subsample 1												
Hexane extract	0.4	<0.001	23.7	0.007	0.2	0.003	0.4	0.002	0.6	0.001	0.8	<0.001
Hexane phase	--	--	17.8	0.005	--	--	--	--	--	--	--	--
ACN phase	--	--	2.0	0.002	--	--	--	--	--	--	--	--
EtOAc extract(s)	72.4	0.046	61.2	0.018	23.8	0.408	69.0	0.278	45.9	0.066	6.7	0.001
ACN extract	15.1	0.010	6.4	0.002	49.8	0.852	14.5	0.059	20.9	0.029	16.0	0.002
Acidified ACN extract	4.0	0.003	2.9	0.001	18.8	0.323	4.2	0.017	13.0	0.019	17.1	0.002
Combined extracts [3]	80.5	0.051	NR	NR	94.3	1.615	61.8	0.249	67.6	0.097	37.5	0.004
Tembotrione	90.5	0.057			84.8	1.451	87.6	0.354	79.7	0.114	18.2	0.002
Unknown (Rt = 3.2-3.7 min)	1.6	0.001			1.8	0.030	--	--	--	--	6.6	0.001
Hydroxy metabolite (Rt=23.3/25.7 min)	--	--			3.6	0.061	--	--	--	--	--	--
Unknown (Rt = 25.7 min)	--	--			--	--	--	--	--	--	11.4	0.001
Unknown (Rt=24.1/28.2 min)	--	--			2.3	0.040	--	--	--	--	3.5	<0.001
Upper phase			13.3	0.003								
Lower phase			25.3	0.008								
Tembotrione			23.3	0.007								
Nonextractable	8.1	0.005	5.8	0.002	7.6	0.131	1.9	0.008	16.8	0.024	51.4	0.005
Protease EtOAc					5.1	0.087			4.9	0.007		
Tembotrione					5.0	0.085						
Unknown (Rt = 22.9 min)					0.1	0.002						
Protease ACN					0.8	0.014			0.1	<0.001		
MeOH rinse					0.1	0.001						
Nonextractable					1.7	0.029			12.2	0.018		
Subsample 2												
Protease EtOAc							73.5	0.297				
Protease ACN							16.6	0.067				
Comb. EtOAc + ACN							64.4	0.260				
Tembotrione							90.1	0.364				
MeOH rinse							0.9	0.004				
Nonextractable							1.8	0.007				

[1] Shading indicates that the extraction step and/or characterization analysis was not conducted (or is not applicable) for the matrix in question. Selected %TRR values were calculated by the study reviewer from % region values provided by the petitioner. NR = Not reported.

[2] Sum of two extracts for skin.

Combined ethyl acetate, ACN and acidified ACN extracts, after freeze drying, for HPLC analysis.

[3] Includes EtOAc, ACN, and acidified ACN for muscle, liver, skin, and egg white, and EtOAc, ACN, acidified ACN, and ACN phase of hexane extract for fat.

TABLE C.2.3. Summary of Characterization and Identification of Radioactive Residues in Laying Hen Matrices Following Administration of [cyclohexyl-U-^{14}C]Tembotrione Once a Day for 14 Days at 12.34 ppm.

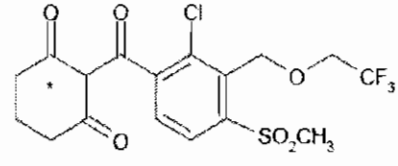
Metabolite Fraction	Muscle		Fat		Liver		Skin[1]		Egg Yolk, Day 13		Egg White, Day 13	
	TRR=0.063 ppm		TRR=0.030 ppm		TRR=1.712 ppm		TRR=0.404 ppm		TRR=0.143 ppm		TRR=0.011 ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Tembotrione	90.5	0.057	23.3	0.007	89.8	1.536	90.1	0.364	79.7	0.114	18.2	0.002
Hydroxy metabolite	--	--	--	--	3.6	0.061	--	--	--	--	--	--
Unknowns	1.6	0.001	--	--	4.2	0.072	--	--	--	--	21.5	<0.003
Hexane soluble	0.4	<0.001	17.8	0.005	0.2	0.003	--	--	0.6	0.001	0.8	<0.001
Organic upper phase	--	--	13.3	0.003	--	--	--	--	--	--	--	--
Protease EtOAc	--	--	--	--	--	--	--	--	4.9	0.007	--	--
Protease ACN	--	--	--	--	0.8	0.014	--	--	0.1	<0.001	--	--
Protease MeOH rinse	--	--	--	--	0.1	0.001	0.9	0.004	--	--	--	--
Total identified	90.5	0.057	23.3	0.007	93.4[2]	1.597	90.1	0.364	79.7	0.114	18.2	0.002
Total characterized	2.0	0.001	13.3	0.003	5.3	0.090	0.9	0.004	5.6	0.008	22.3	0.003
Total extractable	91.9	0.059	94.2	0.028	98.6	1.688	91.0	0.368	85.4	0.122	40.6	0.005
Unextractable[3]	8.1	0.005	5.8	0.002	1.7	0.029	1.8	0.007	12.2	0.018	51.4	0.005
Accountability[4]	102		100		100		92.8		97.9		90.9	

[1] Subsample 2 results reported.
[2] Includes the hydroxy metabolite which was tentatively identified by HPLC/MS; no structure provided by the petitioner.
[3] Residues remaining after exhaustive extractions.
[4] Accountability = (Total extractable + Total unextractable)/(TRR from combustion analysis; see TABLE C.2.1) * 100.

C.3. Proposed Metabolic Profile

Based on the results of the CY-labeled hen metabolism study, tembotrione was not extensively metabolized in hens, with the major component in all tissues being parent compound. Only one other minor residue was tentatively identified in liver, the hydroxy metabolite of the parent compound, and a structure was not proposed. A metabolic pathway was not proposed.

TABLE C.3.1. Identification of Compounds from Metabolism Study

Common name/code	Chemical name (CAS)	Chemical structure
Tembotrione (parent)	2-[2-Chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione	

D. CONCLUSION

Following oral dosing for 14 days with CY-labeled tembotrione at 1.14 ppm in the diet, TRR in laying hen matrices were 0.001 ppm in egg whites, <0.001-0.018 ppm in egg yolks, 0.011 ppm in muscle, 0.004 ppm in fat, 1.688 ppm in liver, and 0.053 ppm in skin with attached fat. TRR in hen matrices following dosing at 12.34 ppm were 0.002-0.017 ppm in egg whites, <LOQ-0.196 ppm in egg yolks, 0.063 ppm in muscle, 0.030 ppm in fat, 1.712 ppm in liver, and 0.404 ppm in skin with attached fat. At both dose levels, radioactivity was highest in liver. Radioactivity plateaued after 3 days of dosing in egg whites and after 6 days of dosing in egg yolk. The majority of the radioactivity (~92-96% of the administered dose) was excreted.

Metabolic profiling was conducted on tissues and egg whites and yolk (Day 13) from the high-dose hens. Samples were subjected to sequential solvent extraction with hexane, ethyl acetate, ACN and acidified ACN. The nonextractable residues of liver and egg yolk were subjected to protease hydrolysis, which released additional residues, and a separate subsample of skin was subjected to protease hydrolysis without prior solvent extraction. These procedures adequately extracted the majority of residues from all hen matrices except egg whites, where nonextractable residues accounted for only 0.005 ppm.

The major and only residue identified was the parent, tembotrione. Tembotrione was identified at ~91% TRR in muscle, 23% TRR in fat, 90% TRR in liver, 90% TRR (0.364 ppm) in skin with attached fat, 80% TRR (0.114 ppm) in egg yolk, and 18% TRR (0.002 ppm) in egg whites. A single hydroxy metabolite was tentatively identified in liver at 3.6% TRR.

Based on the results of the CY-labeled hen metabolism study, tembotrione was not extensively metabolized in hens, with the major component in all tissues being parent compound. The submitted study is acceptable and successfully delineates the amount and distribution of TRR in poultry matrices following dosing with CY-labeled tembotrione.

E. REFERENCES

None.

F. DOCUMENT TRACKING

RDI: RAB1 Chemists (12/13/06)
Petition Number: PP#5F7009
DP#s: 325349, 325663, and 331222
PC Code: 012801

Template Version June 2005

Tembotrione/AE 0172747/PC Code 012801/Bayer CropScience/264
DACO 7.2.1, 7.2.2, and 7.2.3/OPPTS 860.1340/OECD IIA 4.2.5, 4.2.6 and 4.3
Residue Analytical Method – Poultry Tissues and Egg

Primary Evaluator	George F. Kramer, Ph.D., Senior Chemist Registration Action Branch (RAB1) Health Effects Division (HED) (7509P)	Date: 18-JUL-2007
Approved by	P.V. Shah, Ph.D., Branch Senior Scientist RAB1/HED (7509P)	Date: 18-JUL-2007

This DER was originally prepared under contract by Dynamac Corporation (2275 Research Boulevard, Suite 300; Rockville, MD 20850; submitted 11/10/2006). The DER has been reviewed by HED and revised to reflect current Office of Pesticide Programs (OPP) policies.

STUDY REPORTS:

46695539 Bognar, R.; Coopersmith, H.; Williams, L. E. (2004) AE 0172747: An Analytical Method for the Determination of Residues of AE 0172747 in Poultry Tissues and Eggs Matrices Using LC/MS/MS. Project Number; RAAEX002. Unpublished study prepared by Bayer CropScience. 36 pages.

46695541 Summer, S. J. (2005) Independent Laboratory Validation of "AE 0172747: An Analytical Method for the Determination of Residues of AE 0172747 in Poultry Tissues and Egg Matrices Using LC/MS/MS". Project Number RAAEX004; Study No.: N106801. Unpublished study prepared by Battelle. 79 pages.

The petitioner has submitted an evaluation template for the above-listed studies, which was used to generate this DER; selected sections were copied without alteration or were copied and modified to more specifically reflect the Agency's data evaluation requirements.

EXECUTIVE SUMMARY:

Bayer CropScience has submitted descriptions and validation data for liquid chromatography/mass spectroscopy (LC/MS)/MS Method AE-004-A04-02. The method determines residues of tembotrione *per se* in poultry tissues (skin, muscle, and liver) and eggs (white and yolk). It was the data-collection method used for determination of tembotrione residues in samples collected from a poultry feeding study (refer to 46695605.der.doc) and is also one of the proposed enforcement methods associated with PP#5F7009.

Using Method AE-004-A04-02, residues in poultry matrices are extracted with acetonitrile (ACN):deionized water (1:1,v:v) using accelerated solvent extraction. Extracted residues of tembotrione are fortified with the internal standard, diluted, and an aliquot of the diluted extract is filtered and concentrated. A 6% formic acid solution is added to the concentrated extract. The extract is diluted and filtered for LC/MS/MS analysis. Quantitation of AE 0142747 is done against a known amount of deuterated internal standard. Identifications are confirmed by comparing the ion ratio of the analyte to that of the analytical standard. The validated limit of quantitation (LOQ) reported in the method submission is 0.010 ppm for all matrices. The calculated limits of detection (LODs) for whole egg, poultry skin, poultry muscle, and poultry liver were 0.0018 ppm, 0.0031 ppm, 0.0025 ppm, and 0.0025 ppm, respectively.

The initial validation of Method AE-004-A04-02, performed by the petitioner, was conducted using control samples of whole eggs and chicken skin, muscle, and liver. The method recoveries were adequate and within the acceptable range of 70-120%. Following fortification of samples at 0.010 ppm (LOQ), 0.050 ppm and 0.200 ppm, recoveries of tembotrione ranged 77-102% in chicken skin, 71-97% in whole egg, 74-98% in chicken muscle, and 79-106% in chicken liver. The concurrent method recoveries from the analysis of samples from the poultry feeding study were also acceptable and indicate that Method AE-004-A04-02 is adequate for data collection.

Method AE-004-A04-02 was successfully validated by an independent laboratory using whole eggs as the matrix. The mean recoveries were 92.9%, 90.1%, and 92.8% at spike levels of 0.01, 0.02, and 0.10 ppm, respectively. Although not identified by its method designation number, a similar LC/MS/MS method was adequately radiovalidated using aged samples of whole eggs obtained from a laying hen metabolism study; the results of the radiovalidation study which included data for both beef liver and poultry eggs are summarized in 46695536.der.doc.

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the analytical method test data are classified as acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document [DP# 325349].

COMPLIANCE:

Signed and dated Good Laboratory Practice (GLP), Quality Assurance and Data Confidentiality statements were provided. No deviations from regulatory requirements were reported which would have an impact on the validity of the study.

A. BACKGROUND INFORMATION

Tembotrione, a new herbicide with broad use against mono- and dicotyledons in selected crops such as corn, is a 4-hydroxyphenylpyruvate deoxygenase (HPPD) inhibitor (bleacher). The test compound nomenclature and physiochemical properties of the test compound are presented in Tables A.1 and A.2, respectively.

TABLE A.1. Test Compound Nomenclature for Tembotrione.

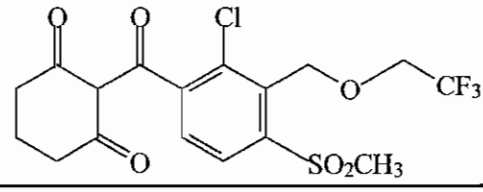
Compound: Tembotrione	Chemical Structure 
Proposed common name	Tembotrione
Company experimental name	AE 0172747

TABLE A.1. Test Compound Nomenclature for Tembotrione.	
IUPAC name	2-{2-chloro-4-mesyl-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl}cyclohexane-1,3-dione
CAS name	2-[2-chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione
CAS #	335104-84-2
End-use product/EP	AE 0172747 Herbicide, EPA Reg No. 264-xxx

TABLE A.2. Physicochemical Properties of Technical Grade Tembotrione.		
Parameter	Value	Reference (MRID#)
Melting point	117 °C	46695402
pH @ 24 °C	3.63	
Density (g/mL @ 20 °C)	1.56	
Water solubility (mg/L @ 20 °C)	0.22 at pH 4 28.3 at pH 7 29.7 at pH 9	
Solvent solubility (g/L at 20 °C) DMSO Methylene Chloride Acetone Ethyl Acetate Toluene Hexane Ethanol	 >600 >600 300-600 180.2 75.7 47.6 8.2	
Vapor pressure (Torr, 20 °C)	8.25×10^{-11}	
Dissociation constant (pK_a)	3.2	
Octanol/water partition coefficient (P_{ow} @ 23 °C) (P_{ow} @ 24 °C) (P_{ow} @ 23 °C)	 0.0430 at pH 9.0 0.0807 at pH 7.0 144.9 at pH 2.0	
UV/visible absorption spectrum (nm)	Primary: 205 Secondary: 284 Tertiary: 240	

B. MATERIALS AND METHODS

B.1. Data-Gathering Method

Method AE-004-A04-02 was the data-collection method used for the analysis tembotrione residues in egg and poultry tissue samples collected from a poultry feeding study (refer to 46695605.der.doc) and is entitled "AE 0172747: An Analytical Method for the Determination of Residues of AE 0172747 in Poultry Tissues and Egg Matrices Using LC/MS/MS."

B.1.1. Principle of the Method:

Briefly, poultry and egg matrices are extracted with ACN:deionized water (1:1,v:v) using accelerated solvent extraction; see Table B.1.1. Extracted residues of tembotrione are fortified with the internal standard, diluted, and an aliquot of the diluted extract is filtered and concentrated. A 6% formic acid solution is added to the concentrated sample. The extract is

diluted and filtered for LC/MS/MS analysis. Quantitation of tembotrione is done against a known amount of deuterated internal standard. Identifications are confirmed by comparing the ion ratio of the analyte to that of the analytical standard.

TABLE B.1.1. Summary Parameters for the Analytical Method Used for the Quantitation of Tembotrione Residues in Poultry Tissue and Egg Matrices.

Method ID	AE-004-A04-02
Analyte(s)	Tembotrione
Extraction solvent/teehnique	Homogenized samples are extracted through an ASE 200 accelerated solvent extractor with ACN:deionized water (1:1,v:v).
Cleanup strategies	The extracts are fortified with thc internal standard, diluted and an aliquot of the diluted extract is filtered and concentrated. A 6% formic acid solution is added to the concentrated sample. The extract is diluted and then filtered.
Instrument/Detector	TSQ 7000/ SymmetryShield™ RP 8 5µm 3.0 x 150 mm/MS/MS
Standardization method	External and internal standardization. Five calibration standards, containing internal standards, are injected and a calibration curve is constructed from the rclative responscs (RRs; analyte peak area divided by internal standard) versus standard concentration. Samples arc bracketed by calibration standards at thc beginning and end of the run. Results are calculated using linear regression.
Stability of std solutions	Primary stock solutions of tembotrione are to be stored frozen and prepared every 3 months. Secondary stock standard and calibration standard solutions are to be prepared every 3 months.
Retention times	≈ 6.88 minutes for tembotrione

B.2. Enforcement Method

The proposed enforcement method for poultry matrices is the same as the data-gathering method, AE-004-A04-02.

C. RESULTS AND DISCUSSION

C.1. Data-Gathering Method

The initial validation of Method AE-004-A04-02, performed by the petitioner, was conducted using control samples of whole eggs and chicken skin, muscle, and liver. The results of method validation and verification are presented in Table C.1.1. Following fortification of samples at 0.010 ppm (LOQ), 0.050 ppm and 0.200 ppm, recoveries of tembotrione ranged 77-102% in chicken skin, 71-97% in whole egg, 74-98% in chicken muscle, and 79-106% in chicken liver.

Although not identified by its method designation number, a similar LC/MS/MS method was adequately radiovalidated using aged samples of whole eggs obtained from a laying hen metabolism study; the results of the radiovalidation study which included data for both beef liver and poultry eggs are summarized in 46695536.der.doc.

TABLE C.1.1. Recovery Results from Method Validation of Poultry Tissues and Egg Matrices using the Data-Gathering Analytical Method.

Matrix	Spiking Level (ppm)[1]	Recoveries Obtained	Mean Recovery ± SD (CV)[2]
Chicken Skin	0.01	96, 87, 77, 84, 77, 102, 98	89 ± 10.1 (11.4)
	0.05	89, 94, 78	87 ± 8.2 (9.4)
	0.20	80, 85	83 ± 3.5 (4.3)
Whole Egg	0.01	85, 81, 93, 94, 79, 93, 87	87 ± 6.1 (7.0)
	0.05	85, 97, 85	89 ± 6.9 (7.8)
	0.20	71, 82	77 ± 7.8 (10.2)
Chicken Muscle	0.01	77, 98, 87, 82, 74, 77, 84	83 ± 8.1 (9.8)
	0.05	93, 93, 93	93 ± 0.0 (0.0)
	0.20	85, 86	86 ± 0.7 (0.8)
Chicken Liver	0.01	106, 87, 89, 92, 90, 88, 79	90 ± 8.1 (9.0)
	0.05	87, 91, 91	90 ± 2.3 (2.6)
	0.20	88, 98	93 ± 7.1 (7.6)

[1] Standards were prepared in acetonitrile.
[2] The mean, standard deviation, and coefficients of variance (CVs) were calculated by the petitioner.

TABLE C.1.2. Characteristics for the Data-Gathering Analytical Method Used for the Quantitation of Tembotrione Residues in Poultry Matrices.

Analyte	Tembotrione
Equipment ID	ConstaMetric® 3200 HPLC and ThermoFinnigan TSQ 7000 with triple quadrupole mass spectrometer; SymmetryShield™ RP 8 5µm (3.0mm x 150mm) column
LOQ	0.010 ppm The LOQ was determined as lowest fortification level with adequate recovery.
LOD	whole egg: 0.0018 ppm poultry skin: 0.0031ppm poultry muscle: 0.0026 ppm poultry liver: 0.0025 ppm The method for calculating the LODs was not provided by the petitioner.
Accuracy/Precision	Percent recoveries and CVs indicate acceptable accuracy/precision at 0.01, 0.05, and 0.20 ppm for chicken skin, whole egg, chicken muscle, and chicken liver. Recovery ranges (and CVs) were 77-102% (4.3-11) in chicken skin, 71-97% (7.0-10) in whole egg, 74-98% (0-9.8) in chicken muscle, and 79-106% (2.6-9.0) in chicken liver. See Table C.1.1 above.
Reliability of the Method/ [ILV]	An independent laboratory method validation (ILV) was conducted to verify the reliability of method No. AE-004-A04-02 for the determination of tembotrione residues in poultry matrices. The values obtained are indicative that method AE-004-A04-02 is reliable; see Section C.3.
Linearity	The relative response was linear, with typical coefficient of determination, r2 = 0.9994 for parent, from calibration curves ranging from 5.0 to 500 ppb.
Specificity	The control chromatograms generally have no peaks above the chromatographic background and the spiked sample chromatograms contain only the analyte peak of interest within the retention window. Peaks were well defined and symmetrical. An injection of the blank solvent solution used for final sample dilution is injected between the high standard, the control sample to prevent residue carry-over between that sequences of injections.

C.2. Enforcement Method

The proposed enforcement method for tissue matrices is the same as the data-gathering method, AE-004-A04-02.

C.3. ILV

Method AE-004-A04-02 was subjected to an ILV. The ILV was conducted by Battelle (Research Triangle Park, North Carolina) using eggs as the matrix. Samples of whole eggs were fortified with tembotrione at 0.01 ppm (LOQ), 0.02 ppm, and 0.1 ppm. Fortified and unfortified samples were analyzed using LC/MS/MS method AE-004-A04-02 as described in Table B.1.1.

The method was successfully validated on the first trial; see Table C.3.1. The laboratory reported that the method was followed as written. Recoveries of tembotrione from whole eggs ranged 86-102%. Total tembotrione residues were below the LOQ (<0.01 ppm) in/on two samples of unfortified whole eggs. The laboratory reported that a set of 17 samples could be prepared in 8 hours, plus overnight unattended waiting time for the ASE. The analysis required 16 hours of LC/MS/MS instrument time. The total time to complete analysis of a set of 17 samples would be 1.5 calendar days. No critical steps were identified by the ILV laboratory.

TABLE C.3.1. Recovery Results Obtained by an ILV of the Enforcement Method for the Determination of Tembotrione in Poultry Egg.

Matrix	Spiking Level (ppm)	Recoveries Obtained	Mean Recovery ± SD (CV)
Whole Egg	0.01	92.9, 95.7, 93.2, 95.7, 87.2	92.9 ± 3.4 (3.7)
	0.02	91.2, 96.1, 90.3, 85.9, 87.2	90.1 ± 4.0 (4.4)
	0.10	96.6, 94.3, 94.7, 102, 88.9	92.8 ± 4.4 (4.7)

D. CONCLUSION

Method AE-004-A04-02 is adequate for determination of residues of tembotrione in the tested poultry matrices. Method validation performed by the petitioner using control samples of whole eggs and chicken skin, muscle, and liver at fortification levels of 0.010 ppm (LOQ), 0.050 ppm and 0.200 ppm showed acceptable method recoveries. The method was also successfully validated by an independent laboratory using whole eggs as the matrix at fortification levels of 0.01 ppm, 0.02 ppm, and 0.1 ppm. Finally, the method was adequately radiovalidated using aged samples of poultry eggs that were obtained from a laying hen metabolism study.

E. REFERENCES

46695536.der.doc

F. DOCUMENT TRACKING

RDI: RAB1 Chemists (1/3/07)
Petition Number: PP#5F7009
DP#s: 325349, 325663, and 331222
PC Code: 012801

Template Version June 2005

Tembotrione/AE 0172747/PC Code 012801/Bayer CropScience/264
DACO 7.2.1, 7.2.2, and 7.2.3/OPPTS 860.1340/OECD IIA 4.2.5, 4.2.6 and 4.3
Residue Analytical Method – Beef Tissues and Milk

Primary Evaluator	George F. Kramer, Ph.D., Senior Chemist Registration Action Branch (RAB1) Health Effects Division (HED) (7509P)	Date: 18-JUL-2007
Approved by	P.V. Shah, Ph.D., Branch Senior Scientist RAB1/HED (7509P)	Date: 18-JUL-2007

This DER was originally prepared under contract by Dynamac Corporation (2275 Research Boulevard, Suite 300; Rockville, MD 20850; submitted 11/10/2006). The DER has been reviewed by HED and revised to reflect current Office of Pesticide Programs (OPP) policies.

STUDY REPORTS:

46695536 Spiegel, K. (2005) [Cyclohexyl-UL14C]AE 0172747: Extraction Efficiency of the Residue Analytical Method for the Determination of AE 0172747 in Animal Tissues and Egg Matrices using Aged Residues. Project Number: M9991495-6. Unpublished study prepared by Bayer CropScience. 57 pages.

46695538 Coopersmith, H.; Williams, L. (2005) AE 0172747: An Analytical Method for the Determination of Residues of AE 0172747 in Beef Tissues and Milk Matrices Using LC/MS/MS. Project Number: RAAEX001, AE-003-A04-02. Unpublished study prepared by Bayer CropScience. 67 pages.

46695543 Perez, S. R. (2005) Independent Method Validation of Bayer Method Numbers AE-003-A04-01 AE 0172747: An Analytical Method for the Determination of Residues of AE 0172747 in Beef Tissues and Milk Matrices Using LC/MS/MS. Project Number: RAAEX005. Unpublished study prepared by ADPEN Laboratories, Inc. 45 pages.

The petitioner has submitted an evaluation template for the above-listed studies, which was used to generate this DER; selected sections were copied without alteration or were copied and modified to more specifically reflect the Agency's data evaluation requirements.

EXECUTIVE SUMMARY:

Bayer CropScience has submitted descriptions and validation data for liquid chromatography/mass spectroscopy (LC/MS)/MS Method AE-003-A04-02. The method determines residues of tembotrione *per se* in beef tissues and milk and was the data-collection method used for determination of tembotrione residues in samples collected from a cattle feeding study (refer to 46695604.der.doc). It is also the same as one of the proposed livestock enforcement methods associated with PP#5F7009. Method AE-003-A04-02 is a revision to Method AE-003-A04-01. The only change was the incorporation of ion-confirmation information for tembotrione.

Using Method AE-003-A04-02, residues of tembotrione in milk, eggs, and beef and poultry tissues are extracted with acetonitrile:deionized water (ACN:H_2O, 1:1, v:v) using accelerated solvent extraction. The extracted residues of tembotrione are fortified with the internal standard,

diluted, and an aliquot of the diluted extract is filtered and concentrated. A 6% formic acid solution is added to the concentrated sample; the extract is diluted and filtered for LC/MS/MS analysis. Quantitation of tembotrione is done against a known amount of deuterated internal standard. Identification is confirmed by comparing the ion ratio of the analyte to that of the analytical standard. The validated limit of quantitation (LOQ) is 0.01 ppm for all matrices. The calculated limits of detection (LODs) for tembotrione were ≤0.002 ppm in various livestock matrices.

The initial validation of Method AE-003-A04-02, performed by the petitioner, was conducted using control samples of beef fat, kidney, muscle, liver, whole milk, skim milk, and milk fat. The method recoveries were, overall, adequate and mostly within the acceptable range of 70-120%. Following fortification of samples at 0.010 ppm (LOQ), 0.050 ppm and 0.200 ppm, recoveries of tembotrione ranged 69-85% in beef fat, 70-83% in beef kidney, 81-99% in beef muscle, 83-103% in beef liver, 81-99% in whole milk, 83-99% in skim milk, and 72-100% in milk fat.

The method was also successfully validated by an independent laboratory using beef liver as the matrix at fortification levels of 0.01 ppm, 0.02 ppm, and 0.1 ppm. The fortification levels used in method validations as well as from concurrent analysis of samples from various studies are adequate to bracket expected residue levels. Finally, Method AE-003-A04-02 was adequately radiovalidated using aged samples of beef liver obtained from a previous cattle metabolism study.

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the analytical method test data are classified as tentatively acceptable pending determination of the terminal residues of concern in beef tissues and milk. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document [DP# 325349].

COMPLIANCE:

Signed and dated Good Laboratory Practice (GLP), Quality Assurance and Data Confidentiality statements were provided. No deviations from regulatory requirements were reported which would have an impact on the validity of the study.

A. BACKGROUND INFORMATION

Tembotrione, a new herbicide with broad use against mono- and dicotyledons in selected crops such as corn, is a 4-hydroxyphenylpyruvate deoxygenase (HPPD) inhibitor (bleacher). The test compound nomenclature and physiochemical properties of the test compound are presented in Tables A.1 and A.2, respectively.

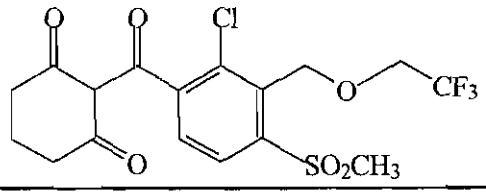
TABLE A.1. Test Compound Nomenclature for Tembotrione.	
Compound: Tembotrione	Chemical Structure 
Proposed common name	Tembotrione
Company experimental name	AE 0172747
IUPAC name	2-{2-chloro-4-mesyl-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl}cyclohexane-1,3-dione
CAS name	2-[2-chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione
CAS #	335104-84-2
End-use product/EP	AE 0172747 Herbicide, EPA Reg No. 264-xxx

TABLE A.2. Physicochemical Properties of Technical Grade Tembotrione.		
Parameter	Value	Reference (MRID#)
Melting point	117 °C	46695402
pH @ 24 °C	3.63	
Density (g/mL @ 20 °C)	1.56	
Water solubility (mg/L @ 20 °C)	0.22 at pH4 28.3 at pH 7 29.7 at pH 9	
Solvent solubility (g/L at 20 °C) DMSO Methylene Chloride Acetone Ethyl Acetate Toluene Hexane Ethanol	 >600 >600 300-600 180.2 75.7 47.6 8.2	
Vapor pressure (Torr, 20 °C)	8.25×10^{-11}	
Dissociation constant (pK_a)	3.2	
Octanol/water partition coefficient (P_{ow} @ 23 °C) (P_{ow} @ 24 °C) (P_{ow} @ 23 °C)	 0.0430 at pH 9.0 0.0807 at pH 7.0 144.9 at pH 2.0	
UV/visible absorption spectrum (nm)	Primary: 205 Secondary: 284 Tertiary: 240	

B. MATERIALS AND METHODS

B.1. Data-Gathering Method

Method AE-003-A04-02 was the data-collection method used for the analysis of tembotrione residues in milk and tissue samples collected from a dairy cattle feeding study (refer to 46695604.der.doc) and is entitled "AE 0172747: An Analytical Method for the Determination of Residues of AE 0172747 in Beef Tissues and Milk Matrices Using LC/MS/MS."

B.1.1. Principle of the Method:

Briefly, residues of tembotrione in beef tissues and milk matrices are extracted with ACN:H_2O (1:1, v:v) using accelerated solvent extraction; see Table B.1.1. The extracted residues of tembotrione are fortified with the internal standard, diluted, and an aliquot of the diluted extract is filtered and concentrated. A 6% formic acid solution is added to the concentrated sample; the extract is diluted and filtered for LC/MS/MS analysis. Quantitation of tembotrione is done against a known amount of deuterated internal standard. Identification is confirmed by comparing the ion ratio of the analyte to that of the analytical standard.

TABLE B.1.1. Summary Parameters for the Analytical Method Used for the Quantitation of Tembotrione Residues in Beef Tissues and Milk Matrices.

Method ID	AE-003-A04-02
Analyte	Tembotrione
Extraction solvent/technique	Tissue samples are first homogenized in the presence of dry ice. Samples are extracted through an ASE 200 accelerated solvent extractor with ACN:H_2O (1:1, v:v).
Cleanup strategies	The extracts are fortified with the internal standard, diluted and an aliquot of the diluted extract is filtered and concentrated. A 6% formic acid solution is added to the concentrated sample; the extract is diluted and then filtered.
Instrument/Detector	High-performance LC utilizing a SymmetryShield™ RP 8 column and a gradient mobile phase of 0.1% acetic acid and ACN, with tandem mass speetrometry (MS/MS) detection using electrospray ionization operating in the negative ion mode for tembotrione. The ion transitions monitored (parent mass →daughter ion) are: tembotrione: m/z 439 → 403 tembotrione internal standard: m/z 443 → 407
Standardization method	External and internal standardization. Five calibration standards, containing internal standards, are injected and a calibration curve is constructed from the relative responses (RRs; analyte peak area divided by internal standard) versus standard concentration. Samples are bracketed by calibration standards at the beginning and end of the run. Results are calculated using linear regression.
Stability of std solutions	Primary stock solutions of tembotrione are to be stored frozen and prepared every 3 months. Secondary stock standard and calibration standard solutions are to be prepared every 3 months; storage conditions were not specified.
Retention times	≈ 6.88 minutes for tembotrione

B.2. Enforcement Method

The proposed enforcement method for livestock commodities is the same as the data-gathering method, AE-003-A04-02.

C. RESULTS AND DISCUSSION

C.1. Data-Gathering Method

The initial validation of Method AE-003-A04-02, performed by the petitioner, was conducted using control samples of beef fat, kidney, muscle, liver, whole milk, skim milk, and milk fat. The results of method validation and verification are presented in Table C.1.1. The method recoveries were, overall, adequate and mostly within the acceptable range of 70-120%. Following fortification of samples at 0.010 ppm (LOQ), 0.050 ppm and 0.200 ppm, recoveries of tembotrione ranged 69-85% in beef fat, 70-83% in beef kidney, 81-99% in beef muscle, 83-103% in beef liver, 81-99% in whole milk, 83-99% in skim milk, and 72-100% in milk fat.

The results of the radiovalidation study are presented in Table C.1.3. The total radioactive residues (TRR) values obtained for beef liver and poultry egg samples in the extraction efficiency testing were in very good agreement with those of the metabolism studies. There was also a good agreement in the amount of the parent identified from both studies. In liver, the parent comprised 92.9% and 90.9% TRR from the metabolism and radiovalidation studies, respectively. In egg, the parent comprised 71.2% and 62.1% TRR from the metabolism and radiovalidation studies, respectively. The submitted extraction efficiency data demonstrate that the extraction procedures of method AE-003-A04-02 adequately extract aged residues of tembotrione from beef liver and poultry egg samples.

TABLE C.1.1. Recovery Results from Method Validation of Beef Tissues and Milk Matrices using the Data-Gathering Analytical Method.

Matrix	Spiking Level (ppm)[1]	Recoveries Obtained	Mean Recovery ± SD (RSD)[2]
Method Verification			
Beef Fat	0.20	79, 80	80
Beef Kidney	0.20	83, 83	83
Beef Muscle	0.05	97	Not applicable
	0.20	95, 96	96
Beef Liver	0.20	85, 87	86
Whole Milk	0.01	80, 82	81
	0.05	85, 86	86
	0.20	91, 96	94
Skim Milk	0.01	84, 86	85
	0.05	88, 90	89
	0.20	90, 91	91
Milk Fat (Cream)	0.01	88, 88	88
	0.05	93, 96	95
	0.20	98, 98	98
Method Validation			
Beef Fat	0.01	72, 76, 72, 69, 69, 76, 77	73 ± 3.4 (4.7)
	0.05	88, 85, 84	81 ± 2.6 (3.2)
Beef Kidney	0.01	75, 75, 76, 70, 70, 79, 82	75 ± 4.3 (5.7)
	0.05	78, 79, 78	78 ± 0.58 (0.7)

TABLE C.1.1. Recovery Results from Method Validation of Beef Tissues and Milk Matrices using the Data-Gathering Analytical Method.

Matrix	Spiking Level (ppm)[1]	Recoveries Obtained	Mean Recovery ± SD (RSD)[2]
Beef Muscle	0.01	95, 97, 81, 84, 95, 96, 89	91 ± 6.3 (6.9)
	0.05	94, 99, 96	97 ± 2.5 (2.6)
Beef Liver	0.01	83, 97, 103, 88, 96, 86, 100	93 ± 7.6 (8.2)
	0.05	90, 89, 88	89 ± 1.0 (1.1)
Whole Milk	0.01	82, 96, 95, 92, 94, 96, 92	92 ± 4.9 (5.3)
	0.05	99, 96, 99	98 ± 1.7 (1.7)
Skim Milk	0.01	87, 96, 99, 83, 84, 85, 87	89 ± 6.2 (7.0)
	0.05	90, 97, 86	91 ± 5.6 (6.2)
Milk Fat (Cream)	0.01	91, 94, 81, 86, 72, 92, 90	87 ± 7.7 (8.9)
	0.05	100, 99, 97	99 ± 1.5 (1.5)

[1] Standards were prepared in acetonitrile.
[2] The mean for the method verification was calculated by the study reviewer; the mean, standard deviation (SD) and relative standard deviation (RSD) for the method validation were calculated by the petitioner.

TABLE C.1.2. Characteristics for the Data-Gathering Analytical Method Used for the Quantitation of Tembotrione Residues in Livestock.

Analyte	Tembotrione
Equipment ID	ConstaMetric® 3200 HPLC and ThermoFinnigan TSQ 7000 with triple-quadrupole MS; SymmetryShield™ RP 8 5µm (3.0mm x 150mm) column
LOQ	0.010 ppm The LOQ was determined as lowest fortification level with adequate recovery.
LOD	whole milk: 0.0019 ppm; skim milk: 0.0016 ppm; milk fat (cream): 0.0020 ppm; beef liver: 0.0024 ppm; beef muscle: 0.0020 ppm; beef kidney: 0.0014 ppm; and beef fat: 0.0011 ppm. The LODs were calculated for each analyte in each matrix by multiplying the standard deviation of the LOQ recoveries by the $t_{0.99}$ value for the number of measurements.
Accuracy/Precision	Percent recoveries and coefficients of variance (CVs) indicate acceptable accuracy/precision at 0.01, 0.05, and 0.20 ppm for beef fat, kidney, muscle, and liver, and whole milk, skim milk, and milk fat (cream). Recovery ranges (and CVs) were 69-103% (0.7-8.2) for tembotrione in beef matrices and 72-100% (1.5-8.9) for tembotrione in milk matrices. See Table C.1.1 above.
Reliability of the Method/ [ILV]	An independent laboratory method validation (ILV) was conducted to verify the reliability of method No. AE-003-A04-02 for the determination of tembotrione residues in livestock matrices. The values obtained are indicative that method AE-003-A04-02 is reliable; see Section C.3.
Linearity	The relative response was linear, with typical coefficient of determination, $r^2 = 0.9994$ for tembotrione, from calibration curves ranging from 0.005 to 0.500 ppm.
Specificity	The control chromatograms generally have no peaks above the chromatographic background, and the spiked sample chromatograms contain only the analyte peak of interest within the retention window. Peaks were well defined and symmetrical. A blank of the injection solvent solution was injected between the high standard and the control sample to prevent carry-over between injections.

A study was conducted to determine the efficiency of Method AE-003-A04-02 in extracting residues of tembotrione from aged samples of liver tissue and eggs that were respectively obtained from a cow metabolism study (refer to 46695531.der.doc) and a laying hen metabolism study (refer to 46695533.der.doc). Both studies used [cyclohexyl-U-^{14}C]tembotrione as the test substance.

The liver originated from a study, in which the test substance was administered orally to a Holstein Friesian strain lactating cow twice daily for seven consecutive days at a nominal dose level of 10 ppm in the livestock diet.

The eggs originated from a laying hen study, in which the animals were administered orally for 14 consecutive days at a nominal dose level of 10 ppm in the diet. The eggs were sampled twice daily and separated in egg yolks and egg whites. For the radiovalidation study, the egg yolk samples of Day 10 to Day 12 were combined as well as the egg white samples of Day 10 to Day 12. A portion of 20 g of the combined yolk sample was thoroughly mixed with a portion of 90 g of the combined egg white sample to generate a representative sample of whole eggs.

All samples were stored in a freezer at <-10 °C until the start of the extraction efficiency testing (storage up to 36 months). The TRR of the tissue and egg samples were determined in the present study and were compared to the values obtained in the metabolism studies. Additional subsamples were analyzed according to the written procedures for Method AE-003-A04-02.

TABLE C.1.3. Extraction Efficiency of the Enforcement Analytical Method (Method AE-003-A04-02) Using Radiolabeled Samples from Beef and Egg Metabolism Studies.

Matrix	Metabolism Study		Residue Method		Extraction Efficiency (%)
	%TRR	ppm	%TRR	ppm	
Beef liver					
TRR	100	3.082	100	3.118	---
Extract	96.5	2.973	93.8	2.927	97.2
Tembotrione (parent)	92.9	2.865	90.9	2.834	97.8
Whole Egg					
TRR	100	0.031	100	0.037	--
Extract	77.4	0.024	64.8	0.024	83.7
Tembotrione (parent)	71.2	0.022	62.1	0.023	87.2

C.2. Enforcement Method

The proposed enforcement method for plant commodities is the same as the data-gathering method, AE-003-A04-02.

C.3. Independent Laboratory Validation (ILV)

Method AE-003-A04-01 was subjected to an ILV. It is noted that Method AE-003-A04-02 is a revision to method AE-003-A04-01. The only change was the incorporation of ion confirmation information for tembotrione. The ILV was conducted by ADPEN Laboratories (Jacksonville, Florida) using beef liver as the matrix. Samples of beef liver were fortified with tembotrione at 0.01 ppm (LOQ), 0.02 ppm, and 0.1 ppm. Fortified and unfortified samples were analyzed using LC/MS/MS method AE-003-A04-01 as described in Table B.1.1.

The method was successfully validated on the first trial; see Table C.3.1. The laboratory reported that the method was followed as written. Recoveries of tembotrione from beef liver ranged 72-108%. Total tembotrione residues were below the LOQ (<0.01 ppm) in/on two

samples of unfortified beef liver. The laboratory reported that a set of 17 samples could be prepared in 8 hours, plus overnight unattended analysis and data processing the following morning. The total time to complete analysis of a set of 17 samples would be 1.5 calendar days. No critical steps were identified by the ILV laboratory.

TABLE C.3.1. Recovery Results Obtained by an ILV of the Enforcement Method for the Determination of Tembotrione in Beef Matrices.

Matrix	Spiking Level (ppm)	Recoveries Obtained	Mean Recovery ± SD (RSD)
Beef Liver	0.010	96.1, 101, 90.0, 92.7, 104	96.8 ± 6.0 (6.2)
	0.020	87.5, 92.0, 88.0, 89.5, 108	92.9 ± 8.4 (9.0)
	0.100	83.1, 86.3, 97.6, 88.8, 71.8	85.5 ± 11.0 (12.9)

D. CONCLUSION

Method AE-003-A04-02 is adequate for determination of residues of tembotrione in tested beef matrices. Method validation performed by the petitioner using control samples of beef fat, kidney, muscle and liver, and whole milk, skim milk and milk fat at fortification levels of 0.01 ppm, 0.05 ppm and 0.20 ppm showed acceptable method recoveries. The method was also successfully validated by an independent laboratory using beef liver as the matrix at fortification levels of 0.01 ppm, 0.02 ppm, and 0.1 ppm. Finally, Method AE-003-A04-02 was adequately radiovalidated using aged samples of liver tissue and eggs that were respectively obtained from a cow metabolism study and a laying hen metabolism study.

E. REFERENCES

46695604.der.doc
46695531.der.doc
46695533.der.doc

F. DOCUMENT TRACKING

RDI: RAB1 Chemists (12/13/06)
Petition Number: PP#5F7009
DP#s: 325349, 325663, and 331222
PC Code: 012801

Template Version June 2005

Tembotrione/AE 0172747/PC Code 012801/Bayer CropScience/264
DACO 6.2/OPPTS 860.1300/OECD II 6.2.2, 6.2.3 & IIIA 8.2, 8.4.1, 8.4.2
Nature of the Residues in Livestock – Metabolite AE 1417268 in Ruminant

Primary Evaluator	George F. Kramer, Ph.D., Senior Chemist Registration Action Branch (RAB1) Health Effects Division (HED) (7509P)	Date: 18-JUL-2007
Approved by	P.V. Shah, Ph.D., Branch Senior Scientist RAB1/HED (7509P)	Date: 18-JUL-2007

This DER was originally prepared under contract by Dynamac Corporation (2275 Research Boulevard, Suite 300; Rockville, MD 20850; submitted 11/10/2006). The DER has been reviewed by HED and revised to reflect current Office of Pesticide Programs (OPP) policies.

STUDY REPORT:

46695535 Needham, D.; Swalwell, L.; Fisher, P. (2005) (Carbon 14)-AE 1417268:- Absorption, Distribution, Metabolism, and Excretion Following Repeated Oral Administration to the Lactating Cow: Final Report. Project Number: 2014/080, 2014/080/D1145, MEAEX077. Unpublished study prepared by Covance Laboratories, Ltd. 91 p.

The petitioner has submitted an evaluation template for the study (Bayer CropScience DER to Study 2014-080), which was used to generate this DER; selected sections were copied without alteration or were copied and modified to more specifically reflect the Agency's data evaluation requirements.

EXECUTIVE SUMMARY:

Bayer CropScience has submitted a study investigating the metabolism of [cyclohexyl-U-^{14}C]AE 1417268 (CY label; specific activity 0.7596 MBq/mg), a plant metabolite of the herbicide tembotrione, in lactating cows. The test substance was administered orally to a single cow at 10 ppm in the diet. The actual average dose, based on feed consumption during the experiment, was 11.8 ppm. The cow was dosed two times daily for 5 consecutive days. Milk was collected twice daily throughout the study, and tissues (muscle, fat, liver, and kidney) were collected at sacrifice, ~24 hours after the final dose.

Total radioactive residues (TRR) following dosing at 11.8 ppm were 0.003-0.012 ppm in milk, below the limit of quantitation (<LOQ) in muscle and fat (renal and omental), 0.176 ppm in kidney, and 0.611 ppm in liver. TRR were highest in liver, and the highest residues in milk were observed just prior to final dosing. The majority of the radioactivity (~74% of the administered dose) was excreted.

Metabolic profiling was conducted on kidney, liver, and milk (sample designated Day 6 a.m.). Solvent extraction with hexane, ethyl acetate, acetonitrile (ACN), and acidified ACN released ~87-88% of the TRR in kidney and liver, and solvent extraction with ACN and methanol released ~36% TRR in milk. Nonextractable residues following solvent extraction were 11.1% TRR (0.020 ppm) in kidney and 64.1% TRR (0.008 ppm) in milk. Nonextractable residues in liver were subjected to methanol extraction and subsequent protease hydrolysis, which released

an additional 6.2% and 6.5% TRR, respectively. Nonextractable residues in liver after exhaustive extractions were 2.9% TRR (<0.02 ppm).

The extraction procedures were adequate; and the accountabilities were 100-103%. Residues were identified and quantitated by high-performance liquid chromatography (HPLC) equipped with a flow-through radiodetector and confirmed by liquid chromatography/mass spectroscopy (LC/MS). Supporting storage stability data are not required because samples were analyzed within <6 months of collection.

The major and only residue identified in tissues was the unchanged metabolite, AE 1417268. AE 1417268 was identified at 81.4% TRR (0.143 ppm) in kidney and 76.1% TRR (0.466 ppm) in liver. Two minor metabolites were observed in kidney (both ≤4.2% TRR) and liver (both ≤8% TRR), but were not further investigated.

Based on the cow metabolism study with CY-labeled metabolite AE 1417268, the metabolite undergoes minimal metabolism in ruminants, with the major component in tissues and excreta being the unchanged AE 1417268.

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the livestock metabolism data are classified as scientifically acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document [DP# 325349].

COMPLIANCE:

Signed and dated Good Laboratory Practice (GLP), Quality Assurance and Data Confidentiality statements were provided. No GLP deviations were reported which would impact the study results or their interpretation.

A. BACKGROUND INFORMATION

AE 1417268 (M-5) is a plant metabolite of the herbicide tembotrione. The herbicide has broad use against mono- and dicotyledons in selected crops such as corn. AE 1417268 was not seen as a metabolite in cows dosed with tembotrione. Hence, this study was designed to determine the nature of the residues which may ultimately occur in food products.

The test compound nomenclature and physiochemical properties of the test compounds are presented in Tables A.1 and A.2., respectively.

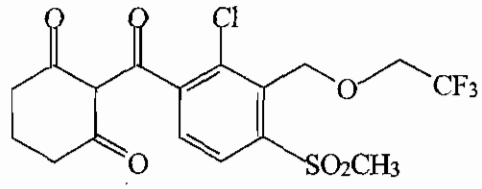
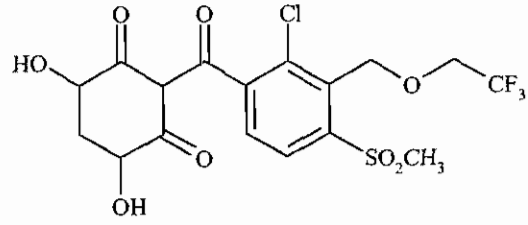
TABLE A.1. Test Compound Nomenclature for Tembotrione.	
Compound: Tembotrione	Chemical Structure 
Proposed common name	Tembotrione
Company experimental name	AE 0172747
IUPAC name	2-{2-Chloro-4-mesyl-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl}cyclohexane-1,3-dione
CAS name	2-[2-Chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione
CAS #	335104-84-2
End-use product/EP	AE 0172747 Herbicide, EPA Reg No. 264-xxx
AE 1417268	*Chemical Structure* 
Common name	None assigned.
Company experimental name	AE 1417268 (M5)
IUPAC name	2-{2-Chloro-4-mesyl-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl}-4,6-dihydroxy-cyclohexane-1,3-dione
CAS name	2-[2-chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione
CAS #	None assigned.
End-use product/EP	Not applicable.

TABLE A.2. Physicochemical Properties of Technical Grade		
Parameter	Value	Reference
Tembotrione		
Melting point	117 °C	46695402
pH @ 24 °C	3.63	
Density (g/mL @ 20 °C)	1.56	
Water solubility (mg/L @ 20 °C)	0.22 at pH4 28.3 at pH 7 29.7 at pH 9	
Solvent solubility (g/L at 20 °C) DMSO Methylene Chloride Acetone Ethyl Acetate Toluene Hexane Ethanol	 >600 >600 300-600 180.2 75.7 47.6 8.2	

TABLE A.2. Physicochemical Properties of Technical Grade		
Parameter	Value	Reference
Vapor pressure (Torr, 20 °C)	8.25×10^{-11}	
Dissociation constant (pK_a)	3.2	
Octanol/water partition coefficient (P_{ow} @ 23 °C) (P_{ow} @ 24 °C) (P_{ow} @ 23 °C)	 0.0430 at pH 9.0 0.0807 at pH 7.0 144.9 at pH 2.0	
UV/visible absorption spectrum (nm)	Primary: 205 Secondary: 284 Tertiary: 240	
AE 1417268		
No data available.		

B. EXPERIMENTAL DESIGN

A single lactating cow was dosed orally with CY-labeled AE 1417268 for 5 consecutive days at a nominal rate of 10 ppm in the diet. The cow was maintained in a metabolism cage and fed a commercial feed concentrate and hay twice daily at milking. The cow was dosed two times daily following morning and afternoon milkings. Information pertaining to the test animal and dietary and dosing regimes is presented in Tables B.1.1 - B.1.3.

B.1. Livestock

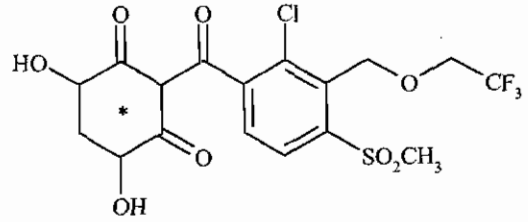
TABLE B.1.1. General Test Animal Information					
Species	Breed	Age years	Weight at study initiation (kg)	Health Status	Description of housing/holding area
Lactating cow (*Bos taurus*)	Holstein Friesian	6	613	Good	Metabolism cage in unit controlled at 16-20 °C, 26-58% RH, 16-hr fluorescent light/day, 10 air exchanges/hr.

TABLE B.1.2. Test Animal Dietary Regime				
Composition of Diet	Feed consumption (kg/day), average	Water	Acclimation period	Predosing
1.5 kg/2x/day commereial feed concentrate Hay twice a day Consumption measured	14.3 kg/day (acclimation period) 12.4 kg/day (dosing period)	*Ad libitum*	11 days	None

TABLE B.1.3. Test Animal Dosing Regime			
Treatment Type	Feeding Level (ppm test material in food)	Vehicle	Timing/Duration
Oral	10 ppm nominal (11.8 ppm actual)	gelatin capsule, using balling gun	Twice/day for 5 days; following morning and afternoon milkings

B.2. Test Materials

The radiolabeled test substance was prepared in gelatin capsules for dosing. The test material characteristics are presented in Table B.2.1.

TABLE B.2.1. Test Material Characteristics.	
Chemical structure	
Radiolabel position	[cyclohexyl-U-^{14}C]AE 1417268
Lot No.	BECH1702
Purity	95.61% (by HPLC)
Specific activity (Bq) [1]	0.7596 MBq/mg

[1] Bq = disintegrations per second

B.3. Sampling Information

The cow was milked twice daily, and excreta were collected once daily. The cow was sacrificed ~24 hours after the last dosing, and tissues and blood were collected.

TABLE B.3.1. Sample Collection Information			
Milk collected	Urine, feces and cage wash collected	Interval from last dose to sacrifice	Tissues harvested and analyzed
Twice daily prior to dose administration; average milk production was 18.14 kg/day during the acclimation period and 16.49 kg/day during the dosing period.	Once daily	23.5 hours	Muscle, fat (renal and omental), liver, and kidneys

B.4. Identification/Characterization of Residues

B.4.1. Sample Handling and Preparation

Milk from the morning and afternoon milkings were subsampled prior to assay and storage. Tissue samples were homogenized, solubilized, and subsampled on the day of collection prior to storage. All milk and tissue samples were stored at <-10 °C. The in-life and analytical phases of the study were conducted at the same facility (Covance Laboratories, Ltd., Harrogate, England); therefore, samples were not shipped.

Kidney and liver samples were subjected to sequential solvent extraction with hexane, ethyl acetate, ACN, and acidified ACN (1% formic acid). Each fraction was collected following centrifugation. The ACN and acidified ACN extracts were combined and concentrated for HPLC analysis. Although radioactivity in milk was low, Day-6 a.m. subsamples (prior to final dose) were extracted with ACN and methanol for residue characterization.

The nonextractable residues of liver were further extracted with methanol, and the remaining residues were subjected to enzyme hydrolysis with protease (in 0.1 M phosphate buffer, pH 7.5, overnight at 37 °C). Residues were then extracted sequentially with ethyl acetate and acidified ACN. Following centrifugation, the ethyl acetate extract separated into two phases (ethyl acetate

and aqueous phases).

The extraction scheme for liver, which is representative of kidney, is outlined below in Figure B.4.1.1, and the protease hydrolysis procedure for liver is presented in Figure B.4.1.2. These figures were copied without alteration from MRID 46695535.

FIGURE B.4.1.1. Extraction Scheme for Liver.

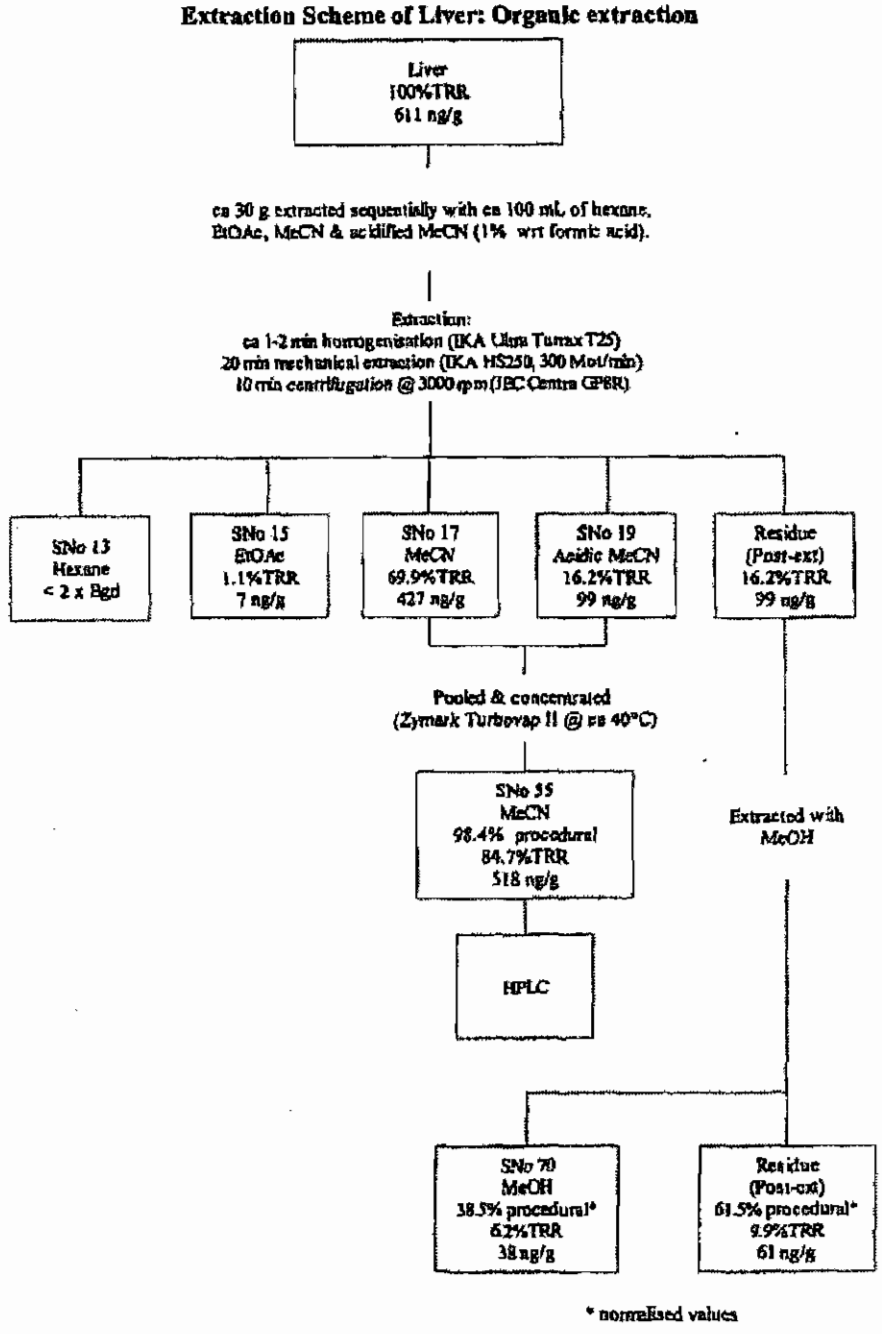
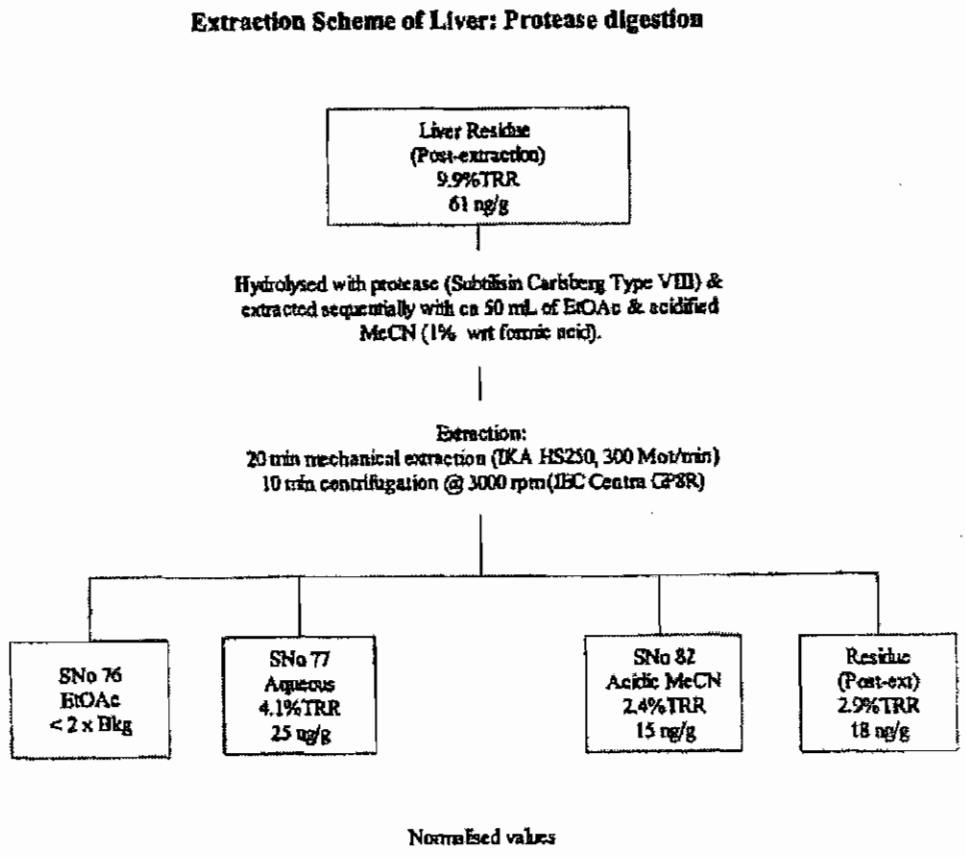


FIGURE B.4.1.2. Protease Hydrolysis of Nonextractable Residues of Liver.



B.4.2. Analytical Methodology

TRR were determined by liquid-scintillation counting (LSC), either directly or following solubilization or combustion. Radioactivity in extracts and hydrolysates was determined by direct LSC, and nonextractable radioactivity was determined by combustion/LSC. Extracts containing sufficient radioactivity were processed further for chromatographic analysis. The LOQ for TRR determinations was defined as 2x background.

Extracts of kidney and liver were analyzed by reverse-phase HPLC, using a system equipped with a C18 column, a UV detector at 254 nm, and a flow-through radiodetector. A gradient mobile phase of water adjusted to pH 2 with trifluoroacetic acid:ACN was used. Residues were identified by retention time comparison with a non-labeled reference standard of AE 1417268.

Residue identification was confirmed by HPLC/MS. A quadrupole ion trap mass spectrometer with electrospray LC/MS interface was coupled to a gradient HPLC system with conditions as described above. Negative-ion electrospray mass-spectrometric analysis was carried out with a capillary temperature of 250 °C and a spray voltage of 4.5 kV. The scan range was *m/z* 125 to 600.

C. RESULTS AND DISCUSSION

The storage conditions and intervals for cow matrices are presented in Table C.1. The petitioner did not provide the dates of sample extraction and analysis; however, dated chromatograms and spectra reflecting confirmatory analysis for identification of AE 1417268 were included in the submission indicating that HPLC/MS analyses were conducted within 197 days (3.2 months) of sacrifice. The petitioner should note for future submissions that the critical study dates are required for each sample.

TRR in milk and tissues are presented in Table C.2.1. Following oral dosing of CY-labeled AE 1417268 for 5 days at 11.8 ppm in the diet, TRR were 0.003-0.012 ppm in milk, <LOQ in muscle and fat (renal and omental), 0.176 ppm in kidney, and 0.611 ppm in liver. TRR were highest in liver, and the highest residues in milk were observed just prior to final dosing. The majority of the radioactivity (~74% of the administered dose) was excreted.

Metabolic profiling was conducted on kidney, liver, and milk (sample designated Day 6 a.m.). The distribution of the radioactivity in lactating cow matrices is presented in Table C.2.2. Solvent extraction with hexane, ethyl acetate, ACN, and acidified ACN released ~87-88% of the TRR in kidney and liver, and solvent extraction with ACN and methanol released ~36% TRR in milk. Nonextractable residues following solvent extraction were 11.1% TRR (0.020 ppm) in kidney and 64.1% TRR (0.008 ppm) in milk. Nonextractable residues in liver were subjected to methanol extraction and subsequent protease hydrolysis, which released an additional 6.2% and 6.5% TRR, respectively. Nonextractable residues in liver after exhaustive extractions were 2.9% TRR (<0.02 ppm). The extraction procedures were adequate; and the accountabilities were 100-103%. Residues were identified and quantitated by HPLC and confirmed by LC/MS.

The characterization and identification of residues in lactating cow matrices are summarized in Table C.2.3. The major and only residue identified in tissues was the unchanged metabolite, AE 1417268. AE 1417268 was identified at 81.4% TRR (0.143 ppm) in kidney and 76.1% TRR (0.466 ppm) in liver. Two minor metabolites were observed in kidney (both ≤4.2% TRR) and liver (both ≤8% TRR), but were not further investigated.

C.1. Storage Stability

All samples were homogenized and subsampled on the day of collection prior to storage; processed samples were stored at <-10 °C. The petitioner did not provide the dates of sample extraction and analysis; however, dated chromatograms and spectra reflecting confirmatory analysis for identification of AE 1417268 were included in the submission indicating that HPLC/MS analyses were conducted within 197 days (3.2 months) of sacrifice.

TABLE C.1. Summary of Storage Conditions.

Matrix	Storage Temperature (°C)	Actual Storage Duration	Interval of Demonstrated Storage Stability
Milk, kidney, and liver	<-10	97 days (3.2 months): HPLC/MS	Not required because samples were analyzed within 6 months of collection.

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

TABLE C.2.1. TRR in Milk, Tissue and Excreta.

Matrix	Collection Timing	Cow Dosed at 11.8 ppm[1]	
		% AD	ppm
Urine	Daily; study duration	1.996	--
Feces	Daily; study duration	70.074	--
Cage wash	Daily; study duration	2.065	--
Cage debris	Daily; study duration	0.126	
Total excreta		74.261	--
Milk	Day 1 p.m. (prior to 1st dose)	<LOQ	<LOQ
	Day 2 a.m.	0.003	0.003
	Day 2 p.m.	0.002	0.004
	Day 3 a.m.	0.007	0.008
	Day 3 p.m.	0.004	0.008
	Day 4 a.m.	0.007	0.008
	Day 4 p.m.	0.003	0.010
	Day 5 a.m.	0.008	0.010
	Day 5 p.m.	0.004	0.010
	Day 6 a.m. (prior to last dose)	0.008	0.012
	Day 6 p.m.	0.003	0.011
	Day 7 a.m./sacrifice	0.006	0.009
	Total; study duration	0.054	--
Muscle, skeletal	sacrifice	<LOQ	<LOQ
Fat, renal		<LOQ	<LOQ
Fat, omental		<LOQ	<LOQ
Kidney		0.039	0.17562
Liver		0.610	0.61141
Blood		<LOQ	<LOQ
Sum of Administered Dose (%)		75.661	--

[1] The LOQ for LSC determinations was defined as 2x background.

FIGURES C.2.1-C.2.3. Pharmacokinetics of AE 1417268 in Excreta and Milk of Lactating Cow.

Figure C.2.1. Cumulative Recovery of Radioactivity In Excreta Following Twice Daily Oral Administration of [cyclohexyl-U-14C]-AE 1417268 for Five Days at e Dose of 11.8 ppm Based on Diet.

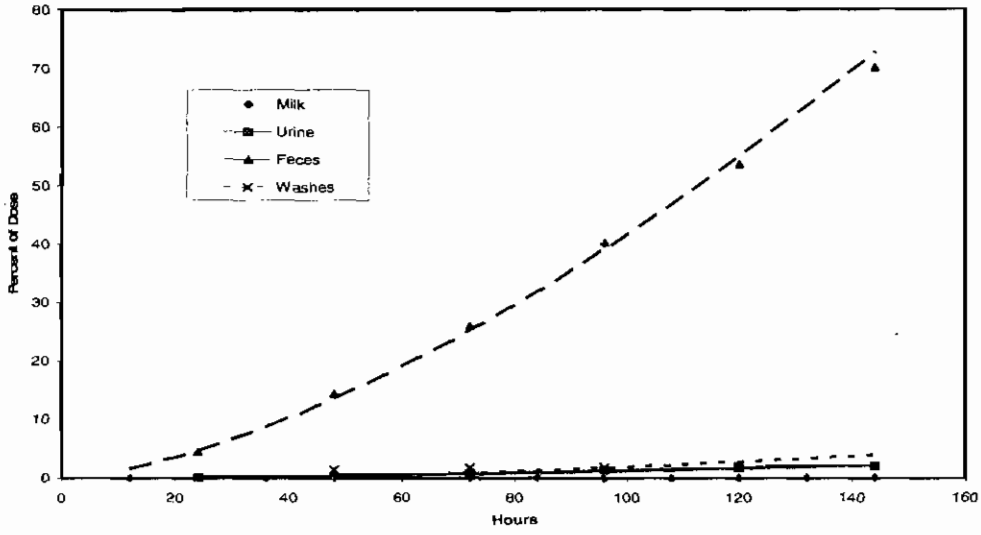


Figure C.2.2. Cumulative Recovery of Radioactivity In Milk, Urine and Washes Following Twice Daily Oral Administration of [cyclohexyl-U-14C]-AE 1417268 for Five Days at a Dose of 11.8 ppm Based on Diet.

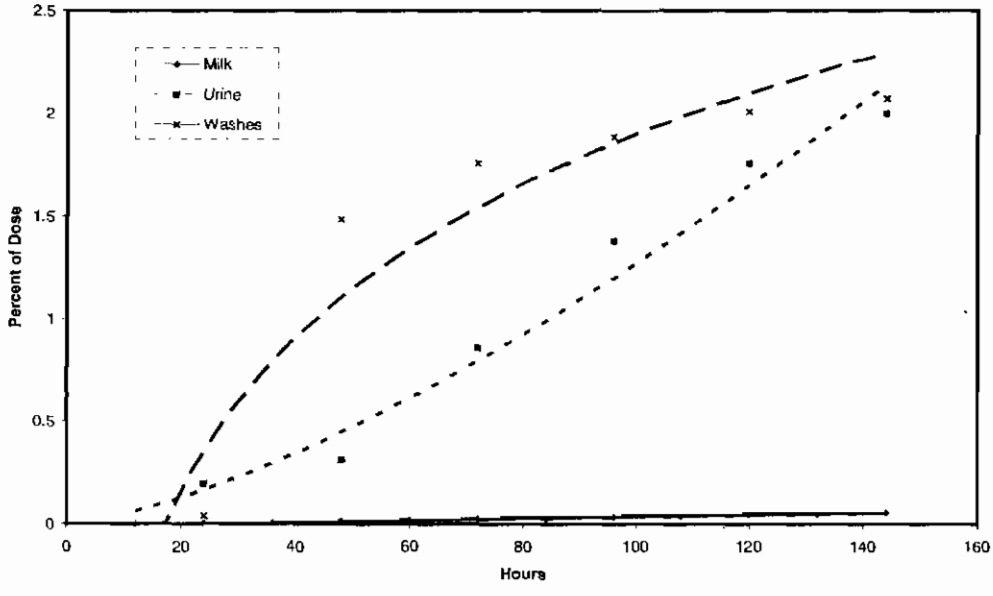


Figure C.2.3. At Milking and Cumulative Recovery of Radioactivity in Milk Following Twice Daily Oral Administration of [cyclohexyl-U-14C]-AE 1417268 for Five Days at a Dose of 11.8 ppm Based on Diet..

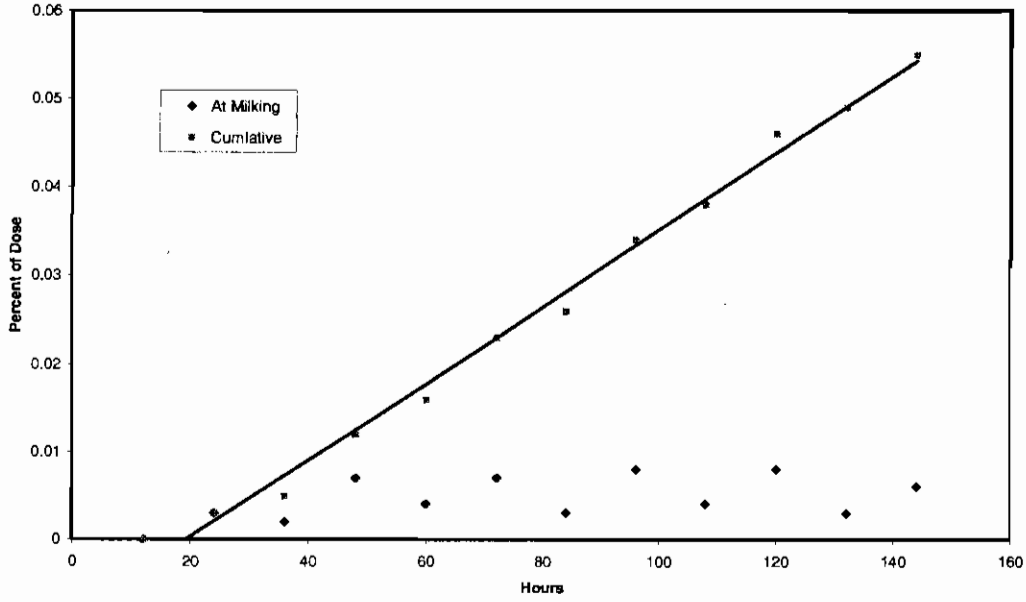


TABLE C.2.2. Distribution of AE 141768 and Metabolites in Bovine Matrices Following Administration of [cyclohexyl-U-^{14}C]AE 1417268 Twice a Day for 5 Days at 11.8 ppm.[1]

Metabolite Fraction	Kidney		Liver		Milk (Day 6 a.m.)	
	TRR = 0.176 ppm		TRR = 0.611 ppm		TRR = 0.012 ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm
Hexane extract	<0.1	<0.001	<0.1	<0.001		
Ethyl acetate extract	<0.1	<0.001	1.1	0.007		
ACN extract	75.5	0.133	69.9	0.427	26.3	0.003
Acidified ACN extract	12.9	0.023	16.2	0.099		
Combined ACN extracts	85.4	0.150	84.7	0.518		
AE 1417268	81.4	0.143	76.1	0.466		
Unknowns [2]	4.7	0.008	8.5	0.052		
Methanol extract					9.6	0.001
Nonextractable	11.1	0.020	16.2	0.099	64.1	0.008
Methanol			6.2	0.038		
Nonextractable			9.9	0.061		
Protease EtOAc			<0.1	<0.001		
Protease Aqueous			4.1	0.025		
Protease ACN			2.4	0.015		
Nonextractable			2.9	0.018		

[1] Shading indicates that the extraction step and/or characterization analysis was not conducted for the matrix in question.
[2] Consisting of two components each in kidney (Rt = 8.2 and 22.7 min) at 0.5% and 4.2% TRR (≤0.007 ppm), and liver (Rt = 18.6 and 21.3 min) at 1.7% and 6.8% TRR (≤0.042 ppm).

TABLE C.2.3. Summary of Characterization and Identification of Radioactive Residues in Bovine Matrices Following Administration of [cyclohexyl-U-^{14}C]AE 1417268 Twice a Day for 5 Days at 11.8 ppm.

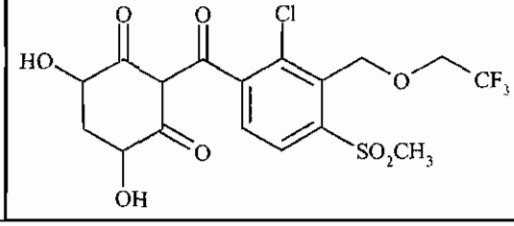
Metabolite Fraction	Kidney		Liver		*Milk (Day 6 a.m.)*	
	TRR = 0.176 ppm		TRR = 0.611 ppm		TRR = 0.012 ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm
AE 1417268	81.4	0.143	76.1	0.466	--	--
Unknowns	4.7	0.008	8.5	0.052	--	--
Hexane Soluble	<0.1	<0.001	<0.1	<0.001	--	--
Ethyl Acetate Soluble	<0.1	<0.001	1.1	0.007	--	--
ACN Soluble	--	--	--	--	26.3	0.003
Methanol Soluble	--	--	6.2	0.038	9.6	0.001
Protease EtOAc	--	--	<0.1	<0.001	--	--
Protease Aqueous	--	--	4.1	0.025	--	--
Protease ACN	--	--	2.4	0.015	--	--
Total identified	81.4	0.143	76.1	0.466	--	--
Total characterized	4.7	0.008	22.3	0.137	35.9	0.004
Total extractable	88.4	0.156	99.9	0.611	35.9	0.004
Unextractable[1]	11.1	0.020	2.9	0.018	64.1	0.008
Accountability[2]	100		103		100	

[1] Residues remaining after exhaustive extractions.
[2] Accountability = (Total extractable + Total unextractable)/(TRR from combustion analysis; see TABLE C.2.1) * 100.

C.3. Proposed Metabolic Profile

Based on the cow metabolism study with CY-labeled metabolite AE 1417268, the metabolite undergoes minimal metabolism in ruminants, with the major component in tissues and excreta being the unchanged AE 1417268. Because the only analyte identified during this study was AE 1417268, a metabolic scheme was not proposed.

TABLE C.3.1. Identification of Compounds from Metabolism Study

Common name/code	Chemical name (CAS)	Chemical structure
AE 1417268	2-[2-Chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione	

D. CONCLUSION

Following 5 days of oral dosing of CY-labeled AE 1417268 (a plant metabolite of the herbicide tembotrione) at 11.8 ppm in the diet, TRR were 0.003-0.012 ppm in milk, <LOQ in muscle and fat (renal and omental), 0.176 ppm in kidney, and 0.611 ppm in liver. Radioactivity was highest in liver, and the highest residues in milk were observed just prior to final dosing. The majority of the radioactivity (~74% of the administered dose) was excreted.

Metabolic profiling was conducted on kidney, liver, and milk (sample designated Day 6 a.m.). Kidney and liver were subjected to solvent extraction with hexane, ethyl acetate, ACN, and acidified ACN, and milk was extracted with ACN and methanol. In addition, the nonextractable residues in liver were subjected to methanol extraction and subsequent protease hydrolysis, which released additional residues. These procedures adequately extracted residues from cow matrices.

Residues were identified and quantitated by HPLC and confirmed by LC/MS. Supporting storage stability data are not required because samples were analyzed within <6 months of collection.

The major and only residue identified in tissues was the unchanged metabolite, AE 1417268. AE 1417268 was identified at 81.4% TRR in kidney and 76.1% TRR in liver. Based on these results, the metabolite AE 1471268 undergoes minimal metabolism in ruminants.

The submitted study is acceptable and successfully delineates the amount and distribution of TRR in ruminant matrices following dosing with CY-labeled AE 1417268.

E. REFERENCES

None.

F. DOCUMENT TRACKING

RDI: RAB1 Chemists (12/13/06)
Petition Number: PP#5F7009
DP#s: 325349, 325663, and 331222
PC Code: 012801

Template Version June 2005

Tembotrione/AE 0172747/PC Code 012801/Bayer CropScience/264
DACO 7.2.1, 7.2.2, and 7.2.3/OPPTS 860.1340/OECD IIA 4.2.5, 4.2.6 and 4.3
Residue Analytical Method - Plants

Primary Evaluator	George F. Kramer, Ph.D., Senior Chemist Registration Action Branch (RAB1) Health Effects Division (HED) (7509P)	Date: 18-JUL-2007
Approved by	P.V. Shah, Ph.D., Branch Senior Scientist RAB1/HED (7509P)	Date: 18-JUL-2007

This DER was originally prepared under contract by Dynamac Corporation (2275 Research Boulevard, Suite 300; Rockville, MD 20850; submitted 11/10/2006). The DER has been reviewed by HED and revised to reflect current Office of Pesticide Programs (OPP) policies.

STUDY REPORTS:

46695537 Coopersmith, H.; Williams, L. (2005) AE 0172747: An Analytical Method for the Determination of Residues of AE 0172747 and its Major Metabolites AE 0456148, AE 1417268, and AE 1392936 in Plant Matrices Using LC/MS/MS. Project No. 20105901. Study No. RAAEX019. Unpublished study prepared by Bayer CropScience. 92 pages.

46695540 Harbin, A.M.; Williams, L. (2005) Extraction Efficiency of Bayer Method AE/03/01 AE 0172747: Analytical Method for the Determination of Residues of AE 0172747 and its Major Metabolites AE 0456148, AE 1417268, and AE 1392936 in Plant Matrices Using LC/MS/MS. Study No. RAAEX008. Unpublished study prepared by Bayer CropScience. 29 pages.

46695542 McLean, N. (2005) Independent Laboratory Validation Of Method 201059, AE 0172747: An Analytical Method for the Determination of Residues of AE 0172747 and its Major Metabolites AE 0456148, AE 1417268, and AE 1392936 in Plant Matrices Using LC/MS/MS for AE 0172747 and Metabolites in Corn. Laboratory Study No.: 05ILV01BAY. Laboratory Report No. 05BAY23.REP. Unpublished study prepared by Enviro-Test Laboratories. 168 pages.

46695544 Allison, N.; Coopersmith, H.; Williams, L. (2004) AE 0172747: Validation of Analytical Method AE/03/01 for AE 0172747 and its major Metabolites AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2) in Plant Matrices Using LC/MS/MS. Bayer CropScience Study No. 03RAAEX019. Unpublished study prepared by Bayer CropScience. 94 pages.

The petitioner has submitted an evaluation template for the study reports listed above, which was used to generate this DER; selected sections were copied without alteration or were copied and modified to more specifically reflect the Agency's data evaluation requirements.

EXECUTIVE SUMMARY:

Bayer CropScience has submitted descriptions and validation data for liquid chromatography/mass spectroscopy (LC/MS)/MS Method AE/03/01 (also referred to as Method 201059 in one study report). The method determines residues of tembotrione (parent) and its metabolites AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2) in/on plant

commodities. Method AE/03/01 was the data-collection method used for determination of residues of the parent and its metabolites (M6, M5, and M2) in/on plant samples collected from supporting studies (storage stability, crop field trials, processing, and limited field rotational trials) associated with PP#5F7009. It is also the proposed enforcement method.

Using Method AE/03/01, residues of tembotrione and its metabolites M2, M5, and M6 are extracted from crop matrices with acetonitrile:water (1:1, v:v) using accelerated solvent extraction. Internal standards of the deuterated analytes are added to the extract. For analysis of parent, M5, and M6, an aliquot of the extract is concentrated via Turbo-Vap. For analysis of M2, an aliquot of the extract is loaded onto a strong-anion-exchange (SAX) solid-phase extraction (SPE) cartridge and eluted with oxalic acid. The SPE eluate is concentrated. The concentrates are reconstituted in 0.1% formic acid and filtered for LC/MS/MS analysis. Quantitation of tembotrione and its metabolites is done against a known amount of deuterated internal standard. Identification is confirmed by comparing the ion ratio of the analyte to that of the analytical standard. The limit of quantitation (LOQ), determined as the lowest fortification level with adequate recovery, is 0.010 ppm for each analyte. The calculated limits of detection (LODs) for the parent and its metabolites were each ≤0.004 ppm in corn matrices.

The initial validation of Method AE/03/01, performed by the petitioner, was conducted using control samples of: field corn forage, fodder, and grain (early and mature grains); sweet corn grain (early and mature grains); sugarcane; and turnip roots. Two fortification levels of 0.01 and 0.05 ppm were used for each combination of matrix and analyte. The method recoveries were, overall, adequate and within the acceptable range of 70-120% with the exception of turnip root samples fortified with M5 which yielded average recoveries of 124% and 130% at the respective fortification levels of 0.01 and 0.05 ppm, and field corn forage fortified with M5 at 0.05 ppm which yielded an average recovery of 129%.

The method was also successfully validated by an independent laboratory using corn grain and forage at fortification levels of 0.01 ppm (LOQ), 0.05 ppm, and 0.50 ppm. The fortification levels used in method validations as well as from concurrent analysis of samples from various studies are adequate to bracket expected residue levels. Finally, Method AE/03/01 was adequately validated using weathered samples of corn stover obtained from a previous corn metabolism study.

The method has been shown to be specific for the target analytes. The method used LC-MS/MS for detection and quantitation of the analytes. The study report for MRID 46695537 stated that Revision AE/03/01-01, once signed and issued, will supersede Method AE/03/01; however, no descriptions of the revisions were included except a statement that the revision is essentially the same as the original method and further provides a second ion transition which may be used for confirmation purposes.

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the analytical method test data are classified as acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document [DP# 325349].

COMPLIANCE:

Signed and dated Good Laboratory Practice (GLP), Quality Assurance and Data Confidentiality statements were provided. No deviations from regulatory requirements were reported which would have an impact on the validity of the study.

A. BACKGROUND INFORMATION

Tembotrione, a new herbicide with broad use against mono- and dicotyledons in selected crops such as corn, is a 4-hydroxyphenylpyruvate deoxygenase (HPPD) inhibitor (bleacher). The specialized method is designed to directly measure residues of tembotrione, and its metabolites AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2) in plant matrices.

Details of the test compound nomenclature (tembotrione and its metabolites) and physiochemical properties of tembotrione are given in Tables A.1 and A.2.

TABLE A.1. Test Compound Nomenclature for Tembotrione and its Metabolites AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2).

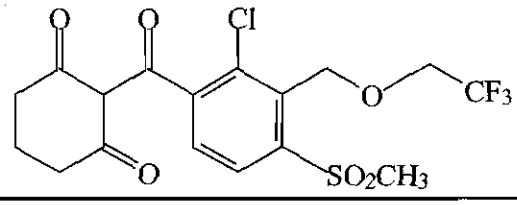
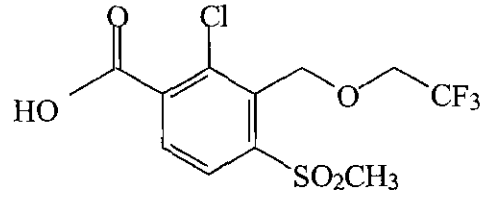
Compound: Tembotrione	Chemical Structure 
Common name	Tembotrione (Parent)
Company experimental name	AE 0172747
IUPAC name	2-{2-Chloro-4-mesyl-3-[(2,2,2-trifluoroethoxy)methyl]*benzoyl*}cyclohexane-1,3-dione
CAS name	2-[2-Chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-*1*,3-cyclohexanedione
CAS #	335104-84-2
End-use product/EP	AE 0172747 Herbicide, EPA Reg No. 264-*xxx*
Compound: AE 0456148	Chemical Structure 
Common name	Metabolite M6
Company experimental name	AE 0456148
IUPAC name	None provided
CAS name	2-chloro-4-mesyl-3-[(2,2,2-trifluroethoxy)methyl]benzoic acid
CAS #	None provided

TABLE A.1. Test Compound Nomenclature for Tembotrione and its Metabolites AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2).

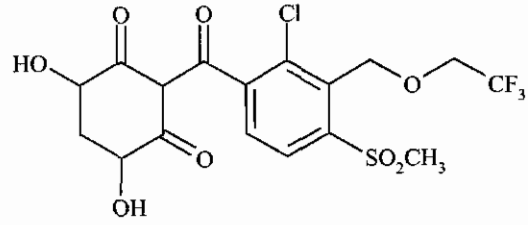
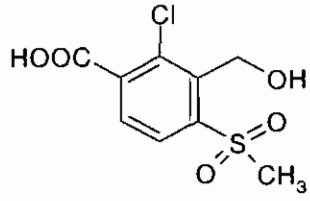
Compound: AE 1417268	Chemical Structure 
Common name	Metabolite M5
Company experimental name	AE 1417268
IUPAC name	None provided
CAS *name*	2-[2-chloro-4-(methylsulfonyl)-3-[2,2,2-trifluoroethoxy)methyl]benzoyl]-4,6-dihydroxycyclohexan-1,3-dione
CAS #	None provided
Compound: AE 1392936	Chemical Structure 
Common name	Metabolite M2
Company experimental name	AE 1392936
IUPAC name	None provided
CAS name	2-chloro-3-hydroxymethyl-4-mesylbenzoic acid
CAS #	None provided

TABLE A.2. Physicochemical Properties of Technical Grade Tembotrione.

Parameter	Value	Reference (MRID#)
Melting point	117 °C	46695402
pH @ 24 °C	3.63	
Density (g/mL @ 20 °C)	1.56	
Water solubility (mg/L @ 20 °C)	0.22 at pH4 28.3 at pH 7 29.7 at pH 9	
Solvent solubility (g/L at 20 °C) DMSO Methylene Chloride Acetone Ethyl Acetate Toluene Hexane Ethanol	 >600 >600 300-600 180.2 75.7 47.6 8.2	
Vapor pressure (Torr, 20 °C)	8.25×10^{-11}	
Dissociation constant (pK_a)	3.2	

TABLE A.2. Physicochemical Properties of Technical Grade Tembotrione.		
Parameter	Value	Reference (MRID#)
Oetanol/water partition coefficient (P_{ow} @ 23 °C) (P_{ow} @ 24 °C) (P_{ow} @ 23 °C)	 0.0430 at pH 9.0 0.0807 at pH 7.0 144.9 at pH 2.0	
UV/visible absorption spectrum (nm)	Primary: 205 Secondary: 284 Tertiary: 240	

B. MATERIALS AND METHODS

B.1. Data-Gathering Method

Method AE/03/01 (also referred to as Method 201059) was the data-collection method used for determination of residues of tembotrione (parent) and its metabolites AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2) in/on plant samples collected from supporting studies (storage stability, crop field trials, processing, and limited field rotational crop) associated with the current petition, PP#5F7009. The LC/MS/MS method was entitled "AE 0172747: An Analytical Method for the Determination of Residues of AE 0172747 and its major Metabolites AE 0456148, AE 1417268, and AE 1392936 in Plant Matrices Using LC/MS/MS."

B.1.1. Principle of the Method

Using Method AE/03/01, residues of tembotrione and its metabolites M2, M5, and M6 are extracted from corn and other crop matrices with acetonitrile:water (1:1, v:v) using accelerated solvent extraction; see Table B.1.1. Internal standards of the deuterated analytes are added to the extract. For analysis of parent, M5, and M6, an aliquot of the extract is concentrated via Turbo-Vap. For analysis of M2, an aliquot of the extract is loaded onto a SAX SPE cartridge and eluted with oxalic acid. The SPE eluate is concentrated. The concentrates are reconstituted in 0.1% formic acid and filtered for LC/MS/MS analysis. Quantitation of tembotrione and its metabolites is done against a known amount of deuterated internal standard. Identifications are confirmed by comparing the ion ratio of the analyte to that of the analytical standard.

TABLE B.1.1. Summary Parameters for the Analytical Method Used for the Quantitation of Residues of Tembotrione and its Metabolites in Plants.	
Method ID	AE/03/01-01
Analytes	Tembotrione (parent), AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2).
Extraction solvent/technique	Samples are homogenized in the presence of dry ice and extracted with acetonitrile:deionized water (1:1, v:v) through an accelerated solvent extraetor (Dionex Corporation, Sunnyvale, CA).
Cleanup strategies	Tembotrione, M6 and M5: The extracts are fortified with the internal standard, diluted, and an aliquot of the diluted extract is filtered and eoncentrated. A 6% formic acid solution is added to the eoncentrated sample, the extract is diluted, and then filtered. M2: The extracts are fortified with the internal standard, diluted, and the residues werc cleaned up via SAX SPE. The extract is concentrated, a 6% formic acid solution is added to the concentrated sample, the extract is diluted, and then filtered.

TABLE B.1.1. Summary Parameters for the Analytical Method Used for the Quantitation of Residues of Tembotrione and its Metabolites in Plants.	
Instrument/Detector	HPLC utilizing a SymmetryShield™ RP 8 column and a gradient mobile phase of 0.1% acetic acid and ACN, with MS/MS detection using electrospray ionization operating in the negative-ion mode. The ion transitions monitored (parent mass →daughter ion) are: tembotrionc: m/z 439→403 tembotrione internal standard: m/z 443→407 M6: m/z 345→301 M6 internal standard: m/z 349→305 M5: m/z 471→435 M5 internal standard: m/z 475→439 M2: m/z 263→189 M2 internal standard: m/z 268→192
Standardization method	External and internal standardization. Five calibration standards, containing internal standards, are injected and a calibration curve is constructed from the relative responses (RRs; analyte peak area divided by internal standard) versus standard concentration. Samples are bracketed by calibration standards at the beginning and end of the run. Results are calculated using linear regression.
Stability of std solutions	Primary stock solutions of tembotrione, AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2).are to be stored frozen and prepared every 3 months. Secondary stock standard and calibration standard solutions are to be prepared every 3 months.
Retention times	≈ 6.88 minutes for tembotrione ≈ 9.05 minutes for AE 0456148 (M6) ≈ 9.85 minutes for AE 1417268 (M5) ≈ 4.91 minutes AE 1392936 (M2)

B.2. Enforcement Method

The proposed enforcement method for plant commodities is the same as the data-gathering method (AE/03/01).

C. RESULTS AND DISCUSSION

C.1. Data-Gathering Method

The initial validation of Method AE/03/01, performed by the petitioner, was conducted using control samples of: field corn forage, fodder, and grain (early and mature grains); sweet corn grain (early and mature grains); sugarcane; and turnip roots. Two fortification levels of 0.01 and 0.05 ppm were used for each combination of matrix and analyte. The results of method validation are presented in Table C.1.1. The method recoveries are, overall, adequate and within the acceptable range of 70-120% with the exception of turnip root samples fortified with M5 which yielded average recoveries of 124% and 130% at the respective fortification levels of 0.01 and 0.05 ppm, and field corn forage fortified with M5 at 0.05 ppm which yielded an average recovery of 129%.

The results of a radiovalidation study are presented in Table C.1.3. The amounts of total radioactive residues (TRR) in corn stover as well as in the extract are comparable between the metabolism and radiovalidation studies. The proportions of the metabolites found in the metabolism study are also consistent with those found in the radiovalidation study. The

submitted extraction efficiency data demonstrate that the extraction procedures of method AE/03/01 adequately extract aged residues of tembotrione and its metabolites from corn stover samples.

TABLE C.1.1. Recovery Results from Method Validation of Plant Matrices using the Data-Gathering Analytical Method (MRID 46695537).

Matrix	Spiking Level (ppm)[1]	Percent Recoveries Obtained	Mean Recovery ± SD (RSD)[2]
Tembotrione (Parent)			
Field Corn Forage	0.01	78.1, 80.7, 81.5, 85.3, 86.8, 88.6	83.5 ± 4.03 (4.8)
Field Corn Forage	0.05	100, 101, 103	101 ± 1.53 (1.5)
Sweet Corn Early Grain	0.01	81.9, 83.2, 85.7, 85.7, 86.1, 88.7	85.2 ± 2.39 (2.8)
Sweet Corn Early Grain	0.05	89, 97	93
Sweet Corn Early Grain	0.05	77, 80, 80	79 ± 1.73 (2.2)
Field Corn Mature Grain	0.01	83.9, 84.7, 89.3, 90.2, 90.5, 91.1, 93.5	89 ± 3.49 (3.9)
Field Corn Mature Grain	0.05	93, 95, 97	95 ± 2 (0.1)
Field Corn Fodder	0.01	76, 77, 80.3, 80.6, 81.8, 82.2, 84.4	80.3 ± 2.95 (3.7)
Field Corn Fodder	0.05	81, 90, 94	88.3 ± 6.66 (7.5)
Sugar Cane	0.01	71.7, 83.2, 91.0, 92.9, 93.2, 95.2, 96.1	87.6 ± 8.2 (9.4)
Sugar Cane	0.05	90, 92, 94	92 ± 2.0 (2.2)
Turnip Root	0.01	76.4, 84.1, 89.3, 93.4, 94.9, 95.1, 99.6	88.8 ± 6.76 (7.6)
Turnip Root	0.05	106, 107, 116	110 ± 5.51 (5.0)
AE 0456148 (M6)			
Field Corn Forage	0.01	74.9, 76.8, 81.4, 86.7, 87.5, 90.1	82.9 ± 6.18 (7.5)
Field Corn Forage	0.05	99, 101, 104	101 ± 2.52 (2.5)
Sweet Corn Early Grain	0.01	95.8, 96.1, 96.4, 97, 97.4, 108	98.5 ± 4.71 (4.8)
Sweet Corn Early Grain	0.05	111, 111	111
Sweet Corn Early Grain	0.05	108, 110, 118	112 ± 5.29 (4.7)
Field Corn Mature Grain	0.01	92, 93.8, 101, 013, 105, 117, 113	104 ± 9.2 (8.8)
Field Corn Mature Grain	0.05	105, 113, 114	111 ± 4.93 (4.4)
Field Corn Fodder	0.01	71.5, 72.4, 79.3, 86, 86.3, 89.2, 109	84.7 ± 12.71 (15.0)
Field Corn Fodder	0.05	94, 100, 102	98.7 ± 4.16 (4.2)
Sugar Cane	0.01	81.1, 90.8, 93.1, 95.3, 99.3, 100, 109	95.5 ± 8.68 (9.1)
Sugar Cane	0.05	105, 116, 118	113 ± 7.0 (6.2)
Turnip Root	0.01	98.9, 103, 104, 106, 114, 116, 117	108 ± 7.16 (6.6)
Turnip Root	0.05	111, 113, 119	114 ± 4.16 (3.6)
AE 1417268 (M5)			
Field Corn Forage	0.01	101, 102, 103, 105, 116, 116	107 ± 6.97 (6.5)
Field Corn Forage	0.05	124, 126, 138	129 ± 7.57 (5.9)
Sweet Corn Early Grain	0.01	84.2, 95.8, 95.8, 99.7, 103, 105	97.3 ± 7.4 (7.6)
Sweet Corn Early Grain	0.05	100, 120	110
Sweet Corn Early Grain	0.05	112, 113, 120	115 ± 4.36 (3.8)
Field Corn Mature Grain	0.01	72.2, 73.5, 78.8, 83.6, 85.8, 91, 91.8	82.4 ± 7.87 (9.6)
Field Corn Mature Grain	0.05	105, 106, 109	107 ± 2.08 (1.9)
Field Corn Fodder	0.01	74.8, 75.3, 77.9, 79.3, 80.4, 83.5, 85.7	79.6 ± 4.03 (5.1)
Field Corn Fodder	0.05	78, 87, 94	86.3 ± 8.02 (9.3)
Sugar Cane	0.01	85.4, 93.3, 99.5, 97.5, 106, 108, 109	99.9 ± 8.61 (8.6)

TABLE C.1.1. Recovery Results from Method Validation of Plant Matrices using the Data-Gathering Analytical Method (MRID 46695537).

Matrix	Spiking Level (ppm)[1]	Percent Recoveries Obtained	Mean Recovery ± SD (RSD)[2]
Sugar Cane	0.05	104, 109, 109	107 ± 2.89 (2.7)
Turnip Root	0.01	113, 115, 127, 125, 129, 129, 133	124 ± 7.55 (6.1)
Turnip Root	0.05	126, 128, 137	130 ± 5.86 (4.5)
AE 1392936 (M2)			
Field Corn Forage	0.01	88.7, 93.7, 95, 96.4, 103, 106	97.1 ± 6.34 (6.5)
Field Corn Forage	0.05	111, 113, 118	114 ± 3.61 (3.2)
Sweet Corn Early Grain	0.01	90.8, 94.6, 102, 102, 103, 104	99.4 ± 5.38 (5.4)
Sweet Corn Early Grain	0.05	104, 106	105
Sweet Corn Early Grain	0.05	102, 107, 113	107 ± 5.51 (5.1)
Field Corn Mature Grain	0.01	89, 94.3, 95.9, 98.1, 102, 102, 104	97.9 ± 5.28 (5.4)
Field Corn Mature Grain	0.05	98, 106, 114	106 ± 8 (7.5)
Field Corn Fodder	0.01	71.6, 85.7, 86.5, 86.9, 91.4, 93.1, 94.9	87.2 ± 7.72 (8.9)
Field Corn Fodder	0.05	86, 106, 116	103 ± 15.3 (14.9)
Sugar Cane	0.01	84.9, 87.1, 100, 103, 105, 110, 118	101 ± 11.9 (11.8)
Sugar Cane	0.05	96, 111	104
Turnip Root	0.01	81.1, 93.1, 95.1, 96.5, 99.2, 110, 110	97.8 ± 10.7 (10.9)
Turnip Root	0.05	108, 109, 112	110 ± 2.08 (1.9)

[1] Standards were prepared in acetonitrile.
[2] The standard deviation (SD) and relative standard deviation (RSD) were calculated by the petitioner.

TABLE C.1.2. Characteristics for the Data-Gathering Analytical Method Used for the Quantitation of Residues of Tembotrione and its Metabolites in Plants.

Analyte	Tembotrione (parent), AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2).
Equipment ID	ConstaMetric® 3200 HPLC and ThermoFinnigan TSQ 7000 with triple-quadrupole mass spectrometer
LOQ	0.010 ppm The LOQ was determined as lowest fortification level with adequate recovery.
LOD	Tembotrione: 0.0011 ppm, corn grain; 0.0014 ppm, forage; 0.0009 ppm, stover AE 0456148 (M6): 0.0029 ppm, corn grain; 0.0021 ppm, forage; 0.0040 ppm, stover AE 1417268 (M5): 0.0025 ppm, corn grain; 0.0023 ppm, forage; 0.0013 ppm, stover AE 1392936 (M2): 0.0017 ppm, corn grain; 0.0021 ppm, forage; 0.0024 ppm, stover The LODs were calculated for each analyte in each matrix by multiplying the standard deviation of the LOQ recoveries by the $t_{0.99}$ value for the number of measurements.
Accuracy/Precision	Percent recoveries and coefficients of variance (CVs) indicate acceptable accuracy/precision at 0.01 and 0.05, ppm for corn forage, early corn grain, mature corn grain, corn fodder, turnip root, and sugar cane. The respective recovery ranges (and CVs) from the above matrices were 71.7-116% (2.8-9.4) for tembotrione, 71.5-119% (7.5-15) for M6, 72.2-138% (6.1-9.6) for M5, and 71.6-118% (5.4-14.9) for M2. See Table C.1.1 above.
Reliability of the Method/ [ILV]	An independent laboratory method validation (ILV) was conducted to verify the reliability of Method AE/03/01 for the determination of tembotrione residues of concern in plants. The values obtained are indicative that method AE/03/01 is reliable; see Section C.3.
Linearity	The relative response was linear typical coefficient of determination. $r^2 = 0.9994$ for parent, $r^2 = 0.9910$ for M6, $r^2 = 0.9969$ for M5 and $r^2 = 9995$ for M2, within the calibration range from 5.0ppb to 500 ppb.

TABLE C.1.2. Characteristics for the Data-Gathering Analytical Method Used for the Quantitation of Residues of Tembotrione and its Metabolites in Plants.	
Specificity	The control chromatograms generally have no peaks above the chromatographic background and the spiked sample chromatograms contain only the analyte peak of interest within the retention window. Peaks were well defined and symmetrical. A blank of the injection solvent solution was injected between the high standard and the control sample to prevent carry-over between injections.

A study (MRID 46695540) was conducted to determine the efficiency of Method AE/03/01 in extracting residues of tembotrione and its metabolites using weathered samples of corn stover as the matrix. Sample of corn stover were obtained from the corn metabolism study (MRID 46695530) where the plants (growth stage BBCH 12-14) were treated with a foliar spray of [phenyl-U-^{14}C]tembotrione at a rate of 200 g ai/ha. Mature stover (BBCH 97) was harvested 124 days following this treatment. The sample was homogenized and stored frozen (≤-18 °C). Upon receipt of the sample at the analytical laboratory (Bayer Research Park, Stillwell, KS), the stover was transferred to a freezer for storage (≤-20 °C). The combined storage time for this sample before the extraction efficiency test was conducted was about 48 months.

The TRR of the corn stover sample were determined in the radiovalidation study and were compared to the value obtained in the corn metabolism study. The TRR was determined by summing the radioactivity in the extractable and nonextractable residues quantitated by LSC and combustion/LSC, respectively. Additional subsamples were analyzed according to the written procedures for Method AE/03/01.

TABLE C.1.3. Extraction Efficiency of the Enforcement Analytical Method (Method AE/03/01) Using Radiolabeled Samples from Corn Metabolism Studies.

Matrix	Metabolism Study		Residue Method		Extraction Efficiency (%)
	%TTR	ppm	%TTR	ppm	
Corn Stover					
TRR	100	0.124	100.0	0.127	---
Extract	78.7	0.098	77.6	0.099	98.6
Tembotrione (parent)	Not Detected		Not Detected		---
AE 0456148 (M6)	39.6	0.049	47.7	0.061	120
AE 1392936 (M2)	11.6	0.014	6.7	0.008	58
AE 1417268 (M5)	5.5	0.007	3.9	0.005	71
Total	56.7	0.070	58.3	0.074	103

C.2. Enforcement Method

The proposed enforcement method for plant commodities is the same as the data-gathering method, AE/03/01.

C.3. Independent Laboratory Validation (ILV)

Method AE/03/01 was subjected to an ILV. The lLV was conducted by Enviro-Test Laboratories (Edmonton, Alberta) using samples of corn grain and forage. Samples of untreated corn grain and forage were fortified with tembotrione, AE 0456148 (M6), AE 1417268 (M5),

and AE 1392936 (M2) at 0.01 ppm (LOQ), 0.05 ppm and 0.50 ppm. Fortified and unfortified samples were analyzed using LC/MS/MS Method AE/03/01 as described in Table B.1.1.

The method was successfully validated on the first trial; see Table C.3.1. The laboratory reported that the method was followed as written. Recoveries of tembotrione, AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2) from corn grain and forage ranged 70-112%. Total tembotrione, AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2) residues were below the LOQ (<0.01 ppm) in/on two samples each of unfortified corn grain and corn forage.

The laboratory reported that a set of 17 samples could be prepared in 8 hours, plus overnight unattended waiting time for the ASE. The analysis required 16 hours of LC/MS/MS instrument time. The total time to complete analysis of a set of 17 samples would be 1.5 calendar days. No critical steps were identified by the ILV laboratory.

TABLE C.3.1. Recovery Results Obtained by an ILV of the Enforcement Method for the Determination of Tembotrione in Plants.

Matrix	Spiking Level (ppm)	Recoveries Obtained	Mean Reeovery ± SD (RSD)
Tembotrione (parent)			
Corn Grain	0.010	93, 84, 101, 88, 90	91 ± 6.4 (7.0)
	0.050	83, 91, 96, 86, 91	89 ± 5.0 (5.6)
	0.500	92, 81, 89, 91, 94	89 ± 5.0 (5.6)
Corn Forage	0.010	106, 110, 110, 107, 104	107 ± 2.6 (2.4
	0.050	95, 88, 85, 94, 94	91 ± 4.4 (4.8)
	0.500	88, 92, 93, 92, 93	92 ± 2.1 (2.3)
AE 0456148 (M6)			
Corn Grain	0.010	102, 94, 79, 92, 87	91 ± 8.5 (9.3)
	0.050	104, 92, 104, 103, 98	100 ± 5.2 (5.2)
	0.500	89, 90, 86, 88, 91	89 ± 1.9 (2.1)
Corn Forage	0.010	79, 108, 120, 107, 76	98 ± 19 (20)
	0.050	93, 104, 106, 87, 105	99 ± 8.5 (8.6)
	0.500	73, 74, 72, 90, 90	80 ± 9.3 (12)
AE 1417268 (M5)			
Corn Grain	0.010	78, 86, 96, 87, 91	88 ± 6.7 (7.6)
	0.050	86, 92, 102, 95, 95	94 ± 5.8 (6.2)
	0.500	102, 103, 112, 109, 96	104 ± 6.3 (6.1)
Corn Forage	0.010	92, 70, 74, 73, 82	78 ± 8.9 (11)
	0.050	93, 91, 87, 88, 92	90 ± 2.6 (2.9)
	0.500	90, 104, 105, 99, 102	100 ± 6.0 (6.0)
AE 1392936 (M2)			
Corn Grain	0.010	91, 77, 101, 94, 97	92 ± 9.2 (10)
	0.050	90, 90, 93, 99, 96	94 ± 3.9 (4.1)
	0.500	92, 98, 102, 103, 100	99 ± 4.4 (4.4)
Corn Forage	0.010	79, 104, 107, 93, 105	98 ± 12 (12)
	0.050	97, 97, 95, 99, 97	97 ± 1.4 (1.4)
	0.500	101, 102, 101, 101, 103	102 ± 0.89 (0.87)

D. CONCLUSION

Method AE/03/01 is adequate for the determination of residues of tembotrione, AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2) in tested plant commodities. Method validation performed by the petitioner using control samples of field corn matrices, sweet corn matrices, sugarcane, and turnip roots at fortification levels of 0.01 and 0.05 ppm showed adequate method recoveries. The method was also successfully validated by an independent laboratory using corn grain and forage at fortification levels of 0.01 ppm (LOQ), 0.05 ppm, and 0.50 ppm. Finally, Method AE/03/01 was adequately radiovalidated using aged samples of corn stover obtained from a corn metabolism study.

E. REFERENCES

46695530.der.doc

F. DOCUMENT TRACKING

RDI: RAB1 Chemists (1/3/07)
Petition Number: PP#5F7009
DP#s: 325349, 325663, and 331222
PC Code: 012801

Template Version June 2005

Tembotrione/AE 0172747/PC Code 012801/Bayer CropScience/264
DACO 7.2.1, 7.2.2, and 7.2.3/OPPTS 860.1340/OECD IIA 4.2.5, 4.2.6 and 4.3
Residue Analytical Method – Livestock Commodities

Primary Evaluator	George F. Kramer, Ph.D., Senior Chemist Registration Action Branch (RAB1) Health Effects Division (HED) (7509P)	Date: 18-JUL-2007
Approved by	P.V. Shah, Ph.D., Branch Senior Scientist RAB1/HED (7509P)	Date: 18-JUL-2007

This DER was originally prepared under contract by Dynamac Corporation (2275 Research Boulevard, Suite 300; Rockville, MD 20850; submitted 11/10/2006). The DER has been reviewed by HED and revised to reflect current Office of Pesticide Programs (OPP) policies.

STUDY REPORTS:

46695545 Lakaschus, S. (2005) ILV of the of the Bayer CropScience Method No. 00967 for the Determination of Residues of AE 0172747 and its Metabolite AE 1417268 in/on Animal Material by HPLC-MS/MS. Study No. RAAEX055. Specht and Partner Report No. BAY-0521V. Unpublished study prepared by Dr. Specht & Partner Chemische Laboratorien GmbH. 71 pages.

46940601 Class, T. (2005) Development and Validation of a Residue Enforcement Method for the Determination of Residues of E 0172747 and its Metabolite in/on Animal Material by HPLC-MS/MS. Demonstration of a LC/MS/MS Confirmatory Method. PTRL Europe Study/Report No. P/B 884 G. Unpublished study prepared by Bayer CropScience. 42 pages.

The petitioner has submitted an evaluation template for the study reports listed above, which was used to generate this DER; selected sections were copied without alteration or were copied and modified to more specifically reflect the Agency's data evaluation requirements.

EXECUTIVE SUMMARY:

Bayer CropScience has submitted descriptions and validation data for liquid chromatography/mass spectroscopy (LC/MS)/MS Method No. 00967. The method determines residues of tembotrione and its dihydroxy metabolite AE 1417268 (M5) in meat, milk, and eggs. Method No. 00967 was the data-collection method used for the analysis of AE 1417268 (M5) residues in samples taken from a cattle feeding study (refer to 46695605.der.doc). It is also one of the proposed livestock enforcement methods.

Using Method No. 00967, residues of tembotrione and AE 1417268 (M5) are extracted from poultry eggs, bovine meat, kidney and liver with a mixture of acetonitrile (ACN):water (8:2, v:v). For milk, the extraction is performed with ACN. After centrifugation and a second extraction with subsequent centrifugation, the supernatant of the extract is partitioned twice with hexane. The hexane phase is discarded, and the ACN fraction is removed *in vacuo*. Methanol and acetic acid are added resulting in a final mixture of methanol:0.2% acetic acid (1:1, v:v). Quantification of tembotrione and AE 1417268 is performed with reversed-phase high-performance (HP) LC and tandem MS. The LC/MS/MS method includes measurement of a second MS transition for both analytes to serve as the confirmatory method. The validated limits

of quantitation (LOQs) for each analyte are 0.002 ppm in whole milk and 0.010 ppm in other matrices. The estimated limits of detection (LODs) for each analyte were 0.005 ppm in whole milk and 0.002 ppm for beef meat, kidney and liver, and poultry egg.

The initial validation of Method No. 00967, performed by the petitioner, was conducted using control samples of chicken eggs, whole milk, and beef meat, liver, and kidney. The results demonstrated adequate method recoveries of tembotrione and AE 1417268 (M5) from all tested matrices. The fortification levels for both analytes in all matrices were at the LOQ and 10x LOQ. For milk, the fortification levels were 0.002 ppm and 0.02 ppm. For eggs and beef meat, liver, and kidney, the fortification levels were 0.01 ppm and 0.10 ppm. Recoveries of tembotrione and AE 1417268, respectively, ranged: 92-105% and 91-108% in chicken eggs; 86-108% and 88-110% in beef meat; 86-113% and 85-114% in beef liver; 90-117% and 88-109% in beef kidney; and 93-100% and 79-99% in whole milk. The petitioner also conducted method validation analysis at the second ion transition for all matrices with overall recoveries in the range of 76-114% for tembotrione and 81-113% for AE 1417268.

The method was also successfully validated by an independent laboratory using the same matrices and fortification levels cited above. Method recoveries ranged 70-115% for tembotrione and 63-101% for AE 1417268 for all matrices.

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the analytical method test data are classified as acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document [DP# 325349].

COMPLIANCE:

Signed and dated Good Laboratory Practice (GLP), Quality Assurance and Data Confidentiality statements were provided. No deviations from regulatory requirements were reported which would have an impact on the validity of the study.

A. BACKGROUND INFORMATION

Tembotrione, a new herbicide with broad use against mono- and dicotyledons in selected crops such as corn, is a 4-hydroxyphenylpyruvate deoxygenase (HPPD) inhibitor (bleacher). The test compound nomenclature and physiochemical properties of the test compound are presented in Tables A.1 and A.2, respectively.

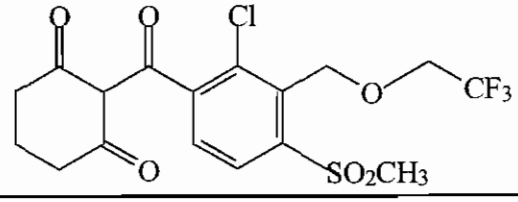
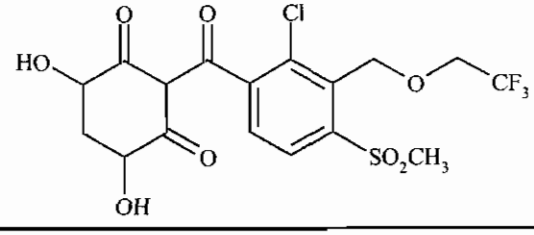
TABLE A.1. Test Compound Nomenclature for Tembotrione and its Metabolite AE 1417268 (M5).	
Compound: Tembotrione	Chemical Structure 
Common name	Tembotrione (Parent)
Company experimental name	AE 0172747
IUPAC name	2-{2-Chloro-4-mesyl-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl}cyclohexane-1,3-dione
CAS name	2-[2-Chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione
CAS #	335104-84-2
End-use product/EP	AE 0172747 Herbicide, EPA Reg No. 264-xxx
Compound: AE 1417268	Chemieal Structure 
Common name	Metabolite M5
Company experimental name	AE 1417268
IUPAC name	None provided
CAS name	2-[2-chloro-4-(methylsulfonyl)-3-[2,2,2-trifluoroethoxy)methyl]benzoyl]-4,6-dihydroxycyclohexan-1,3-dione
CAS #	None provided

TABLE A.2. Physicochemical Properties of Technical Grade Tembotrione.		
Parameter	Value	Reference (MRID#)
Melting point	117 °C	46695402
pH @ 24 °C	3.63	
Density (g/mL @ 20 °C)	1.56	
Water solubility (mg/L @ 20 °C)	0.22 at pH4 28.3 at pH 7 29.7 at pH 9	
Solvent solubility (g/L at 20 °C) DMSO Methylene Chloride Acetone Ethyl Acetate Toluene Hexane Ethanol	 >600 >600 300-600 180.2 75.7 47.6 8.2	
Vapor pressure (Torr, 20 °C)	8.25×10^{-11}	
Dissociation constant (pK_a)	3.2	

TABLE A.2. *Physicochemical Properties of Technical Grade Tembotrione.*		
Parameter	Value	Reference (MRID#)
Octanol/water partition coefficient (P_{ow} @ 23 °C) (P_{ow} @ 24 °C) (P_{ow} @ 23 °C)	 0.0430 at pH 9.0 0.0807 at pH 7.0 144.9 at pH 2.0	
UV/visible absorption spectrum (nm)	Primary: 205 Secondary: 284 Tertiary: 240	

B. MATERIALS AND METHODS

B.1. Data-Gathering Method

LC/MS/MS Method 00967 was the data-collection method used for the analysis of AE 1417268 (M5) residues in milk and tissue samples collected from a dairy cattle feeding study (refer to 46695606.der.doc) and is entitled "Development and Validation of a Residue Enforcement Method for the Determination of Residues of AE 0172747 and its Metabolite in/on Animal Material by HPLC-MS/MS. Demonstration of a LC/MS/MS Confirmatory Method."

B.1.1. Principle of the Method:

Briefly, livestock and dairy matrices are extracted with ACN:deionized water (4:1, v:v), centrifuged, and the supernatant decanted. Milk samples are extracted with ACN; see Table B.1.1. The samples are extracted/centrifuged a second time, the supernatants are combined and partitioned twice with hexane. The hexane phase is discarded, and the combined acetonitrile phases are evaporated to near dryness. The remaining sample is redissolved in methanol, acetic acid, and water, and filtered for analysis. Quantification of tembotrione and AE 1417268 is performed with reversed-phase LC-MS/MS.

Table B.1.2 lists a comparison of the HPLC parameters used in the different laboratories for method validation and independent method validation. Table B.1.3 compares the mass spectrometer parameters used for method development and method validation.

TABLE B.1.1. Summary Parameters for the Analytical Method Used for the Quantitation of Tembotrione and AE 1417268 (M5) Residues in Eggs, Bovine Tissues and Milk Matrices.	
Method ID	Bayer CropScience Method No. 00967
Analytes	Tembotrione and AE 1417268 (M5)
Extraction solvent/technique	Homogenized samples (except milk) are extracted with ACN: water (4:1, v:v) for 30 sec., centrifuged at 3500 rpm for 3 minutes, and the supernatant is decanted. The extraction is repeated. Milk samples are extracted with ACN.
Cleanup strategies	The supernatants are combined and partitioned with 10 mL of hexane (2x). The hexane phase is discarded, and the combined acetonitrile phases are evaporated to < 5mL. The remaining sample is redissolved in 10 mL methanol with 20 µL acetic acid, and diluted to 20 mL with water. The samples are filtered or centrifuged (if necessary) for analysis.
Instrument/Detector (Method Validation)	HPLC utilizing a SymmetryShield™ RP 8 column and a gradient mobile phase of ACN:water with 0.1% formic acid, with MS/MS detection using electrospray ionization operating in the negative ion mode for tembotrione. The ion transitions monitored (parent mass → daughter

	ion) are: Tembotrione: m/z 439 → 403 AE 1417268 (M5): m/z 471 → 435
Standardization method	External standardization, using matrix matehed ealibration standards of tembotrione and AE 1417268 to generate a standard curve through linear regression.
Stability of standard solutions	Appeared stable during method development ~(8 days, refrigerated). Appeared stable during the validation study (~4 days, refrigerated)
Retention times	≈ 5.8 minutes for tembotrione ≈ 6.0 minutes for AE 1417268

TABLE B.1.2. HPLC Parameters Comparison of Facilities.

Event	Method Validation			Independent Lab Validation (ILV)		
System	Agilent 1100 Series HPLC			Agilent 1100 Series HPLC		
Column	Waters SymmetryShield™ C8, 5µm, 3.0 x 150 mm			Phenomenex C8 5µm, 2.0 x 150 mm		
Column Temperature	30°C			30°C		
Injection Volume	25µL			30µL		
Mobile Phase	A = 0.1% formic acid in acetonitrile B = 0.1% formic acid in water			A = 0.1% formie acid in acetonitrile B = 0.1% formic acid in water		
Flow Rate	600 µL/min			500 µL/min		
Gradient	Time. Min 0.0 1.0 → 4.0 4.0 → 7.5 7.5 → 7.6 7.6 → 10	%A 50 50 → 95 95 95 → 50 50	%B 50 50 → 5 5 5 → 50 50	Time. Min 0.0 1.0 → 4.0 4.0 → 8.0 8.0 8.0 → 12	%A 30 30 → 95 95 30 30	%B 70 70 → 5 5 70 70
Retention Times	≈ 5.8 minutes for tembotrione ≈ 6.0 minutes for AE 1417268			≈ 6 minutes for tembotrione ≈ 5 minutes for AE 1417268		

TABLE B.1.3. Comparison of Mass Spectrometer Parameters.

Event	Method Development				Method Validation			
System	Applied Biosystems MDS Sciex API 3000 Triple Quadrapole				Perkin Elmer API 4000 QTrap Tandem			
Interface	Turbo Ion spray				Ion spray			
Ion spray Voltage (IS)	-3800				-4500			
Ion spray Heater, °C	400				400			
Curtain Gas (CUR)	11				25			
Collision Gas (CAD)	4.0				50			
Nebulizer Gas (NEB)	13				70			
Ion Mode	Negative Multiple Reaction Monitoring				Negative Multiple Reaction Monitoring			
	AE0172747 Primary	AE0172747 Qualifier	AE1417268 Primary	AE1417268 Qualifier	AE0172747 Primary	AE0172747 Qualifier	AE1417268 Primary	AE1417268 Qualifier
Transition, Q1→Q3	439→403	439→226	471→435	471→417	439→403	439→226	471→435	471→417
Dwell Time, seconds	0.200	0.250	0.250	0.250	0.250	0.250	0.250	0.250
Declustering Potential, V	-46	-46	-46	-46	-50	-50	-35	-35
Collision Energy, V	-18	-50	-22	-34	-16	-44	-22	-34

B.2. *Enforcement Method*

The proposed enforcement method for eggs, beef tissues and milk matrices is the same as the data-gathering method, Bayer Method 00967.

C. RESULTS AND DISCUSSION

C.1. Data-Gathering Method

The initial validation of Method No. 00967, performed by the petitioner, was conducted using control samples of chicken eggs, whole milk, and beef meat, liver, and kidney. The results (see Table C.1.1) demonstrated adequate method recoveries of tembotrione and AE 1417268 (M5) from all tested matrices. The fortification levels for both analytes in all matrices were at the LOQ and 10x LOQ. For milk, the fortification levels were 0.002 ppm and 0.02 ppm. For eggs and beef meat, liver, and kidney, the fortification levels were 0.01 ppm and 0.10 ppm. Recoveries of tembotrione and AE 1417268, respectively, ranged: 92-105% and 91-108% in chicken eggs; 86-108% and 88-110% in beef meat; 86-113% and 85-114% in beef liver; 90-117% and 88-109% in beef kidney; and 93-100% and 79-99% in whole milk. The petitioner also conducted method validation analysis at a second ion transition for all matrices with overall recoveries in the range of 76-114% for tembotrione and 81-113% for AE 1417268.

TABLE C.1.1. Recovery Results from Method Validation of Egg, Beef Tissues and Milk Matrices using the Data-Gathering Analytical Method.

Matrix	Spiking Level (ppm)[1]	Transition (m/z)	Recoveries Obtained	Mean Recovery ± SD (CV)[2]
Tembotrione				
Chicken Eggs	0.01	439 → 403	92, 96, 97, 100, 104	98 ± 4.9 (5)
		439 → 226	93, 98, 102, 104, 112	102 ± 7.1 (7)
	0.10	439 → 403	92, 96, 103, 103, 105	100 ± 5.0 (5)
		439 → 226	97, 102, 106, 108, 111	105 ± 5.3 (5)
Beef Meat	0.01	439 → 403	86, 97, 98, 105, 108	99 ± 8.9 (9)
		439 → 226	87, 98, 103, 103, 111	100 ± 9.0 (9)
	0.10	439 → 403	92, 97, 100, 101, 105	99 ± 5.0 (5)
		439 → 226	89, 100, 102, 103, 106	100 ± 6.0 (6)
Beef Liver	0.01	439 → 403	86, 97, 97, 109, 113	101 ± 11 (11)
		439 → 226	89, 96, 98, 109, 111	101 ± 9.1 (9)
	0.10	439 → 403	91, 94, 96, 105, 107	99 ± 6.9 (7)
		439 → 226	88, 92, 92, 104, 106	96 ± 7.7 (8)
Beef Kidney	0.01	439 → 403	90, 105, 105, 108, 117	105 ± 9.4 (9)
		439 → 226	98, 98, 101, 103, 112	102 ± 6.1 (6)
	0.10	439 → 403	100, 108, 109, 110, 112	108 ± 4.3 (4)
		439 → 226	104, 104, 108, 108, 114	108 ± 4.3 (4)
Whole Milk	0.002	439 → 403	96, 96, 98, 100, 100	98 ± 2.0 (2)
		439 → 226	76, 87 88, 88, 99	88 ± 7.9 (9)
	0.02	439 → 403	93, 94, 94, 96, 98	95 ± 1.9 (2)
		439 → 226	90, 90, 94, 95, 99	94 ± 3.8 (4)

TABLE C.1.1. Recovery Results from Method Validation of Egg, Beef Tissues and Milk Matrices using the Data-Gathering Analytical Method.

Matrix	Spiking Level (ppm)[1]	Transition (m/z)	Recoveries Obtained	Mean Recovery ± SD (CV)[2]
AE 1417268 (M5)				
Chicken Eggs	0.01	471 → 435	95, 104, 91, 105, 104	99.8 ± 6.4 (6.4)
		471 → 417	87, 101, 97, 103, 111	99.8 ± 8.8 (8.8)
	0.10	471 → 435	103, 108, 104, 107, 105	105.4 ± 2.1 (2.0)
		471 → 417	106, 107, 102, 106, 113	106.8 ± 4.0 (3.7)
Beef Meat	0.01	471 → 435	88, 104, 100, 102, 93	97.4 ± 6.7 (6.9)
		471 → 417	92, 101, 105, 105, 98	100.2 ± 5.4 (5.4)
	0.10	471 → 435	99, 110, 107, 107, 106	105.8 ± 4.1 (3.9)
		471 → 417	101, 108, 105, 107, 104	105.0 ± 2.7 (2.6)
Beef Liver	0.01	471 → 435	93, 100, 90, 86, 85	90.8 ±6.1 (6.7)
		471 → 417	96, 102, 90, 92, 91	94.2 ± 4.9 (5.2)
	0.10	471 → 435	98, 99, 101, 114, 111	104.6 ± 7.4 (7.0)
		471 → 417	98, 98, 104, 112, 107	103.6 ± 6.3 (6.1)
Beef Kidney	0.01	471 → 435	91, 106, 88, 89, 103	95.4 ± 8.4 (8.9)
		471 → 417	91, 105, 84, 101, 113	98.8 ± 11.5 (11.6)
	0.10	471 → 435	106, 109, 108, 109, 104	107.2 ± 2.2 (2.0)
		471 → 417	104, 106, 109, 113, 109	108.2 ± 3.4 (3.2)
Whole Milk	0.002	471 → 435	81, 79, 90, 91, 84	85.0 ± 5.3 (6.2)
		471 → 417	91, 81, 99, 109, 90	94.0 ± 10.5 (11.2)
	0.020	471 → 435	94, 95, 93, 99, 97	95.6 ± 2.4 (2.5)
		471 → 417	93, 94, 87, 101, 100	95.0 ± 5.7 (6.0)

[1] Standards were prepared in acetonitrile.
[2] The mean and standard deviation and coefficients of variance (CVs) for AE 1417268 were calculated by the petitioner. For tembotrione, the mean and standard deviation were calculated by the petitioner and the RSD was calculated by the study reviewer.

TABLE C.1.2. Characteristics for the Data-Gathering Analytical Method Used for the Quantitation of Residues of Tembotrione and AE 1417268 in Livestock Matrices.

Analyte	Tembotrione and AE 1417268 (M5)
Equipment ID	Agilent 1100 Series HPLC with Waters SymmetryShield™ C8 5µm 3.0 x 150 mm coupled with an Applied Biosystems MDS Seiex API 3000 triple quadruple LC/MS/MS with a Turbo Ion spray ESI source.
LOQ	0.002 mg/kg (ppm) for milk 0.010 mg/kg (ppm) for eggs, bovine meat, liver and kidneys (determined as lowest fortification level with adequate recovery)
LOD	0.0005 mg/kg (ppm) for milk (25% of the LOQ) 0.002 mg/kg (ppm) for eggs, bovine meat, liver and kidneys. (20% of the LOQ)
Aceuracy/Precision	Percent recoveries and CVs indicate acceptable accuracy/precision at 0.002 and 0.02 ppm for whole milk, and 0.01 and 0.10ppm for chicken eggs and beef meat, liver, and kidney. Recovery ranges (and CVs) from these matrices were 86-117% (2.0-11) for tembotrione and 79-114% (2.0-8.9) for M5. Sec Table C.1.1 above.
Reliability of the Method/	During the ILV, percent recoveries ranged from 70-115% for tembotrione and 63%-101% for AE 1417268 for all matrices. The values obtained indicate that method 00967 is reliable; see Section C.3.
Linearity	The relative response was linear. For the method validation, the correlation coefficient (r^2) was ≥ 0.999 for tembotrione and AE 1417268 for calibration curves that ranged

	from 0.200 to 20.0 ng/mL.
Specificity	The control chromatograms had no peaks above the chromatographic background and the spiked sample chromatograms contained only the analyte peaks of interest within the retention window. Peaks were well defined and symmetrical.
Selectivity and Confirmation	HPLC separation in combination with tandem mass spectrometric detection using two different transitions for each analyte achieves a high level of selectivity (specificity).

C.2. Enforcement Method

The proposed enforcement method for eggs, beef tissues and milk matrices is the same as the data-gathering method, Bayer Method 00967.

C.3. ILV

Method No. 00967 was subjected to an ILV conducted by Dr. Specht & Partner Chemische Laboratorien GmbH (Hamburg, Germany) using samples of chicken eggs, beef meat, beef liver, beef kidney, and whole milk. Samples were fortified with tembotrione and AE 1417268 at 0.002 ppm (LOQ) and 0.020 ppm for whole milk and 0.010 ppm (LOQ) and 0.10 ppm for all other matrices. Fortified and unfortified samples were analyzed using LC/MS/MS method 00967 as described in Tables B.1.1. and B.1.2.

The method was successfully validated on the first trial; see Table C.3.1. The laboratory reported that the method was followed as written. Recoveries from chicken eggs, beef meat, beef liver, beef kidney, and whole milk ranged 70-115% for tembotrione and 63-101% for AE 1417268. Total tembotrione and AE 1417268 residues were below the LOQ (<0.002 ppm or <0.01 ppm) in/on two samples each of unfortified chicken eggs, beef meat, beef liver, beef kidney, and whole milk. The laboratory did not report the time required to prepare and analyze a set of samples. No critical steps were identified by the ILV laboratory.

TABLE C.3.1. Recovery Results Obtained by an ILV of the Enforcement Method for the Determination of Tembotrione and AE 1417268 in Livestock Matrices.

Matrix	Spiking Level (ppm)	Transition	Recoveries Obtained	Mean Recovery ± SD (CV) %
Tembotrione				
Chicken Eggs	0.01	439 → 403	88, 93, 97, 99, 101	96 ± 5.2 (5.4)
		439 → 226	81, 91, 94, 98, 102	93 ± 8.0 (8.6)
	0.10	439 → 403	89, 90, 97, 99, 99	95 ± 4.9 (5.2)
		439 → 226	90, 90, 97, 97, 103	95 ± 5.5 (5.8)
Beef Meat	0.01	439 → 403	84, 87, 89, 92, 96	90 ± 4.6 (5.1)
		439 → 226	81, 84, 86, 92, 94	87 ± 5.5 (6.3)
	0.10	439 → 403	88, 97, 99, 99, 101	97 ± 5.1 (5.3)
		439 → 226	92, 97, 98, 101, 101	98 ± 3.7 (3.8)
Beef Liver	0.01	439 → 403	79, 80, 82, 90, 91	84 ± 5.7 (6.8)
		439 → 226	81, 82, 87, 94, 95	88 ± 6.5 (7.4)
	0.10	439 → 403	81, 86, 93, 93, 93	89 ± 5.5 (6.2)
		439 → 226	81, 83, 90, 94, 97	89 ± 6.9 (7.8)
Beef Kidney	0.01	439 → 403	73, 75, 77, 81, 94	80 ± 8.8 (11)

TABLE C.3.1. Recovery Results Obtained by an ILV of the Enforcement Method for the Determination of Tembotrione and AE 1417268 in Livestock Matrices.

Matrix	Spiking Level (ppm)	Transition	Recoveries Obtained	Mean Recovery ± SD (CV) %
Whole Milk	0.10	439 → 226	81, 81, 82, 88, 88	84 ± 3.7 (4.4)
		439 → 403	86, 86, 87, 90, 94	89 ± 3.4 (3.8)
		439 → 226	87, 89, 89, 90, 93	90 ± 2.2 (2.4)
	0.002	439 → 403	70, 80, 80, 85, 115	86 ± 17 (20)
		439 → 226	65, 75, 80, 85, 95	80 ± 11 (14)
	0.02	439 → 403	71, 72, 83, 89, 103	84 ± 13 (16)
		439 → 226	73, 74, 83, 88, 103	84 ± 13 (15)
AE 1417268 (M5)				
Chicken Eggs	0.0101	471 → 435	81, 79, 83, 91, 70	80.8 ± 7.6 (9.4)
		471 → 417	79, 83, 82, 86, 66	79.2 ± 7.8 (9.8)
	0.1010	471 → 435	83, 92, 94, 89, 72	86.0 ± 8.9 (10.3)
		471 → 417	82, 91, 96, 91, 76	87.2 ± 8.0 (9.2)
Beef Meat	0.0101	471 → 435	80, 67, 67, 74, 80	73.6 ± 6.5 (8.8)
		471 → 417	77, 68, 68, 76, 82	74.2 ± 6.1 (8.2)
	0.1010	471 → 435	67, 79, 73, 84, 86	77.8 ± 7.9 (10.1)
		471 → 417	67, 80, 73, 86, 87	78.6 ± 8.6 (10.9)
Beef Liver	0.0101	471 → 435	70, 74, 74, 67, 73	71.2 ± 2.8 (3.9)
		471 → 417	66, 76, 72, 68, 74	71.2 ± 4.1 (5.8)
	0.1010	471 → 435	94, 94, 96, 101, 93	95.6 ± 3.2 (3.4)
		471 → 417	91, 93, 96, 98, 92	94.0 ± 2.9 (3.1)
Beef Kidney	0.0101	471 → 435	63, 69, 70, 74, 76	70.4 ± 5.0 (7.1)
		471 → 417	67, 72, 73, 74, 74	72.0 ± 2.9 (4.0)
	0.1010	471 → 435	86, 91, 98, 92, 95	92.4 ± 4.5 (4.9)
		471 → 417	88, 94, 99, 92, 95	93.6 ± 4.0 (4.3)
Whole Milk	0.0020	471 → 435	70, 70, 90, 80, 80	78.0 ± 8.4 (10.7)
		471 → 417	70, 65, 80, 75, 75	73.0 ± 5.7 (7.8)
	0.0201	471 → 435	77, 70, 73, 82, 79	76.2 ± 4.8 (6.3)
		471 → 417	80, 71, 70, 81, 79	76.2 ± 5.3 (6.9)

D. CONCLUSION

Method No. 00967 is adequate for determination of residues of tembotrione and AE 1417268 in the tested livestock matrices. Method validation performed by the petitioner using control samples of chicken eggs, whole milk, and beef meat, liver, and kidney at fortification levels reflecting the LOQ and 10x LOQ showed acceptable method recoveries. The method was also successfully validated by an independent laboratory using the same matrices and fortification levels cited above.

E. REFERENCES

46695605.der.doc
46695606.der.doc

F. DOCUMENT TRACKING

RDI: RAB1 Chemists (1/3/07)
Petition Number: PP#5F7009
DP#s: 325349, 325663, and 331222
PC Code: 012801

Template Version June 2005

Tembotrione/AE 0172747/PC Code 012801/Bayer CropScience/264
DACO 7.3/OPPTS 860.1380/OECD IIA 6.1.1 and IIIA 8.1.1
Storage Stability – Turnip Roots, Mustard Greens, and Yellow Squash

Primary Evaluator	George F. Kramer, Ph.D., Senior Chemist Registration Action Branch (RAB1) Health Effects Division (HED) (7509P)	Date: 18-JUL-2007
Approved by	P.V. Shah P.V. Shah, Ph.D., Branch Senior Scientist RAB1/HED (7509P)	Date: 18-JUL-2007

This DER was originally prepared under contract by Dynamac Corporation (2275 Research Boulevard, Suite 300; Rockville, MD 20850; submitted 11/30/2006). The DER has been reviewed by HED and revised to reflect current Office of Pesticide Programs (OPP) policies.

STUDY REPORT:

46695602 Coopersmith, H. (2005) Storage Stability of AE 0172747, AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2) in Turnip Roots, Mustard Greens and Yellow Squash: Project Number RAAEX035. Unpublished study prepared by Bayer CropScience. 182 pages.

The petitioner has submitted an evaluation template for the study (Bayer CropScience DER for Study RAAEX035), which was used to generate this DER; several sections were copied without alteration or modified to more specifically reflect the Agency's data evaluation requirements.

EXECUTIVE SUMMARY:

Bayer CropScience has submitted the results of storage stability study with tembotrione and its metabolites AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2) in/on turnip roots, mustard greens, and yellow squash. Untreated samples of mustard greens were fortified with tembotrione and its metabolites each at a level of 0.2 ppm. Untreated samples of turnip roots and yellow squash were fortified with tembotrione and its metabolites each at a level of 0.4 ppm. All fortified and control samples were stored frozen (≤-10 °C) and analyzed at intervals of 0, 91 days (~3 months), 182 days (~6 months), and 350-370 days (~11.5-12 months).

The results indicate that under these conditions, residues of the parent, tembotrione, and its metabolites M6 and M2 appear to be relatively stable in/on turnip roots, mustard greens, and yellow squash for up to 350 days (11.5 months). Residues of metabolite M5 appear to be relatively stable in/on turnip roots, mustard greens, and yellow squash for up to 370 days (~12 months.

Samples of turnip roots, mustard greens, and yellow squash were analyzed for residues of tembotrione and its metabolites using liquid chromatography/mass spectroscopy (LC/MS)/MS Method No. AE/03/01. This method is adequate for data collection based on acceptable method recoveries. The validated limit of quantitation (LOQ) is 0.010 ppm for each analyte in crops. The calculated limits of detection (LODs) for the parent and its metabolites were ≤0.0014 ppm in various matrices.

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the storage stability data are classified as scientifically acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document [DP# 325349].

COMPLIANCE:

Signed and dated Good Laboratory Practice (GLP), Quality Assurance and Data Confidentiality statements were provided. No deviations from regulatory requirements were reported which would have an impact on the validity of the study.

A. BACKGROUND INFORMATION

Tembotrione, a new herbicide with broad use against mono- and dicotyledons in selected crops such as corn, is a 4-hydroxyphenylpyruvate deoxygenase (HPPD) inhibitor (bleacher). Details of the test compounds nomenclature (tembotrione and its three metabolites) and physiochemical properties of tembotrione are given in Tables A.1 and A.2.

TABLE A.1. Test Compound Nomenclature for Tembotrione and its Metabolites AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2).

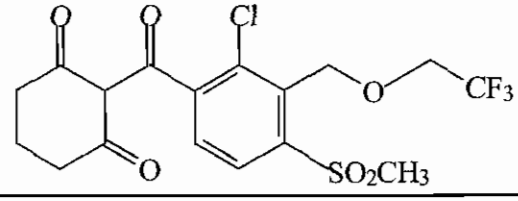
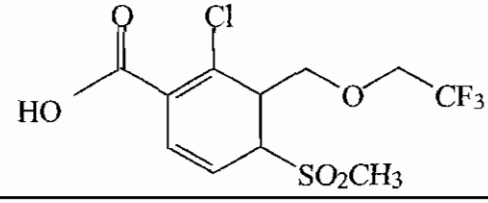
Compound: Tembotrione	Chemical Structure 
Common name	Tembotrione (Parent)
Company experimental name	AE 0172747
IUPAC name	2-{2-Chloro-4-mesyl-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl}cyclohexane-1,3-dione
CAS name	2-[2-Chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione
CAS #	335104-84-2
End-use product/EP	AE 0172747 Herbicide, EPA Reg No. 264-xxx
Compound: AE 0456148	Chemical Structure 
Common name	Metabolite M6
Company experimental name	AE 0456148
IUPAC name	None provided

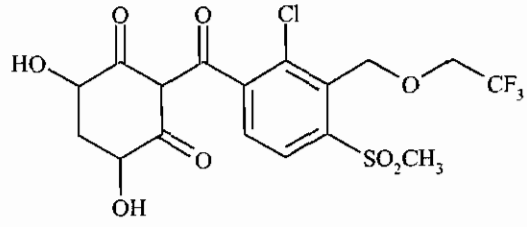
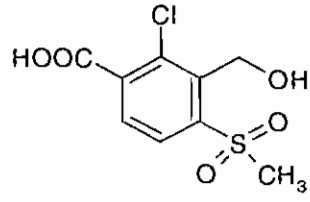
TABLE A.1. Test Compound Nomenclature for *Tembotrione and its Metabolites AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2).*	
CAS name	2-chloro-4-mesyl-3-[(2,2,2-trifluroethoxy)methyl]benzoic acid
CAS #	None provided
Compound: AE 1417268	Chemical Structure 
Common name	Metabolite M5
Company experimental name	AE 1417268
IUPAC name	None provided
CAS name	2-[2-chloro-4-(methylsulfonyl)-3-[2,2,2-trifluoroethoxy)methyl]benzoyl]-4,6-dihydroxycyclohexan-1,3-dione
CAS #	None provided
Compound: AE 1392936	Chemical Structure 
Common name	Metabolite M2
Company experimental name	AE 1392936
IUPAC name	None provided
CAS name	2-chloro-3-hydroxymethyl-4-mesylbenzoic acid
CAS #	None provided

TABLE A.2. Physicochemical Properties of Technical Grade Tembotrione.		
Parameter	Value	Reference (MRID#)
Melting point	117 °C	46695402
pH @ 24 °C	3.63	
Density (g/mL @ 20 °C)	1.56	
Water solubility (mg/L @ 20 °C)	0.22 at pH4 28.3 at pH 7 29.7 at pH 9	
Solvent solubility (g/L at 20 °C) DMSO Methylene Chloride Acetone Ethyl Acetate Toluene Hexane Ethanol	 >600 >600 300-600 180.2 75.7 47.6 8.2	
Vapor pressure (Torr, 20 °C)	8.25×10^{-11}	

TABLE A.2. Physicochemical Properties of Technical Grade Tembotrione.

Parameter	Value	Reference (MRID#)
Dissociation constant (pK_a)	3.2	
Octanol/water partition coefficient (P_{ow} @ 23 °C) (P_{ow} @ 24 °C) (P_{ow} @ 23 °C)	 0.0430 at pH 9.0 0.0807 at pH 7.0 144.9 at pH 2.0	
UV/visible absorption spectrum (nm)	Primary: 205 Secondary: 284 Tertiary: 240	

B. EXPERIMENTAL DESIGN

B.1. Sample Handling and Preparation

Untreated samples of turnip roots and mustard greens were obtained from rotational crop field trials. Untreated samples of yellow squash were obtained by Bayer CropScience (Stilwell, KS) from a local retailer. Homogenized samples were weighed into vials and fortified with a mixed fortification standard of tembotrione, AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2), each at a level of 0.4 ppm for turnip roots and yellow squash and at 0.2 ppm for mustard greens. The mixed fortification standard was prepared in acetonitrile (ACN). The stability of the fortification standards was not reported. Fortified and unfortified samples were stored frozen (≤-10 °C) and analyzed at 0-, 91-, 182- and 350- to 370- day storage intervals.

B.2. Analytical Methodology

Samples of turnip roots, mustard greens and yellow squash were analyzed for residues of the parent compound, tembotrione, and the metabolites AE 1392936 (M2), AE 1417268 (M5), and AE 0456148 (M6) using LC/MS/MS Method No. AE/03/01. This method quantifies all analytes from a single sample using isotopically labeled internal standards.

Briefly, residues of tembotrione and its metabolites M2, M5, and M6 were extracted from crop matrices with ACN:water (1:1, v/v) using accelerated solvent extraction (Dionex Corporation, Sunnyvale, CA). Internal standards of the deuterated analytes were added to the extract. For parent, M5, and M6 analysis, an aliquot of the extract was concentrated via Turbo-Vap. For M2 analysis, an aliquot of the extract was loaded onto a strong-anion exchange (SAX) solid-phase extraction (SPE) cartridge and eluted with oxalic acid. The SPE eluate was concentrated. The concentrates were reconstituted in 0.1% formic acid and filtered through a nylon syringe filter. The total tembotrione residue was quantitated by high-performance LC/MS/MS. Concurrent recoveries were performed during sample analysis to demonstrate acceptable method performance.

The validated LOQ reported in the method is 0.010 ppm for each analyte in crops. The reported LODs for tembotrione, AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2) in turnip roots and yellow squash are 0.0027 ppm, 0.0025 ppm, 0.0031 ppm, and 0.0034 ppm, respectively. The reported LODs for tembotrione, AE 0456148 (M6), AE 1417268 (M5), and

AE 1392936 (M2) in mustard greens are 0.0014 ppm, 0.0021 ppm, 0.0023 ppm, and 0.0021 ppm, respectively.

C. RESULTS AND DISCUSSION

Based on the concurrent method recovery data (see Table C.1), LC/MS/MS Method AE/03/01 is adequate for the determination of residues of tembotrione, AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2) in turnip roots, mustard greens and yellow squash. All concurrent recoveries (71-120%) were acceptable. Apparent residues of tembotrione, AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2) were less than the LOQ (<0.01 ppm) in all control samples for turnip roots, mustard greens, and yellow squash. HED notes that apparent residues above the LOD were found ranging from 0.002-0.010 ppm for tembotrione and AE 0456148 (M6). The petitioner used these results to correct the residue levels in the fortified samples.

The results of the storage stability studies are presented in Table C.2. Based on the reported results, residues of the parent, tembotrione, and metabolites M6 and M2 appear to be relatively stable in/on turnip roots, mustard greens, and yellow squash for up to 350 days (11.5 months). Residues of metabolite M5 appear to be relatively stable in/on turnip roots, mustard greens, and yellow squash for up to 370 days (12.2 months).

TABLE C.1. Summary of Concurrent Recoveries of Tembotrione and Metabolites in Crop Matrices.

Matrix	Spike level (ppm)	Storage Interval (days)[1]	Sample size (n)	Recoveries (%)	Mean ± std dev[2]
Tembotrione (parent)					
Turnip Roots	0.400	0(1)	3	84, 90, 90	88±3.5
	0.200	91(1)	2	90, 91	91
	0.400	182(2)	2	97, 97	97
	0.400	350(6)	2	95, 113	104
Mustard Greens	0.200	0(1)	3	90, 90, 91	90±0.6
	0.200	91(1)	2	88, 100	94
	0.200	182(2)	2	97, 108	103
	0.200	350(6)	2	87, 95	91
Yellow Squash	0.400	0(1)	3	80, 81, 85	82±2.6
	0.200	91(1)	2	88, 91	90
	0.400	182(2)	2	95, 96	96
	0.400	350(6)	2	90, 92	91
AE 0456148 (M6)					
Turnip Roots	0.400	0(1)	3	81, 84, 85	83±2.1
	0.200	91(1)	2	79, 90	85
	0.400	182(2)	2	95, 103	99
	0.400	350(6)	2	100, 114	107
Mustard Greens	0.200	0(1)	3	83, 87, 89	86±3.1
	0.200	91(1)	2	81, 84	83
	0.200	182(2)	2	104, 105	105
	0.200	350(6)	2	112, 112	112

TABLE C.1. Summary of Concurrent Recoveries of Tembotrione and Metabolites in Crop Matrices.

Matrix	Spike level (ppm)	Storage Interval (days)[1]	Sample size (n)	Recoveries (%)	Mean ± std dev[2]
Yellow Squash	0.400	0(1)	3	71, 74, 81	75±5.1
	0.200	91(1)	2	83, 83	83
	0.400	182(2)	2	98, 98	98
	0.400	350(6)	2	98, 99	99
AE 1417268 (M5)					
Turnip Roots	0.400	0(1)	3	84, 84, 89	86±2.9
	0.200	91(1)	2	81, 104	93
	0.400	182(2)	2	116, 118	117
	0.400	370(1)	2	96, 104	100
Mustard Greens	0.200	0(1)	3	75, 78, 83	79±4.0
	0.200	91(1)	2	84, 87	86
	0.200	182(2)	2	117, 117	117
	0.200	370(1)	2	80, 94	87
Yellow Squash	0.400	0(1)	3	72, 74, 87	78±8.1
	0.200	91(1)	2	83, 87	85
	0.400	182(2)	2	115, 117	116
	0.400	370(1)	2	82, 117	100
AE 1392936 (M2)					
Turnip Roots	0.400	0(2)	3	93, 96, 96	95±1.7
	0.200	91(2)	2	99, 102	101
	0.400	182(3)	2	87, 107	97
	0.400	350(7)	2	95, 120	108
Mustard Greens	0.200	0(2)	3	97, 99, 99	98±1.2
	0.200	91(2)	2	87, 95	91
	0.200	182(3)	2	94, 100	97
	0.200	350(7)	2	91, 93	92
Yellow Squash	0.400	0(2)	3	89, 90, 91	90±1.0
	0.200	91(2)	2	83, 116	100
	0.400	182(3)	2	91, 104	98
	0.400	350(7)	2	97, 100	99

[1] The storage interval from fortification to extraction; the days from extraction to analysis are reported in parentheses.
[2] If sample size (n=2), then a standard deviation was not calculated, only the mean was reported.

The following graphs (Figures C.1 through C.4) were copied without alteration from the study profile prepared by the petitioner for MRID 46695602.

Figure C.1. Storage Stability of Tembotrione in Crop Matrices

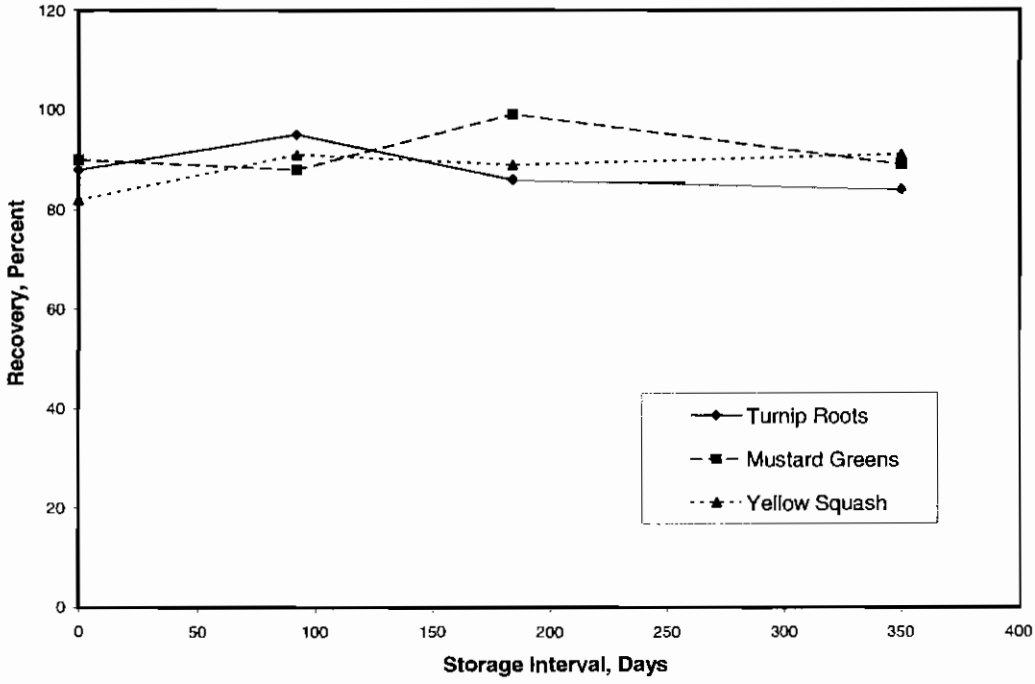


Figure C.2. Storage Stability of AE 0456148 (M6) in Crop Matrices

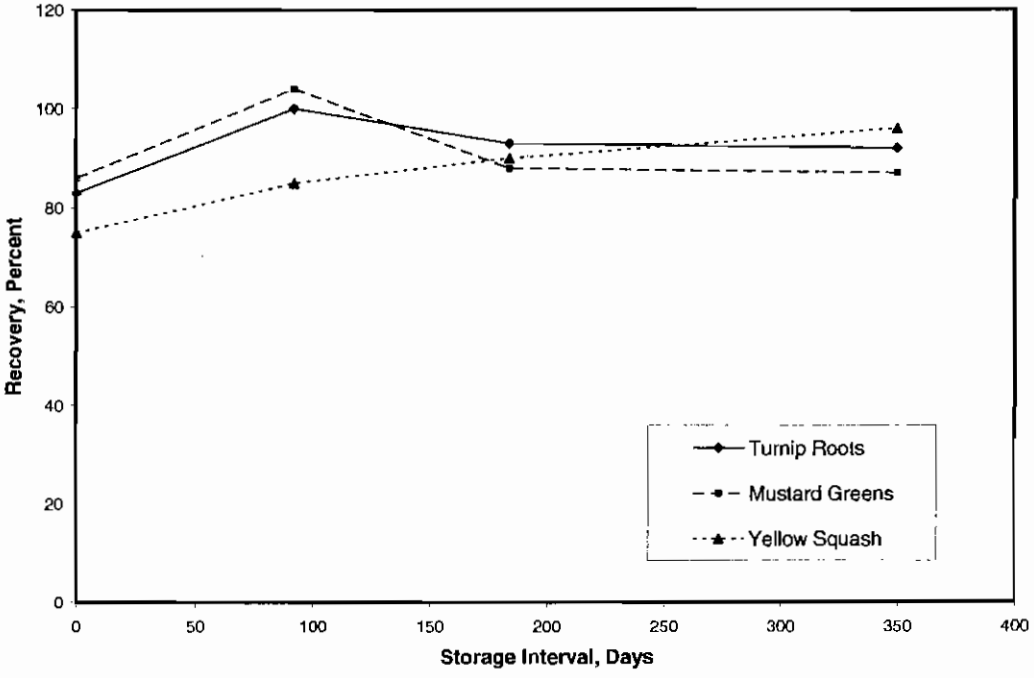


Figure C.3. Storage Stability of AE 1417268 (M5) in Crop Matrices

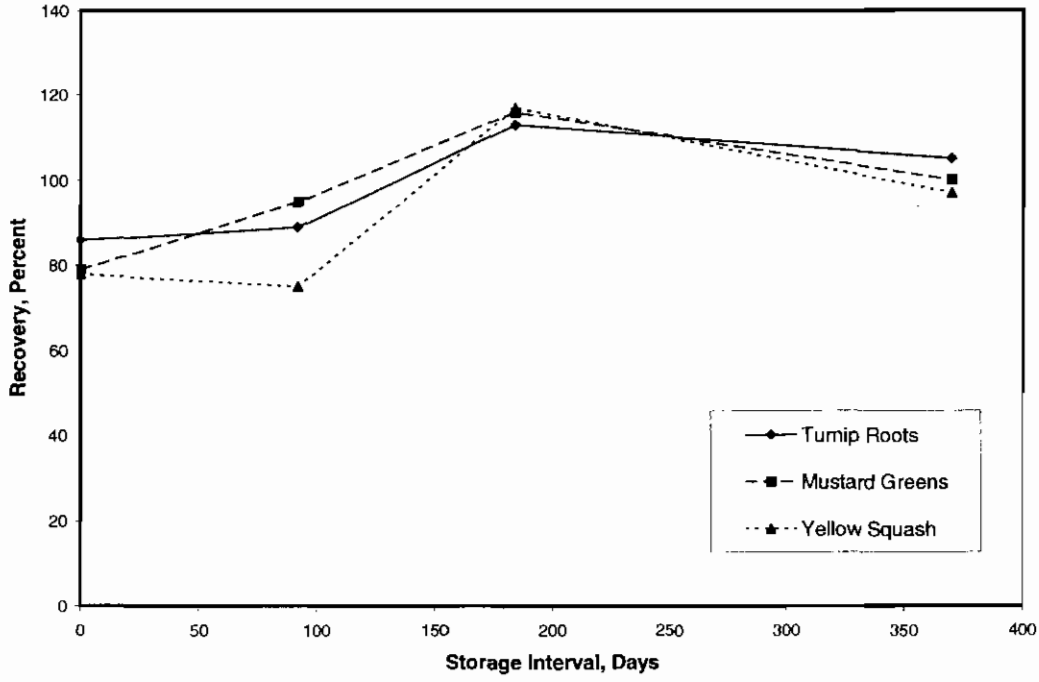


Figure C.4. Storage Stability of AE 1392936 (M2) in Crop Matrices

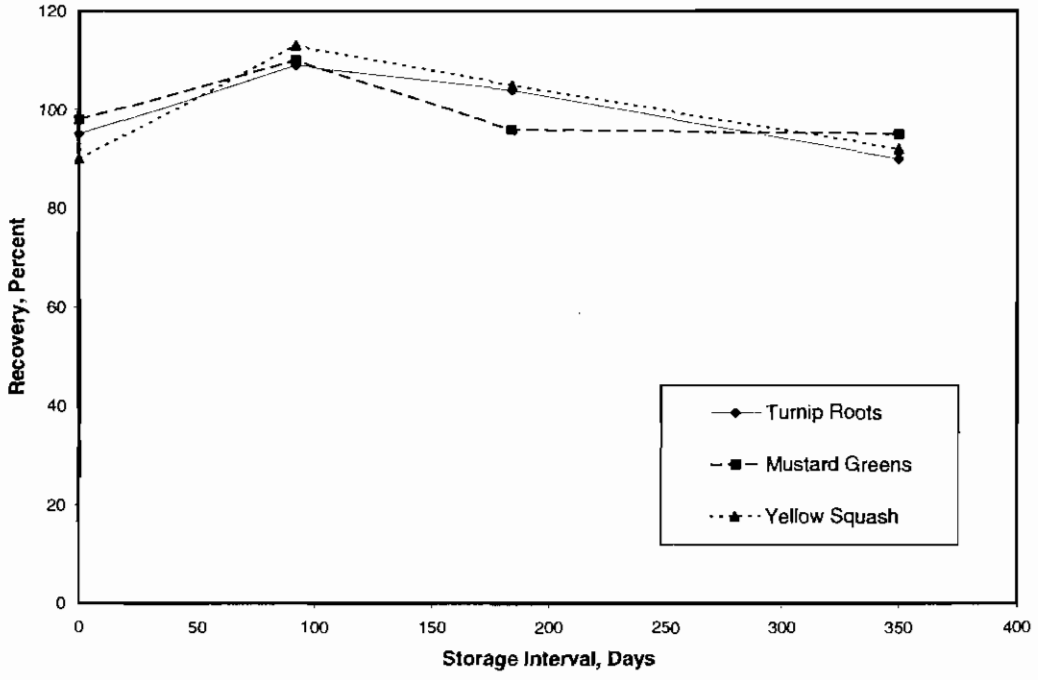


TABLE C.2. Stability of Tembotrione Residues in Selected Crop Matrices Following Storage at ≤10 °C.

Matrix	Spike level (ppm)	Storage Interval (days)[1]	Recovered residues (ppm)	Mean Recovered Residues (ppm)	Mean Recovery (%)	Corrected % recovery[3]
Tembotrione (parent)						
Turnip Roots	0.400	0(1)	0.335, 0.358, 0.359	0.351	88	---
	0.400	91(1)	0.032[2], 0.352	0.352	88	97
	0.400	182(2)	0.332, 0.333	0.333	83	86
	0.400	350(6)	0.332, 0.337	0.335	84	81
Mustard Greens	0.200	0(1)	0.180, 0.181, 0.183	0.181	91	---
	0.200	91(1)	0.033[2], 0.175	0.175	88	93
	0.200	182(2)	0.193, 0.201	0.197	99	96
	0.200	350(6)	0.161, 0.165	0.163	82	90
Yellow Squash	0.400	0(1)	0.319, 0.323, 0.338	0.327	82	---
	0.400	91(1)	0.065[2], 0.336,	0.336	84	93
	0.400	182(2)	0.338, 0.339	0.339	85	88
	0.400	350(6)	0.307, 0.346	0.327	82	90
AE 0456148 (M6)						
Turnip Roots	0.400	0(1)	0.322, 0.337, 0.342	0.334	83	---
	0.400	91(1)	0.119[2], 0.342	0.342	86	101
	0.400	182(2)	0.365, 0.369	0.367	92	93
	0.400	350(6)	0.369, 0.369	0.369	92	86
Mustard Greens	0.200	0(1)	0.165, 0.175, 0.179	0.173	87	---
	0.200	91(1)	0.059[2], 0.173	0.173	87	105
	0.200	182(2)	0.175, 0.176	0.176	88	84
	0.200	350(6)	0.169, 0.178	0.174	87	78
Yellow Squash	0.400	0(1)	0.285, 0.296, 0.325	0.302	76	---
	0.400	91(1)	0.043[2], 0.285,	0.285	71	86
	0.400	182(2)	0.350, 0.352	0.351	88	90
	0.400	350(6)	0.369, 0.391	0.380	95	96
AE 1417268 (M5)						
Turnip Roots	0.400	0(1)	0.335, 0.337, 0.356	0.343	86	---
	0.400	91(1)	0.071[2], 0.329	0.329	82	88
	0.400	182(2)	0.447, 0.453	0.450	113	96
	0.400	370(1)	0.417, 0.423	0.420	105	105
Mustard Greens	0.200	0(1)	0.151, 0.156, 0.165	0.157	79	---
	0.200	91(1)	0.055[2], 0.161	0.161	81	94
	0.200	182(2)	0.231, 0.233	0.232	116	99
	0.200	370(1)	0.164, 0.184	0.174	87	100
Yellow Squash	0.400	0(1)	0.289, 0.296, 0.350	0.312	78	---
	0.400	91(1)	0.039[2], 0.255	0.255	64	75
	0.400	182(2)	0.452, 0.480	0.466	117	100
	0.400	370(1)	0.385, 0.391	0.388	97	97

TABLE C.2. Stability of Tembotrione Residues in Selected Crop Matrices Following Storage at ≤10 °C.

Matrix	Spike level (ppm)	Storage Interval (days)[1]	Recovered residues (ppm)	Mean Recovered Residues (ppm)	Mean Recovery (%)	Correeted % recovery[3]
AE 1392936 (M2)						
Turnip Roots	0.400	0(2)	0.373, 0.384, 0.386	0.381	95	---
	0.400	91(2)	0.220[2], 0.436	0.436	109	108
	0.400	182(3)	0.369, 0.435	0.402	101	104
	0.400	350(7)	0.361, 0.362	0.362	90	84
Mustard Greens	0.200	0(2)	0.194, 0.198, 0.199	0.197	99	---
	0.200	91(2)	0.084[2], 0.200	0.200	71	110
	0.200	182(3)	0.165, 0.206	0.186	93	97
	0.200	350(7)	0.169, 0.183	0.176	88	96
Yellow Squash	0.400	0(2)	0.356, 0.361, 0.362	0.360	90	---
	0.400	91(2)	0.046[2], 0.451	0.451	113	113
	0.400	182(3)	0.371, 0.444	0.408	102	104
	0.400	350(7)	0.348, 0.376	0.362	91	91

[1] The storage interval from fortification to extraction; the days from extraction to analysis are reported in parentheses.
[2] These data were considered anomalous due to the recovery of this analyte at a later interval. This data point was not entered into the averages or Figures C.1, C.2, C.3 or C.4.
[3] Corrected for control interferences and mean concurrent recovery (see TABLE C.1).

D. CONCLUSION

The submitted storage stability results adequately demonstrate the stability of the parent, tembotrione and metabolites AE 0456148 (M6) and AE 1392936 (M2) residues in/on turnip roots, mustard greens, and yellow squash stored frozen for up to 350 days (11.5 months). Residues of metabolite AE 1417268 (M5) appear to be relatively stable in/on turnip roots, mustard greens, and yellow squash stored frozen for up to 370 days (~12 months). An acceptable method was used for the quantitation of residues in turnip roots, mustard greens, and yellow squash.

E. REFERENCES

None.

F. DOCUMENT TRACKING

RDI: RAB1 Chemists (1/10/07)
Petition Number: PP#5F7009
DP#s: 325349, 325663, and 331222
PC Code: 012801

below the LOQ (<0.01 ppm), 0.013 ppm, and 0.058 ppm in samples from the 0.2-, 0.6-, and 2.0-ppm dose groups, respectively. Residues of tembotrione were found in significant amounts in the liver, where maximum residues were 0.504 ppm, 0.618 ppm, and 0.702 ppm in samples from the 0.2-, 0.6-, and 2.0-ppm dose groups, respectively. There was a definite residue-level dose dependence in fat, muscle and skin, and that average residues of tembotrione in liver showed evidence of a slight residue-level dose dependence.

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the data depicting residues in livestock are classified as scientifically acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document [DP# 325349].

COMPLIANCE:

Signed and dated Good Laboratory Practice (GLP), Quality Assurance and Data Confidentiality statements were provided. No GLP deviations were reported which would impact the study results or their interpretation.

A. BACKGROUND INFORMATION

Tembotrione, a new herbicide with broad use against mono- and dicotyledons in selected crops such as corn, is a 4-hydroxyphenylpyruvate deoxygenase (HPPD) inhibitor (bleacher). The test compound nomenclature and physiochemical properties of the test compound are presented in Tables A.1 and A.2, respectively.

TABLE A.1. Test Compound Nomenclature for Tembotrione.

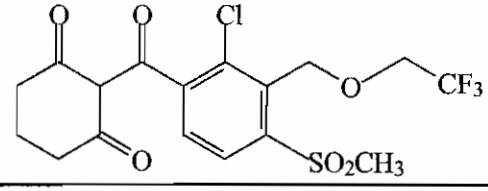
Compound: Tembotrione	Chemical Structure 
Proposed common name	Tembotrione
Company experimental name	AE 0172747
IUPAC name	2-{2-chloro-4-mesyl-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl}cyclohexane-1,3-dione
CAS name	2-[2-chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione
CAS #	335104-84-2
End-use product/EP	AE 0172747 Herbicide, EPA Reg No. 264-xxx

TABLE A.2. Physicochemical Properties of Technical Grade Tembotrione.

Parameter	Value	Reference (MRID#)
Melting point	117 °C	46695402
pH @ 24 °C	3.63	
Density (g/mL @ 20 °C)	1.56	
Water solubility (mg/L @ 20 °C)	0.22 at pH4 28.3 at pH 7 29.7 at pH 9	
Solvent solubility (g/L at 20 °C) DMSO Methylene Chloride Aeetone Ethyl Acetate Toluene Hexane Ethanol	 >600 >600 300-600 180.2 75.7 47.6 8.2	
Vapor pressure (Torr, 20 °C)	8.25×10^{-11}	
Dissociation constant (pK_a)	3.2	
Octanol/water partition coefficient (P_{ow} @ 23 °C) (P_{ow} @ 24 °C) (P_{ow} @ 23 °C)	 0.0430 at pH 9.0 0.0807 at pH 7.0 144.9 at pH 2.0	
UV/visible absorption spectrum (nm)	Primary: 205 Secondary: 284 Tertiary: 240	

B. EXPERIMENTAL DESIGN

The in-life phase of the feeding study was conducted at Genesis Midwest Laboratories (GML; Neillsville, WI). Forty laying hens were divided into three treatment groups of 12 hens consisting of three subgroups of four hens each. The three treatment groups were dosed orally with gelatin capsules containing tembotrione at average levels of 0.2, 0.6, or 2.0 ppm in the feed for 29 consecutive days. Tembotrione was weighed directly into the gelatin capsules, and the capsules were administered once per day after the morning egg collection.

Eggs were collected twice daily; the afternoon and following morning samples were composited for each subgroup. The hens were sacrificed within 3-5 hours of the final dose on Day 29. Following the termination, each animal was examined macroscopically, and representative samples of the following tissues were collected: liver (entire), skin (thigh and breast), fat (abdominal and subcutaneous), and muscle (thigh and breast). Descriptions of the test animals used and the dietary regime are presented in Tables B.1.1 and B.1.2; the dosing regime and sample collection procedures are summarized in Tables B.1.3 and B.1.4.

B.1. Livestock

TABLE B.1.1. Description of Livestock Used in the Feeding Study.

Species	Breed	Age	Weight at study initiation (kg)	Health status	Description of housing/holding area
Laying Hens (*Gallus domesticus*)	White Leghorn	~22 weeks	1.5-1.6	All animals were clinically healthy egg layers at start of study. During the study, one animal in the 2.0-ppm dose group died of a prolapsed cloaca. No other health problems or clinical abnormalities were noted.	Housed in pens by subgroup; four birds/pen. Pens maintained at 66-68 °F and RH = ~57%

TABLE B.1.2. Test Animal Dietary Regime.

Composition of Diet	Feed consumption (average, g/bird/day)	Water	Acclimation period	Predosing
Poultry ration (Vita Plus)[1]	0.2-ppm dose group: 123.2 0.6-ppm dose group: 125.7 2.0-ppm dose group: 123.8	*Ad libitum*	56 days (8 weeks)	None

[1] Crude protein (min. 16%), lysine (min. 0.9%), methionine (min. 0.27%), crude fat (min. 2.6%), crude fiber (max. 4%), calcium (3.7% - 4.7%), phosphorus (min. 16%), and salt (0.2% - 0.4%).

TABLE B.1.3. *Dosing Regime.*

Treatment group	Treatment Type	Level administered (mg/day) [1]	Residue intake in diet (ppm)	Vehicle	Timing/ Duration (days)
0.2 ppm	Oral	0.025 – 0.028	0.20 – 0.23	Gelatin capsule	29
0.6 ppm		0.073 – 0.082	0.63 – 0.67		
2.0 ppm		0.242 – 0.252	1.93 – 2.21		

[1] Based on actual feed consumption by the group during the previous week.

TABLE B.1.4. Sample Collection.

Eggs collected	Number of eggs produced during normal production[1]	Urine, feces and cage wash collected	Interval from last dose to sacrifice	Tissues harvested and analyzed
Eggs collected twice daily; the afternoon and following morning samples were composited by subgroup for samples collected on days 0, 1, 3, 7, 10, 14, 17, 21, 24, 26, and 28	3-4 per day per subgroup	Not collected	3-5 hours	Liver (entire), skin (thigh and breast), fat (abdominal and subcutaneous), and muscle (thigh and breast)

[1] Egg production range for all hen subgroups throughout the study. Egg production in all animals was consistent throughout the course of the study.

B.2. Sampling Handling and Preparation

Eggs were collected from each subgroup twice daily (afternoon and morning). Afternoon samples for each study time point were refrigerated overnight and combined with the following morning samples. Egg production in all animals was consistent throughout the course of the study. On study days 0, 1, 3, 7, 10, 14, 17, 21, 24, 26, and 28, the whites and yolks were combined and weighed. The yolks were broken with a knife, and the eggs were thoroughly mixed by vigorous shaking then sub-divided into approximately equal aliquots. The aliquots

were frozen (~-20 °C) and were shipped weekly on dry ice via overnight express to Bayer CropScience (Stillwell, KS) for analysis. The egg samples remained in frozen storage (<-15 °C) at all times except during analysis.

After sample collection and weighing, tissue samples from each subgroup were composited and placed into labeled plastic storage bags, then immediately transferred to a freezer (~-20 °C). The frozen samples were subsequently pulverized in the presence of dry ice using a commercial food processor. Tissue samples were shipped within one week of collection on dry ice to Bayer CropScience (Stillwell, KS), where samples were placed in frozen storage (<-15 °C) at all times except during analysis.

B.3. Analytical Methodology

Samples of eggs (combined yolks and whites; 2.0-ppm dose group only) and tissues were analyzed for residues of tembotrione using the proposed LC/MS/MS enforcement method, Method AE-004-A04-01 (refer to 46695539.der.doc for a complete description of the method). A brief summary of the method, which uses an isotopically labeled internal standard of deuterated tembotrione for quantification of the analyte, was included in the submission.

Briefly, samples were extracted with acetonitrile:water (1:1, v:v) using accelerated solvent extraction. The internal standard was added, and the sample was filtered, concentrated, and reconstituted in dilute formic acid prior to quantitation by LC/MS/MS. The validated LOQ, determined as the lowest level of method validation (LLMV) for tembotrione was 0.01 ppm for eggs and tissues. The estimated LODs were 0.0018 ppm for eggs; 0.0031 ppm for skin and fat; 0.0026 ppm for muscle; and 0.0025 ppm for liver. The LODs were determined by multiplying the standard deviation of recovery measurements at the LOQ by $t_{0.99}$ (where $t_{0.99}$ is the one-tailed t-statistic at the 99% confidence level for n-1 replicates) and adding average residue found in the untreated control samples.

The results of method validation conducted prior to sample analysis and concurrent method validation were included in the submission.

C. RESULTS AND DISCUSSION

Sample storage conditions and intervals are summarized in Table C.2. The petitioner submitted extraction and analysis dates indicating that egg samples were stored frozen for up to 23 days, and tissue samples were stored frozen for up to 14 days prior to analysis. No storage stability data are required because all samples from the poultry feeding study were stored frozen from collection to analysis and were analyzed within 23 days of collection.

Method validation and concurrent recovery data are presented in Table C.1. The LC/MS/MS method, AE-004-A04-01, was adequate for data collection based on acceptable concurrent recovery and method validation data. Recoveries were within the acceptable range of 70-120% for all matrices at all fortifications, and the fortification levels encompassed the residues found in poultry tissues. Apparent residues of tembotrione were below the LOD in all samples of

untreated egg, fat, skin and muscle (11 samples of eggs, 1 sample each of fat and skin, and two samples of muscle) except the Day-0 egg sample, which bore apparent residues of 0.64 ppm (average of duplicate analyses). The petitioner concluded that the 0-day egg sample was contaminated *in vitro* because residues occurred prior to the dosing of any hen with test substance, no other subgroup exhibited similar contamination at any timepoint, and the control subgroup did not have apparent tembotrione residue at any other timepoint. The untreated liver sample bore apparent residues of 0.040 ppm (average of replicate analyses). Adequate sample calculations and chromatograms were provided.

The results of the feeding study are reported in Table C.3, and a summary of the residues of tembotrione in eggs and poultry tissues is presented in Table C.4. Residues of tembotrione in eggs were below the LOQ (<0.01 ppm) in all samples from the 2.0-ppm dose group. In fat and muscle, residues of tembotrione were below the LOQ (<0.01 ppm) in all samples from the 0.2- and 0.6-ppm dose groups; maximum residues were 0.034 ppm in fat and 0.020 ppm in muscle from the 2.0-ppm dose group. In skin, residues of tembotrione were below the LOQ (<0.01 ppm), 0.013 ppm, and 0.058 ppm in samples from the 0.2-, 0.6-, and 2.0-ppm dose groups, respectively. Residues of tembotrione were found in significant amounts in the liver, where maximum residues were 0.504 ppm, 0.618 ppm, and 0.702 ppm in samples from the 0.2-, 0.6-, and 2.0-ppm dose groups, respectively.

The petitioner noted that there was a definite residue-level dose dependence in fat, muscle and skin, and that average residues of tembotrione in liver showed evidence of a slight residue-level dose dependence, although the correlation coefficient was not high. Graphical presentations of feeding level versus residues found are presented in Figures C.2.1 (fat), C.2.2 (muscle), C.2.3 (skin), and C.2.4 (liver).

TABLE C.1. Summary of Concurrent and Method Validation Recoveries of Tembotrione from Poultry Eggs and Tissues.

Matrix	Analyte	Spike level (ppm)	Sample size (n)	Recoveries (%)	Mean ± std dev[1]
Concurrent Recoveries					
Egg	Tembotrione	0.010	10	106, 106, 106, 107, 108, 109, 110, 110, 111, 117	109 ± 3
Skin		0.010	1	118	118
		0.500	1	92	92
Fat		0.010	1	95	95
		0.500	1	98	98
Muscle		0.010	1	75	75
		0.500	1	77	77
Liver		0.010	1	90	90
		4.00	1	97	97
Method Validation Recoveries					
Eggs	Tembotrione	0.010	7	79, 81, 85, 87, 92, 93, 93	87 ± 6
		0.050	3	85, 85, 97	89 ± 7
		0.200	2	71, 82	77
Skin		0.010	7	77, 77, 84, 87, 96, 98, 102	89 ± 10
		0.050	3	78, 89, 94	87 ± 8
		0.200	2	80, 85	83

TABLE C.1. Summary of Concurrent and Method Validation Recoveries of Tembotrione from Poultry Eggs and Tissues.

Matrix	Analyte	Spike level (ppm)	Sample size (n)	Recoveries (%)	Mean ± std dev[1]
Muscle		0.010	7	74, 77, 77, 82, 84, 87, 98	83 ± 8
		0.050	3	93, 93, 93	93 ± 0
		0.200	2	85, 86	86
Liver		0.010	7	79, 87, 88, 89, 90, 92, 106	90 ± 8
		0.050	3	87, 91, 91	90 ± 2
		0.200	2	88, 98	93

[1] The standard deviation is not applicable for a sample size (n) of less than three.

TABLE C.2. Summary of Storage Conditions.

Matrix (RAC)	Storage Temperature (°C)	Actual Storage Duration[1]	Interval of Demonstrated Storage Stability
Egg	<-15	7-23 days	None submitted or required
Skin	<-15	9 days	
Fat	<-15	14 days	
Liver	<-15	10 days	
Muscle	<-15	10-13 days	

[1] Interval from collection to analysis. All samples were analyzed within 0-3 days of extraction.

TABLE C.3. Residue Data from Poultry Feeding Study with Tembotrione.

Collection time	Feeding Level (ppm)	Residues of Tembotrione (ppm)[1]		
Eggs		**REP08[2]**	**REP09**	**REP10**
Day 0	3.2	<LOD[3]	<LOD[3]	<LOD[3]
Day 1		<LOD	<LOD	<LOD
Day 3		<LOD	<LOD	<LOD
Day 7		(0.00912)	(0.00921)	(0.00688)
Day 10		(0.00474)	(0.00763)	(0.00205)
Day 14		<LOD	(0.00284)	(0.00537)
Day 17[4]		<LOD	<LOD	<LOD
Day 21		<LOD	<LOD	<LOD
Day 24		<LOD	<LOD	<LOD
Day 26		<LOD	<LOD	<LOD
Day 28		(0.00412)	(0.00431)	(0.00849)
Skin				
Day 29	0.2	**REP02**	**REP03**	**REP04**
		(0.00652)	(0.00504)	(0.00740)
	0.6	**REP05**	**REP06**	**REP07**
		0.0129	(0.00945)	0.0111
	2.0	**REP08**	**REP09**	**REP10**
		0.0396	0.0517	0.0581

TABLE C.3. Residue Data from Poultry Feeding Study with Tembotrione.

Collection time	Feeding Level (ppm)	Residues of Tembotrione (ppm)[1]		
Fat				
Day 29	0.2	**REP02**	**REP03**	**REP04**
		(0.00359)	(0.00308)	(0.00378)
	0.6	**REP05**	**REP06**	**REP07**
		(0.00314)	<LOD	<LOD
	2.0	**REP08**	**REP09**	**REP10**
		0.0234	0.0185	0.0335
Liver				
Day 29	0.2	**REP02**	**REP03**	**REP04**
		0.326	0.421	0.504
	0.6	**REP05**	**REP06**	**REP07**
		0.568	0.618	0.583
	2.0	**REP08**	**REP09**	**REP10**
		0.702	0.584	0.666
Muscle				
	0.2	**REP02**	**REP03**	**REP04**
		<LOD	<LOD	<LOD
	0.6	**REP05**	**REP06**	**REP07**
		<LOD	<LOD	<LOD
	2.0	**REP08**	**REP09**	**REP10**
		0.0184	0.0162	0.0196

[1] LOQ = 0.01 ppm for eggs and tissues; the estimated LODs were 0.0018 ppm for eggs; 0.0031 ppm for skin and fat; 0.0026 ppm for muscle; and 0.0025 ppm for liver. Values >LOD and <LOQ are reported in parentheses.
[2] Subgroup identification numbers = REPXX.
[3] Replicate analyses of a single sample; maximum residues are reported.
[4] Data reflect re-analysis of samples due to problems with internal standard in first run.

Table C.4. Summary of Residue Data from Poultry Feeding Study with Tembotrioue.

Matrix	Feeding Level (ppm)	Residue Levels (ppm)[1]					
		n	Min	Max	Median	Mean	Std. Dev.
Eggs Days 0, 1, 3, 7, 10, 14, 17, 21, 24, 26, and 28	2.0	33	<0.010	<0.010	<0.005	<0.005	N/A
Skin Day 29	0.2	3	<0.010	<0.010	<0.005	<0.005	N/A
	0.6	3	<0.010	0.013	0.011	0.010	0.004
	2.0	3	0.040	0.058	0.052	0.050	0.009
Fat Day 29	0.2	3	<0.010	<0.010	<0.005	<0.005	N/A
	0.6	3	<0.010	<0.010	<0.005	<0.005	N/A
	2.0	3	0.019	0.034	0.023	0.025	0.008
Liver Day 29	0.2	3	0.326	0.504	0.421	0.417	0.089
	0.6	3	0.568	0.618	0.583	0.590	0.026
	2.0	3	0.584	0.702	0.666	0.651	0.060
Muscle Day 29	0.2	3	<0.010	<0.010	<0.005	<0.005	N/A
	0.6	3	<0.010	<0.010	<0.005	<0.005	N/A
	2.0	3	0.016	0.020	0.018	0.018	0.002

[1] For calculation of the minimum and maximum, the LOQ (0.01 ppm) was used for residues reported as <LOD in Table C.3. In the calculation of the median, mean, and standard deviation, 0.005 ppm (half the LOQ) was used for residues reported as <LOD or <LOQ.

FIGURE C.2.1. Linear Regression of Residues on Feeding Level in Fat

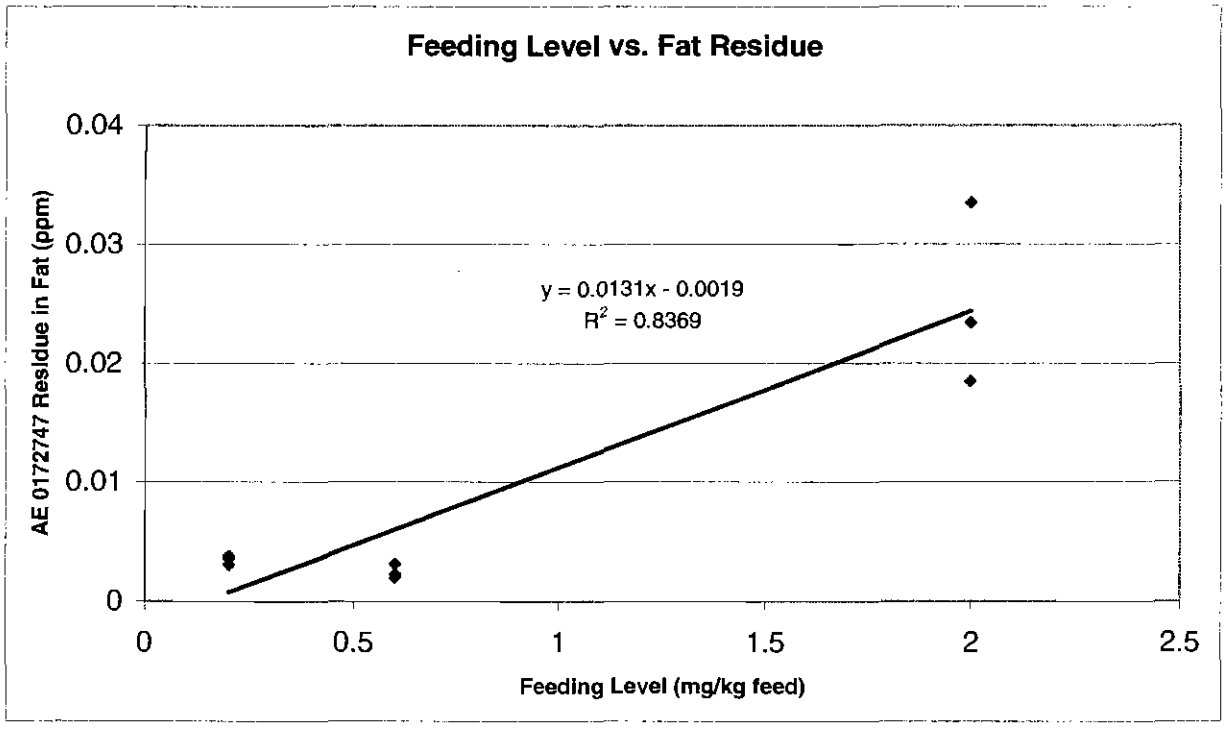


FIGURE C.2.2. Linear Regression of Residues on Feeding Level in Muscle

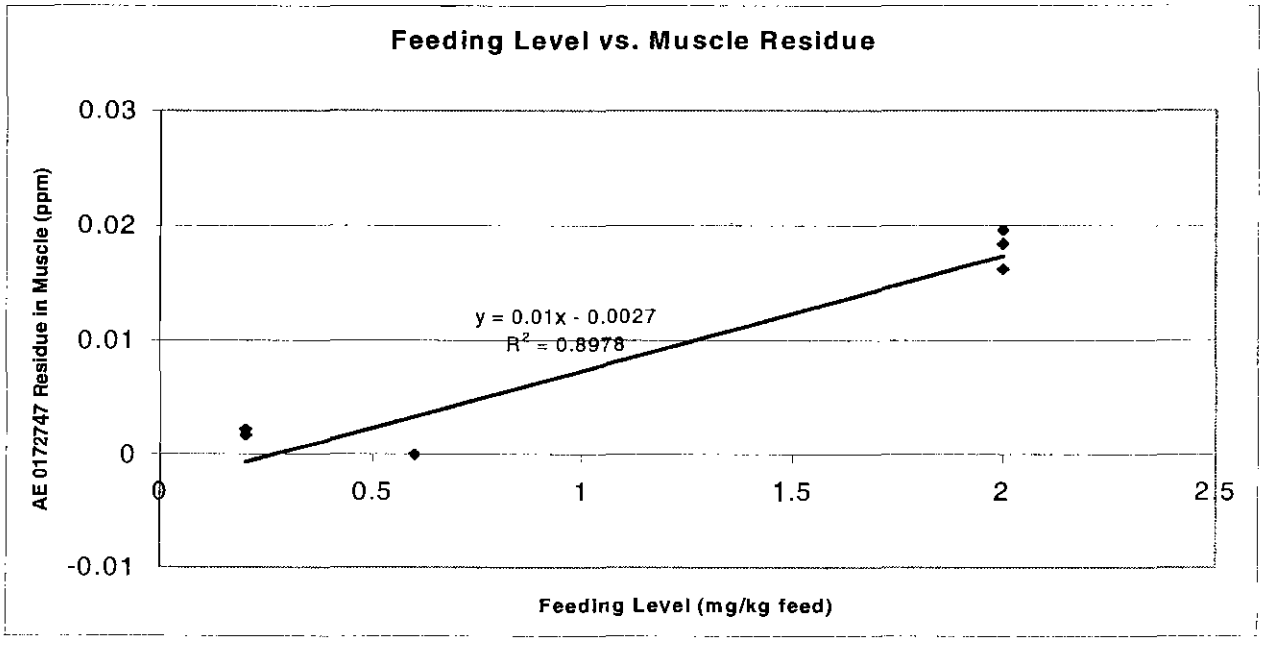


FIGURE C.2.3. Linear Regression of Residues on Feeding Level in Skin

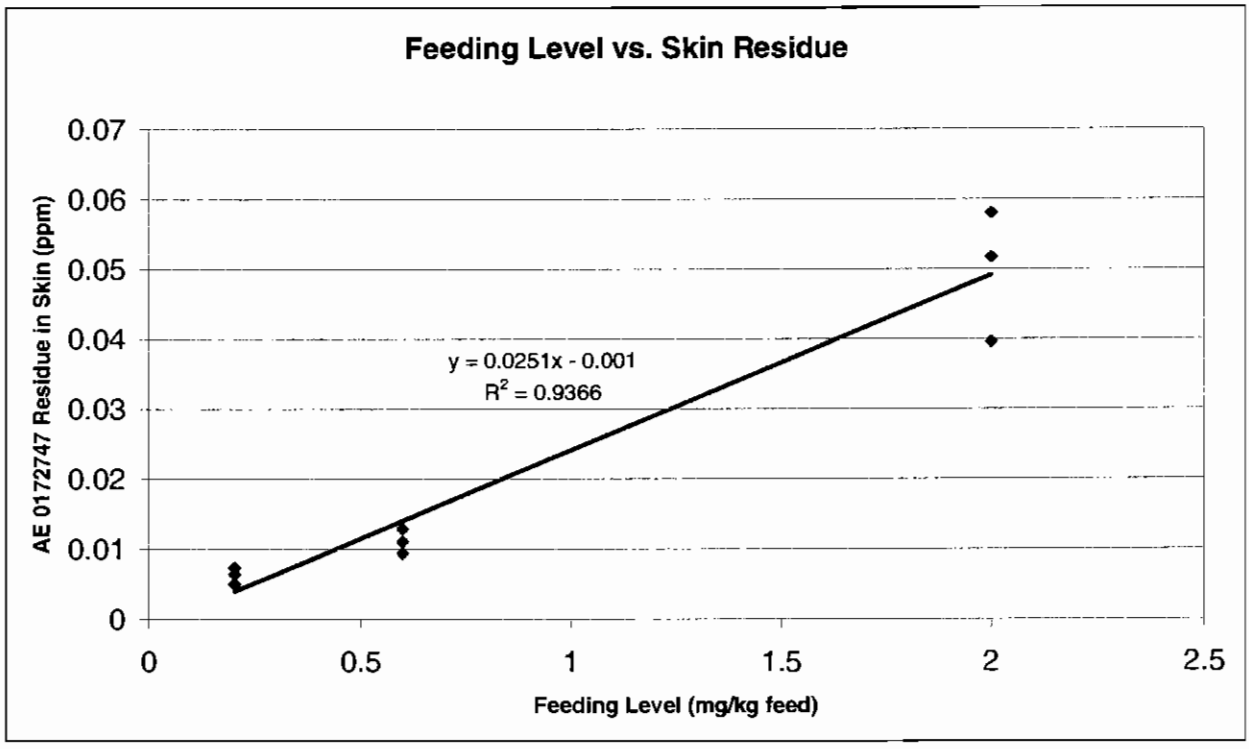
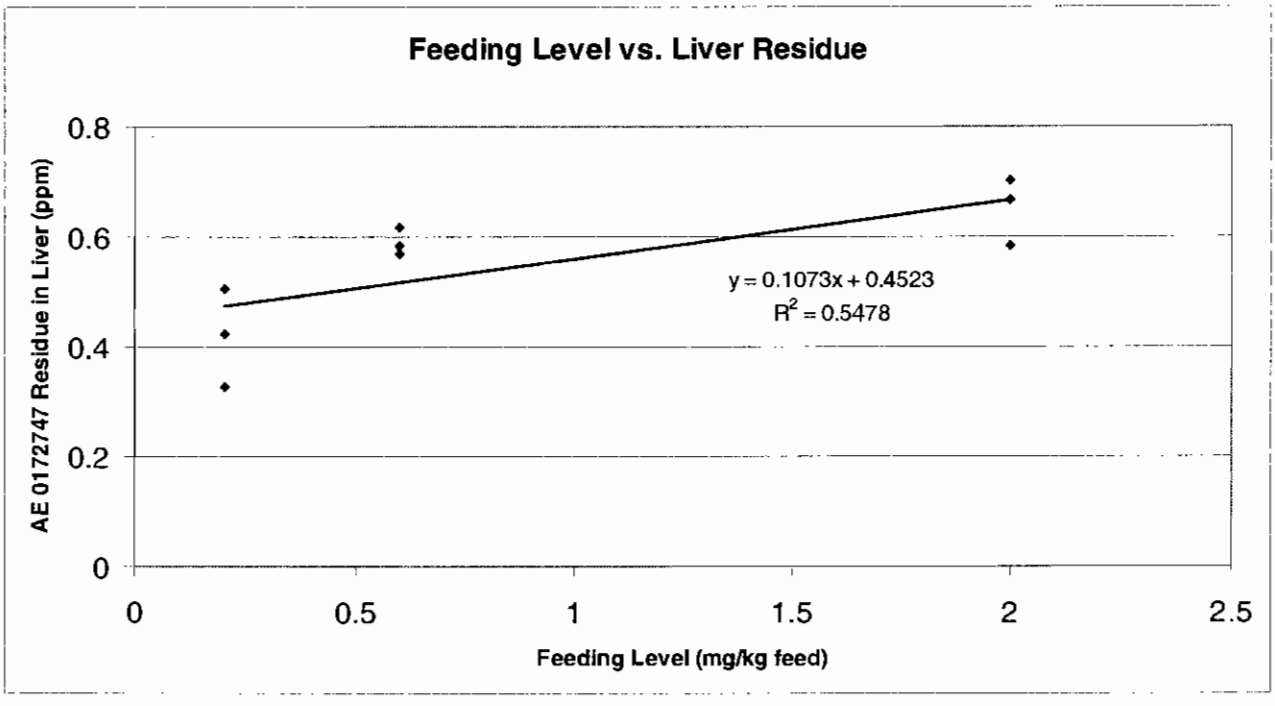


FIGURE C.2.4. Linear Regression of Residues on Feeding Level in Liver



D. CONCLUSION

The submitted poultry feeding study is adequate to demonstrate the magnitude of residues of tembotrione in poultry commodities. The feeding study reflects dietary levels of tembotrione at 0.2, 0.6, and 2.0 ppm. Residues of tembotrione in eggs were below the LOQ (<0.01 ppm) in all samples from the 2.0-ppm dose group. In fat and muscle, residues of tembotrione were below the LOQ (<0.01 ppm) in all samples from the 0.2- and 0.6-ppm dose groups; maximum residues were 0.034 ppm in fat and 0.020 ppm in muscle from the 2.0-ppm dose group. In skin, residues of tembotrione were below the LOQ (<0.01 ppm), 0.013 ppm, and 0.058 ppm in samples from the 0.2-, 0.6-, and 2.0-ppm dose groups, respectively. Residues of tembotrione were found in significant amounts in the liver, where maximum residues were 0.504-0.702 ppm. There was a definite residue-level dose dependence in fat, muscle and skin, and that average residues of tembotrione in liver showed evidence of a slight residue-level dose dependence. Residues were determined using an acceptable method, and no storage stability data are required to support the study.

E. REFERENCES

46695539.der.doc

F. DOCUMENT TRACKING

RDI: RAB1 Chemists (1/10/07)
Petition Number: PP#5F7009
DP#s: 325349, 325663, and 331222
PC Code: 012801

Template Version June 2005

Tembotrione/AE 0172747/PC Code 012801/Bayer CropScience/264
DACO 7.5.1/OPPTS 860.1480/OECD IIA 6.4.1, 6.4.2 and IIIA 8.2, 8.4.1, 8.4.2
Livestock Feeding Study – Metabolite AE 1417268 (M5) in Dairy Cows

Primary Evaluator	George F. Kramer, Ph.D., Senior Chemist Registration Action Branch (RAB1) Health Effects Division (HED) (7509P)	Date: 18-JUL-2007
Approved by	P.V. Shah, Ph.D., Branch Senior Scientist RAB1/HED (7509P)	Date: 18-JUL-2007

This DER was originally prepared under contract by Dynamac Corporation (2275 Research Boulevard, Suite 300; Rockville, MD 20850; submitted 11/30/2006). The DER has been reviewed by HED and revised to reflect current Office of Pesticide Programs (OPP) policies.

STUDY REPORT:

46695606 Dias, N. (2005) M5: Residues in Milk and Tissues of Dairy Cows. Project Number: M/256700/01/1, BAG/395/052591. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 145 p.

The petitioner has submitted an evaluation template for the study (Bayer CropScience DER to Study BAG-05259I), which was used to generate this DER; selected sections were copied without alteration or were modified to more specifically reflect the Agency's data evaluation requirements.

EXECUTIVE SUMMARY:

Bayer CropScience has submitted a cattle feeding study with metabolite AE 1417268 (M5), a plant metabolite of tembotrione. Metabolite M5 was not found in metabolism studies conducted with tembotrione in cows. Four treatment groups of three dairy cows each were dosed orally with M5 in the feed at target dose rates approximating 0.05, 0.5, 1.5, and 5.0 ppm (dry feed weight) for 28-31 consecutive days; three additional cows were dosed at 5.0 ppm for a depuration study.

Cows were milked twice daily, and samples were composited daily for each cow. Cows were sacrificed within 16-24 hours of the final dose, on Days 30-32; the cows for the depuration study were sacrificed 7, 14, and 28 days after the final dose. Samples of liver (whole organ as two subsamples), kidney (both whole organs as two subsamples), fat (two subsample composites of available omental, perirenal, and subcutaneous), and skeletal muscle (two subsample composites of pectoralis and adductor muscle of thigh) were collected from each cow. Samples of milk collected on Days 4, 7, 10, 14, 18, 21, 25, and 28 from all dose levels were retained for analysis; additional samples from Days 1, 12 and 23 from the 5.0-ppm dose group and from Days 31, 35, 38, 42, 45, 49, 52, and 56 from the depuration study were also retained. Samples of cream (milk fat) and skim milk were collected on Days 14 and 28 (all dose levels).

Milk and tissue samples were analyzed for residues of M5 using a liquid chromatography/mass spectroscopy (LC/MS)/MS method that is essentially the same as the proposed LC/MS/MS enforcement method. The validated limits of quantitation (LOQs) for M5 were 0.002 ppm for milk, skim milk, and cream, and 0.01 ppm for fat, kidney, liver, and muscle, and the estimated limits of detection (LODs) were 0.001 ppm for milk, skim milk, and cream, and 0.002 ppm for

tissues. The method is adequate for data collection based on acceptable concurrent recovery data. No storage stability data are required because all milk and tissue samples were stored frozen from collection to analysis and were analyzed within ~30 days of collection.

Residues of M5 were nondetectable (<0.001 ppm) in all samples of milk, skim milk, and cream from all dose groups, except for one sample each of Day 4 milk from the 0.05- and 5.0-ppm dose levels, in which residues were <LOQ (<0.002 ppm). In fat and muscle, residues of M5 were below the LOD (<0.002 ppm) in all samples from all dose groups, with the exception of one sample each of fat and muscle from the 5.0-ppm dose group in which residues were <LOQ (<0.01 ppm). In kidney, maximum residues of M5 were <LOQ, 0.017 ppm, 0.049 ppm, and 0.165 ppm in samples from the 0.05-, 0.50-, 1.5-, and 5.0-ppm dose groups, respectively. No residues of M5 above the LOQ were detected in treated kidney samples collected 7, 14 and 28 days after withdrawal of M5. In liver, maximum residues of M5 were <LOQ, 0.036 ppm, 0.163 ppm, and 0.386 ppm in samples from the 0.05-, 0.50-, 1.5-, and 5.0-ppm dose groups, respectively. Residues of M5 in liver declined rapidly over the withdrawal period, to 0.037 ppm, 0.015 ppm, and <LOD, respectively, 7, 14, and 28 days following cessation of dosing. A linear residue-level dose dependence was observed in kidney and liver.

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the data depicting residues in livestock are classified as scientifically acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document [DP# 325349].

COMPLIANCE:

Signed and dated Good Laboratory Practice (GLP), Quality Assurance and Data Confidentiality statements were provided. No GLP deviations were reported which would impact the study results or their interpretation.

A. BACKGROUND INFORMATION

AE 1417268 (M-5) is a plant metabolite of the herbicide tembotrione, a new herbicide with broad use against mono- and dicotyledons in selected crops such as corn. AE 1417268 was not found as a metabolite in cows dosed with tembotrione. The purpose of this study was to quantify the residues found in tissues and milk of dairy cows following administration of metabolite M5.

The nomenclature of tembotrione and M5 is presented in Table A.1, and the physiochemical properties of tembotrione are presented in Table A.2.

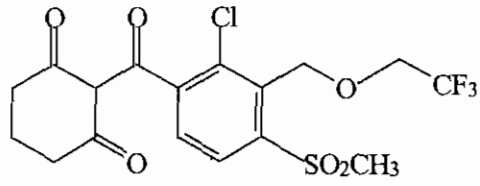
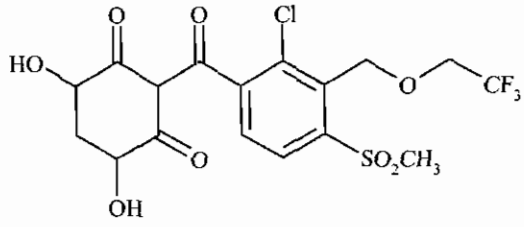
TABLE A.1. Test Compound Nomenclature for Tembotrione.	
Compound: Tembotrione	Chemical Structure 
Proposed common name	Tembotrione
Company experimental name	AE 0172747
IUPAC name	2-{2-Chloro-4-mesyl-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl}cyclohexane-1,3-dione
CAS name	2-[2-Chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione
CAS #	335104-84-2
End-use product/EP	AE 0172747 Herbicide, EPA Reg No. 264-xxx
AE 1417268 (M5)	Chemical Structure 
Common name	None assigned.
Company experimental name	AE 1417268 (M5)
IUPAC name	2-{2-Chloro-4-mesyl-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl}-4,6-dihydroxy-cyclohexane-1,3-dione
CAS name	2-[2-chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione
CAS #	None assigned.
End-use product/EP	Not applicable.

TABLE A.2. Physicochemical Properties of Technical Grade		
Parameter	Value	Reference
Tembotrione		
Melting point	117 °C	46695402
pH @ 24 °C	3.63	
Density (g/mL @ 20 °C)	1.56	
Water solubility (mg/L @ 20 °C)	0.22 at pH4 28.3 at pH 7 29.7 at pH 9	
Solvent solubility (g/L at 20 °C) DMSO Methylene Chloride Acetone Ethyl Acetate Toluene Hexane Ethanol	 >600 >600 300-600 180.2 75.7 47.6 8.2	

TABLE A.2. Physicochemical Properties of Technical Grade		
Parameter	Value	Reference
Vapor pressure (Torr, 20 °C)	8.25×10^{-11}	
Dissociation constant (pK_a)	3.2	
Octanol/water partition coefficient (P_{ow} @ 23 °C) (P_{ow} @ 24 °C) (P_{ow} @ 23 °C)	 0.0430 at pH 9.0 0.0807 at pH 7.0 144.9 at pH 2.0	
UV/visible absorption spectrum (nm)	Primary: 205 Secondary: 284 Tertiary: 240	
AE 1417268		
No data available.		

B. EXPERIMENTAL DESIGN

The in-life phase of the feeding study was conducted at Huntingdon Research Centre (Cambridgeshire, England). Eighteen mature lactating dairy cattle were divided into four treatment groups of three cows each, three cows for a depuration study (dosed at the highest level), and one control group of three cows. The test substance, M5, was prepared as a suspension in corn oil and was incorporated into the feed (concentrate ration + sugar beet pulp). The four treatment groups were dosed orally at levels equivalent to 1, 10, 30, and 100 mg total ai/550 kg/day based on the individual body weights of the cows. The target dose rates approximated 0.05, 0.5, 1.5, and 5.0 ppm (dry feed weight). Cattle were dosed twice a day at milking for 28-31 consecutive days: one cow in each group was dosed for 29 days, one for 30 days, and one for 31 days; cows for the depuration study were dosed for 28 days.

Cows were milked twice daily; the morning and afternoon milk samples for each day were composited for each cow. Cows were sacrificed within 16-24 hours of the final dose, on Days 30-32; the cows for the depuration study were sacrificed 7, 14, and 28 days after the final dose. Following termination, each animal was examined macroscopically, and the following samples were collected: liver (whole organ as two subsamples), kidney (both whole organs as two subsamples), fat (two subsample composites of available omental, perirenal, and subcutaneous), and skeletal muscle (two subsample composites of pectoralis and adductor muscle of thigh). Descriptions of the test animals used and the dietary regime are presented in Tables B.1.1 and B.1.2; the dosing regime and sample collection procedures are summarized in Tables B.1.3 and B.1.4.

B.1. Livestock

TABLE B.1.1. Description of Livestock Used in the Feeding Study.

Species	Breed	Age	Weight at study initiation (kg)	Health status	Description of housing/holding area
Dairy cows (*Bos taurus*)	Holstein	~4-9 years	549.5-718.5	Cows were generally clinieally healthy throughout the study. Six cows exhibited clinical signs of mastitis and were treated accordingly. No other health problems or clinical abnormalities were noted.	Housed in group pens maintained at 4-10 °C and 82% RH

TABLE B.1.2. Test Animal Dietary Regime.

Composition of Diet	Feed consumption (kg/day)[1]	Water	Acclimation period	Predosing
Twice daily: Concentrate ration (HRC Dairy Nuts), 2 kg x 2 Sugar beet pulp, 200 g x 2 Once daily: Hay, 16 kg/animal	20 (nominal individual daily feed consumption on dry weight basis)	*Ad libitum*	12-14 days	None

[1] Individual animal weights, not diet, were used to determine the level of administered M5 dose.

TABLE B.1.3. Dosing Regime.

Treatment group	Treatment type	Level of administered dose (mg/550 kg body wt/dose)[1]	Residue intake in diet (ppm)[2]	Vehicle	Timing/ Duration (days)
Group 2 (Cows 4-6)	Oral	1	0.05 ppm	Feed (M5 suspended in corn oil and incorporated into feed)	29-31
Group 3 (Cows 7-9)		10	0.5 ppm		29-31
Group 4 (Cows 10-12)		30	1.5 ppm		29-31
Group 5 (Cows 13-18)[3]		100	5.0 ppm		28

[1] Total of two doses per day; based on the individual body weights of the cows.
[2] Based on dry feed weight.
[3] Includes cows for depuration study.

TABLE B.1.4. Sample Collection.

Milk collected	Amount of milk produced during normal production (kg/cow/day)	Urine, feces and cage wash collected	Interval from last dose to sacrifice	Tissues harvested and analyzed
Milk collected twice daily from all cows; morning and afternoon milk combined for each time point. Skim milk and cream collected on days 14 and 28.	Average daily milk production: Group 2: 9.0-13.0 Group 3: 11.9-15.3 Group 4: 9.2-12.9 Group 5: 12.-14.5	Not collected	16-24 hours 7, 14, and 28 days: cows for depuration study	Liver, kidneys, fat (composite of omental, perirenal, and subcutaneous), and skeletal muscle (composite of pectoralis/adductor muscle of thigh)

B.2. Sampling Handling and Preparation

Milk was collected from all cows twice daily. Morning milk was stored at 4 °C and combined with the afternoon milk for each study time point. Samples of milk collected on Days 4, 7, 10, 14, 18, 21, 25, and 28 from all dose levels were retained for analysis; additional samples from Days 1, 12, and 23 from the 5.0-ppm dose group and from Days 31, 35, 38, 42, 45, 49, 52, and 56 from the depuration study were also retained. On Days 14 and 28, additional subsamples of milk from each cow were analyzed for fat content and separated into cream and skim milk using a commercial centrifugal cream separator. Samples were stored frozen (<-20 °C) until they were transferred to the analytical laboratory (Eye Research Centre; Suffolk, England) for analysis. At the analytical laboratory samples remained in frozen (<-20 °C) storage at all times except during analysis.

Tissue samples (liver, kidney, fat, and muscle) were washed with water, weighed, and coarsely chopped at the in-life facility, and then immediately transferred into a freezer (<-20 °C). The frozen tissue samples were submitted to the analytical laboratory, where they were homogenized in the presence of dry ice using a commercial food processor. Tissue samples remained in frozen (<-20 °C) storage at all times except during analysis.

B.3. Analytical Methodology

Milk and tissue samples were analyzed for residues of M5 using an LC/MS/MS method that is essentially the same as the proposed LC/MS/MS enforcement method (Bayer Method No. 00967; refer to 46695545.der.doc). A detailed description of the method was included in the submission.

Briefly, samples of milk (including skim milk and cream) were extracted twice with acetonitrile (ACN) and centrifuged, and samples of kidney, liver, and muscle were extracted twice with ACN:water (4:1, v:v) and centrifuged. Samples of fat were extracted with ACN:water (1:1, v:v) and hexane, the hexane was removed by aspiration, and the resulting extract was filtered. The combined supernatants for milk, kidney, liver, and muscle, and the filtrate for fat were then partitioned twice with hexane. The hexane phases were discarded, and the combined ACN phases were evaporated to near dryness and redissolved in methanol/water/acetic acid for analysis. Quantification was performed with reversed-phase high-performance LC/MS/MS. The validated LOQs for M5 were 0.002 ppm for milk, skim milk, and cream, and 0.01 ppm for fat, kidney, liver, and muscle. The estimated LODs were 0.001 ppm for milk, skim milk, and cream, and 0.002 ppm for fat, kidney, liver, and muscle. The LOD was defined as the concentration of the lowest calibration standard chromatographed having a signal to noise ratio ≥3.

HED notes that subsamples of cream were also analyzed for fat content; information/data pertaining to this analysis are not reported herein.

C. RESULTS AND DISCUSSION

Sample storage conditions are summarized in Table C.2. The petitioner stated that milk and tissue samples were stored frozen prior to analysis and that all analyses were completed within one month of sample collection. Extraction and analysis dates were not provided; however, based on the dates of sacrifice and the date residue analysis was completed, samples may have been stored for 6-34 days. No storage stability data are required because all samples from the ruminant feeding study were stored frozen from collection to analysis and were analyzed within ~30 days of collection.

Concurrent recovery data are presented in Table C.1. The LC/MS/MS method was adequate for data collection based on acceptable concurrent recoveries. All recovery values were within the acceptable range of 70-120%; however, HED notes that the fortification levels did not encompass the residues found in kidney and liver. Apparent residues of M5 were below the LOQ (<0.002 ppm for milk, skim milk, and cream, and <0.01 ppm for tissues) in 24 samples each of untreated whole milk, 6 samples each of untreated cream and skim milk, and 3 samples each of untreated fat, kidney, liver, and muscle. Adequate sample calculations and chromatograms were provided.

The results of the feeding study are reported in Tables C.3 and a summary of the residues of M5 in milk and cattle tissues is presented in Table C.4. Residues of M5 were nondetectable (<0.001 ppm) in all samples of milk, skim milk, and cream from all dose groups, except for one sample each of Day 4 milk from the 0.05- and 5.0-ppm dose levels, in which residues were <LOQ (<0.002 ppm). In fat and muscle, residues of M5 were below the LOD (<0.002 ppm) in all samples from all dose groups, with the exception of one sample each of fat and muscle from the 5.0-ppm dose group in which residues were <LOQ (<0.01 ppm). In kidney, maximum residues of M5 were <LOQ, 0.017 ppm, 0.049 ppm, and 0.165 ppm in samples from the 0.05-, 0.50-, 1.5-, and 5.0-ppm dose groups, respectively. No residues of M5 above the LOQ were detected in treated kidney samples collected 7, 14 and 28 days after withdrawal of M5. In liver, maximum residues of M5 were <LOQ, 0.036 ppm, 0.163 ppm, and 0.386 ppm in samples from the 0.05-, 0.50-, 1.5-, and 5.0-ppm dose groups, respectively. Residues of M5 in liver declined rapidly over the withdrawal period, to 0.037 ppm, 0.015 ppm, and <LOD, respectively, 7, 14, and 28 days following cessation of dosing.

A linear residue-level dose dependence was observed in kidney and liver. Graphical presentations of feeding level versus residues found in kidney and liver are presented in Figures C.2.1 and C.2.2.

TABLE C.1. Summary of Concurrent Recoveries of AE 1417268 (M5) from Dairy Cattle Milk and Tissues.

Matrix	Analyte	Spike level (mg/kg)	Sample size (n)	Recoveries (%)	Mean ± std dev
Milk	M5	0.002	5	85, 90, 95, 100, 110	96 ± 9.6
		0.02	5	85, 88, 100, 103, 105	96 ± 9.1
Cream		0.002	5	85, 95, 105, 110, 110	101 ± 10.8
		0.02	5	78, 90, 92, 93, 96	90 ± 6.9
Fat		0.01	5	99, 104, 106, 106, 107	104 ± 3.2
		0.10	5	100, 103, 103, 104, 105	103 ± 1.9
Kidney		0.01	5	81, 92, 104, 106, 107	98 ± 11.2
		0.10	5	89, 90, 99, 100, 100	96 ± 5.6
Muscle		0.01	5	90, 103, 105, 108, 109	103 ± 7.6
		0.10	5	91, 95, 96, 98, 109	98 ± 6.8
Liver		0.01	5	86, 99, 102, 107, 109	101 ± 9.1
		0.10	5	81, 90, 94, 100, 104	94 ± 9.0

TABLE C.2. Summary of Storage Conditions.

Matrix (RAC)	Storage Temperature (°C)	Actual Storage Duration[1]	Interval of Demonstrated Storage Stability
Milk	<-20	6-34 days	None submitted or required
Cream			
Skim milk			
Fat			
Kidney			
Musele			
Liver			

[1] Based on the dates of sacrifice and the date residue analysis was completed.

TABLE C.3. Residue Data from Ruminant Feeding Study with Metabolite AE 1417268 (M5).

Collection time	Feeding Level (ppm)	Residues of M5 (ppm)[1]		
Milk		**4[2]**	**5**	**6**
Day 4	0.05	<LOD	<0.002	<LOD
Day 7		<LOD	<LOD	<LOD
Day 10		<LOD	<LOD	<LOD
Day 14		<LOD	<LOD	<LOD
Day 18		<LOD	<LOD	<LOD
Day 21		<LOD	<LOD	<LOD
Day 25		<LOD	<LOD	<LOD
Day 28		<LOD	<LOD	<LOD
Milk		**7**	**8**	**9**
Day 4	0.50	<LOD	<LOD	<LOD
Day 7		<LOD	<LOD	<LOD
Day 10		<LOD	<LOD	<LOD
Day 14		<LOD	<LOD	<LOD
Day 18		<LOD	<LOD	<LOD
Day 21		<LOD	<LOD	<LOD
Day 25		<LOD	<LOD	<LOD
Day 28		<LOD	<LOD	<LOD

TABLE C.3. Residue Data from Ruminant Feeding Study with Metabolite AE 1417268 (M5).

Collection time	Feeding Level (ppm)	Residues of M5 (ppm)[1]					
Milk		**10**		**11**		**12**	
Day 4	1.5	<LOD		<LOD		<LOD	
Day 7		<LOD		<LOD		<LOD	
Day 10		<LOD		<LOD		<LOD	
Day 14		<LOD		<LOD		<LOD	
Day 18		<LOD		<LOD		<LOD	
Day 21		<LOD		<LOD		<LOD	
Day 25		<LOD		<LOD		<LOD	
Day 28		<LOD		<LOD		<LOD	
Milk		**13**	**14**	**15**	**16**	**17**	**18**
Day 1	5.0	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Day 4		<LOD	<LOD	<LOD	<LOD	<LOD	<0.002
Day 7		<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Day 10		<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Day 12		<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Day 14		<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Day 18		<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Day 21		<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Day 23		<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Day 25		<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Day 28		<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Day 31					<LOD	<LOD	<LOD
Day 35					<LOD	<LOD	<LOD
Day 38						<LOD	<LOD
Day 42						<LOD	<LOD
Day 45							<LOD
Day 49							<LOD
Day 52							<LOD
Day 56							<LOD
Cream		**4**		**5**		**6**	
Day 14	0.05	<LOD		<LOD		<LOD	
Day 28		<LOD		<LOD		<LOD	
Cream		**7**		**8**		**9**	
Day 14	0.5	<LOD		<LOD		<LOD	
Day 28		<LOD		<LOD		<LOD	
Cream		**10**		**11**		**12**	
Day 14	1.5	<LOD		<LOD		<LOD	
Day 28		<LOD		<LOD		<LOD	
Cream		***13***	***14***	***15***	***16***	***17***	***18***
Day 14	5.0	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Day 28		<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Skim milk		**4**		**5**		**6**	
Day 14	0.05	<LOD		<LOD		<LOD	
Day 28		<LOD		<LOD		<LOD	
Skim milk		**7**		**8**		**9**	

TABLE C.3.	**Residue Data from Ruminant Feeding Study with Metabolite AE 1417268 (M5).**						
Collection time	Feeding Level (ppm)	Residues of M5 (ppm)[1]					
Day 14	0.5	<LOD		<LOD		<LOD	
Day 28		<LOD		<LOD		<LOD	
Skim milk		**10**		**11**		**12**	
Day 14	1.5	<LOD		<LOD		<LOD	
Day 28		<LOD		<LOD		<LOD	
Skim milk		**13**	**14**	**15**	**16**	**17**	**18**
Day 14	5.0	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Day 28		<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Fat							
Day 30-32	0.05	**4**		**5**		**6**	
		<LOD		<LOD		<LOD	
	0.5	**7**		**8**		**9**	
		<LOD		<LOD		<LOD	
	1.5	**10**		**11**		**12**	
		<LOD		<LOD		<LOD	
	5.0	**13**		**14**		**15**	
		<LOD		<LOD		<0.01	
Day 36	5.0 (Depuration)	**16**					
		<LOD					
Day 43		**17**					
		<LOD					
Day 57		**18**					
		<LOD					
Kidney							
Day 30-32	0.05	**4**		**5**		**6**	
		<LOD		<0.01		<LOD	
	0.5	**7**		**8**		**9**	
		0.013		0.015		0.017	
	1.5	**10**		**11**		**12**	
		0.037		0.040		0.049	
	5.0	**13**		**14**		**15**	
		0.165		0.122		0.139	
Day 36	5.0 (Depuration)	**16**					
		<0.01					
Day 43		**17**					
		<0.01					
Day 57		**18**					
		<LOD					

TABLE C.3. Residue Data from Ruminant Feeding Study with Metabolite AE 1417268 (M5).				
Collection time	Feeding Level (ppm)	Residues of M5 (ppm)[1]		
Liver				
Day 30-32	0.05	**4**	**5**	**6**
		<0.01	<0.01	<0.01
	0.5	**7**	**8**	**9**
		0.036	0.030	0.029
	1.5	**10**	**11**	**12**
		0.084	0.150	0.163
	5.0	**13**	**14**	**15**
		0.333	0.386	0.305
Day 36	5.0 (Depuration)	**16**		
		0.037		
Day 43		**17**		
		0.015		
Day 57		**18**		
		<LOD		
Muscle				
Day 30-32	0.05	**4**	**5**	**6**
		<LOD	<LOD	<LOD
	0.5	7	**8**	**9**
		<LOD	<LOD	<LOD
	1.5	**10**	**11**	**12**
		<LOD	<LOD	<LOD
	5.0	**13**	**14**	**15**
		<LOD	<0.01	<LOD
Day 36	5.0 (Depuration)	**16**		
		<LOD		
Day 43		**17**		
		<LOD		
Day 57		**18**		
		<LOD		

[1] LOQ = 0.002 *ppm in milk, skim milk, and cream*, and 0.01 *ppm* in tissues; estimated LODs = 0.001 ppm in milk, skim milk, and cream, and 0.002 ppm in tissues.
[2] Animal identification numbers are bolded.

Table C.4. Summary of Residue Data from Ruminant Feeding Study with AE 1417268 (M5).

Matrix	Feeding Level (ppm)	Residue Levels (ppm)					
		n	Min	Max	Median	Mean	Std. Dev.
Milk Days 1-28	0.05	24	<0.002	<0.002	0.001	0.001	N/A
	0.50	24	<0.002	<0.002	0.001	0.001	N/A
	1.5	24	<0.002	<0.002	0.001	0.001	N/A
	5.0	33	<0.002	<0.002	0.001	0.001	N/A
Cream Days 14 and 28	0.05	6	<0.002	<0.002	0.001	0.001	N/A
	0.50	6	<0.002	<0.002	0.001	0.001	N/A
	1.5	6	<0.002	<0.002	0.001	0.001	N/A
	5.0	12	<0.002	<0.002	0.001	0.001	N/A
Skim milk Days 14 and 28	0.05	6	<0.002	<0.002	0.001	0.001	N/A
	0.50	6	<0.002	<0.002	0.001	0.001	N/A
	1.5	6	<0.002	<0.002	0.001	0.001	N/A
	5.0	12	<0.002	<0.002	0.001	0.001	N/A
Fat Days 30-32	0.05	3	<0.01	<0.01	0.005	0.005	N/A
	0.50	3	<0.01	<0.01	0.005	0.005	N/A
	1.5	3	<0.01	<0.01	0.005	0.005	N/A
	5.0	3	<0.01	<0.01	0.005	0.005	N/A
Kidney Days 30-32	0.05	3	<0.01	<0.01	0.005	0.005	N/A
	0.50	3	0.013	0.017	0.015	0.015	0.002
	1.5	3	0.037	0.049	0.040	0.042	0.006
	5.0	3	0.122	0.165	0.139	0.142	0.022
Liver Days 30-32	0.05	3	<0.01	<0.01	0.005	0.005	N/A
	0.50	3	0.029	0.036	0.030	0.032	0.004
	1.5	3	0.084	0.163	0.150	0.132	0.042
	5.0	3	0.305	0.386	0.333	0.341	0.041
Muscle Days 30-32	0.05	3	<0.01	<0.01	0.005	0.005	N/A
	0.50	3	<0.01	<0.01	0.005	0.005	N/A
	1.5	3	<0.01	<0.01	0.005	0.005	N/A
	5.0	3	<0.01	<0.01	0.005	0.005	N/A

For calculation of the minimum and maximum, the LOQ (0.002 ppm for milk, skim milk, and cream, and 0.01 ppm for tissues) was used for residues reported as <LOD in Table C.3. In the calculation of the median, mean, and standard deviation, half the LOQ (0.001 ppm for milk, skim milk, and cream and 0.005 ppm for tissues) was used for residues reported as <LOD or <LOQ.

FIGURE C.2.1. Linear Regression of Residues on Feeding Level in Kidney

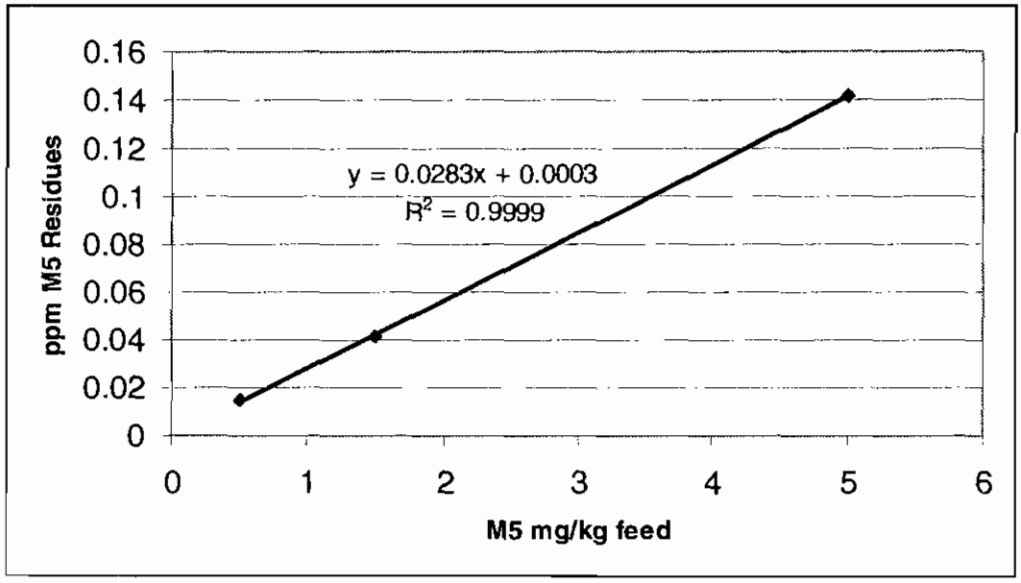
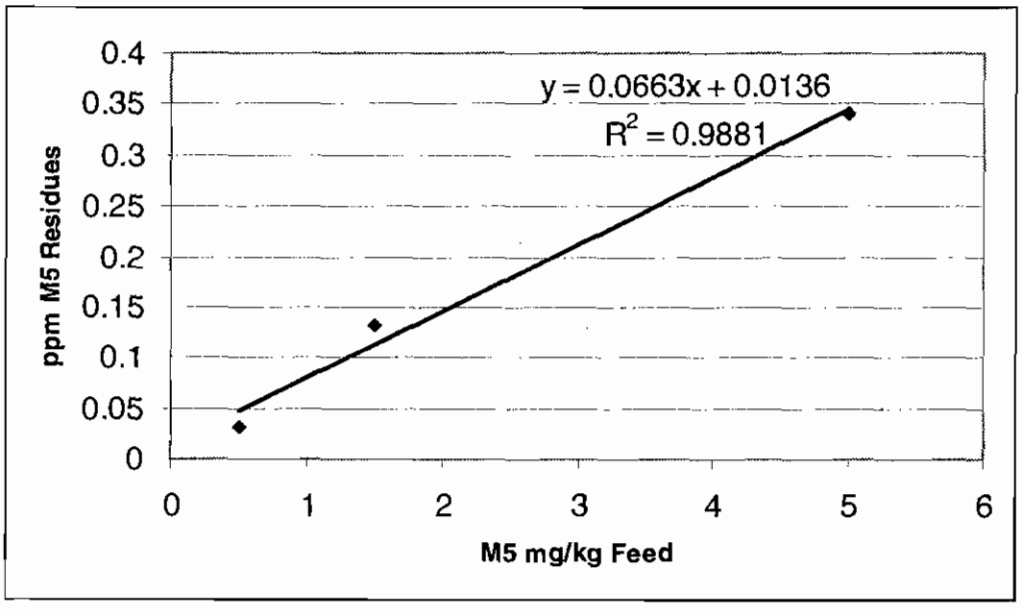


FIGURE C.2.2. Linear Regression of Residues on Feeding Level in Liver



D. CONCLUSION

The submitted dairy cattle feeding study is adequate to demonstrate the magnitude of residues of metabolite M5 in cattle commodities. The feeding study reflects dietary levels of M5 at 0.05, 0.5, 1.5, and 5.0 ppm. No residues of M5 were detected in untreated or treated bovine whole milk, skimmed milk or cream at any dose level with the exception of one sample each of Day-4 whole milk from 0.05- and 5.0-ppm dose levels which had residues <LOQ (<0.002 ppm). No residues of M5 were detected in any of the treated fat or muscle samples, with the exception of one sample each of fat and muscle from the 5.0-ppm dose group which had residues <LOQ (<0.01 ppm) in fat and muscle. Residues of M5 were found in significant amounts in the excretory organs of kidney and liver, and showed a linear residue-level dose dependence with the feeding level, with rapid and almost total depuration within 28 days after cessation of treatment. Residues were determined using an acceptable method, and no storage stability data were required to support the study.

E. REFERENCES

46695545.der.doc

F. DOCUMENT TRACKING

RDI: RAB1 Chemists (1/10/07)
Petition Number: PP#5F7009
DP#s: 325349, 325663, and 331222
PC Code: 012801

Template Version June 2005

Tembotrione/AE 0172747/PC Code 012801/Bayer CropScience/264
DACO 7.4.1/7.4.2/OPPTS 860.1500/OECD IIA 6.3.1, 6.3.2, 6.3.3 and IIIA 8.3.1, 8.3.2, 8.3.3
Crop Field Trial/Residue Decline – Field Corn

Primary Evaluator	George F. Kramer, Ph.D., Senior Chemist Registration Action Branch (RAB1) Health Effects Division (HED) (7509P)	Date: 18-JUL-2007
Approved by	P.V. Shah, Ph.D., Branch Senior Scientist RAB1/HED (7509P)	Date: 18-JUL-2007

This DER was originally prepared under contract by Dynamac Corporation (2275 Research Boulevard, Suite 300; Rockville, MD 20850; submitted 11/30/2006). The DER has been reviewed by HED and revised to reflect current Office of Pesticide Programs (OPP) policies.

STUDY REPORT:

46695607 Harbin, A.; Mackie, S. (2005) AE 0172747 - Magnitude of Residues in Field Corn Resulting from Foliar Applications of AE 0172747 02 SC52 A1 under Maximum Proposed Label Specifications (2003). Project Number: 03RAAEX010, Report Number: RAAEX010. Unpublished study prepared by Bayer CropScience. 896 p.

The petitioner has submitted an evaluation template for the study (Bayer CropScience DER for Study RAAEX010), which was used to generate this DER; selected sections were copied without alteration or were copied and modified to more specifically reflect the Agency's data evaluation requirements.

EXECUTIVE SUMMARY:

Bayer CropScience has submitted field trial data for tembotrione on field corn. Twenty-one field trials were conducted in the United States encompassing Zones 1 (PA; 1 trial), 2 (GA; 1 trial), 5 (IA, IL, IN, KS, MN, MO, NE, OH, SD, and WI; 18 trials), and 6 (TX; 1 trial) during the 2003 growing season.

Each trial site included one control plot and two to four treated plots. Two foliar spray applications of a suspension-concentrate (SC) formulation (AE 0172747 Herbicide) nominally containing 3.50 lb tembotrione ai/gallon (420 g ai/L), were made to field corn at 24- inch and 36-inch height in treated plot A at a target rate of 0.082 lb ai/A/application (0.092 kg ai/ha/application). Field corn in treated plot B received one foliar spray application at 36-inch height and one drop-nozzle (directed) spray one week later at the same target application rates. Additional treated plots (C, D, and E) were included in some trials and these plots received applications at the same use pattern as the treated plot A, but using different spray adjuvants. Applications were made using ground equipment in ~13-17 gal/A (122-161 L/ha). An adjuvant was added to the spray mixture for all applications. The achieved total seasonal rates ranged from 0.160 to 0.174 lb ai/A (0.180 to 0.195 kg ai/ha) for all treated plots at all trial sites. Field corn forage samples were harvested at a preharvest interval (PHI) of 44 to 53 days after the last application. The grain and stover samples were harvested at commercial maturity (BBCH 87 to 89) at PHIs ranging from 76 to 112 days. At two trial locations, field corn matrices were collected at additional sampling intervals to evaluate residue decline: field corn forage was collected 35, 39-41, 44-45, 50, and 55-56 days and field corn grain and stover were collected 77-

85, 84-91, 91-99, 98-106, and 105-112 days following the last application of Treatments A and B.

The harvested field corn raw agricultural commodity (RAC) samples were analyzed for residues of the parent compound, tembotrione, and the metabolites AE 1392936 (M2), AE 1417268 (M5), and AE 0456148 (M6) using a method entitled "AE 0172747: An Analytical Method for the Determination of Residues of AE 0172747, and its major metabolites AE 0456148, AE 1417268, and AE 1392936 in Plant Matrices Using LC/MS/MS." This method is acceptable for data collection based on adequate method validation and concurrent method recovery data. The limits of quantitation (LOQs) for tembotrione, M2, M5, and M6 were each 0.010 ppm in field corn grain, forage and stover; the estimated method limits of detection (LODs) were ≤0.004 ppm for each analyte in corn grain, forage, and stover.

The maximum storage intervals of samples from harvest to analysis were 283 days (9.3 months) for field corn forage, 250 days (8.2 months) for field corn grain, and 260 days (8.5 months) for field corn stover. In addition, one forage sample and one stover sample were reanalyzed for tembotrione only, 490 to 512 days after the initial analysis. Results of the reanalyses were not significantly different from the original analyses; therefore, stability may be inferred for the additional storage interval. Adequate storage stability data for field corn commodities (refer to 860.1380 DER for MRID 46695601) are available to support the storage conditions and intervals of samples from the field corn field trials.

In trials reflecting Treatment A (two foliar applications totaling 0.161-0.170 lb ai/A), the maximum combined residues of parent and its metabolites (M5 + M6 + M2), as parent equivalents, were <0.471 ppm in/on field corn forage, <0.155 ppm in/on field corn grain, and <0.554 ppm in/on field corn stover. In treated stover sample which bore the highest combined residues of <0.554 ppm, Metabolites M5 and M6 comprised 81% and 17% of the total residues, respectively; individual residues of the parent and Metabolite M2 were below the LOQ in the same stover sample.

Following Treatment B (one foliar application and one directed-spray application totaling 0.164-0.174 lb ai/A), the maximum combined residues of parent and its metabolites (M5 + M6 + M2), as parent equivalents, were <0.322 ppm in/on field corn forage, <0.144 ppm in/on field corn grain, and <0.525 ppm in/on field corn stover.

When only residues of the parent and Metabolite M5 are summed, the maximum combined residues following Treatment A were <0.375 ppm in/on field corn forage, <0.022 ppm in/on field corn grain, and <0.450 ppm in/on field corn stover. Following Treatment B, the maximum combined residues were <0.290 ppm in/on field corn forage, <0.025 ppm in/on field corn grain, and <0.445 ppm in/on field corn stover.

Overall, the maximum residues of M5 were 0.860 ppm in/on field corn forage, <0.01 ppm in/on field corn grain, and 0.440 ppm in/on field corn stover; maximum residues of M6 were 0.148 ppm in/on field corn forage, 0.125 ppm in/on field corn grain, and 0.129 ppm in/on field corn stover; and maximum residues of M2 were 0.023 ppm in/on field corn forage, <0.01 ppm in/on field corn grain, and 0.042 ppm in/on field corn stover.

Based on the results of the side-by-side field trials, residues were similar in/on field corn matrices treated with two foliar applications (Treatment A) or treated with one foliar + one directed-spray application (Treatment B). Residues of the parent were nonquantifiable in all field corn matrices from both treatment regimes.

The two residue decline trials indicate that total tembotrione residues do not appear to decline in stover with later sampling intervals, and residues in forage were inconsistent; therefore, no meaningful conclusion could be made regarding a trend. Total residues in grain were near or below the LOQ at all sampling intervals.

The results of the bridging studies, conducted with different spray adjuvant mixtures, indicate that overall the combination of spray adjuvants used had no significant impact on the residue levels in/on treated corn matrices.

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the field trial residue data are classified as scientifically acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document [DP# 325349].

COMPLIANCE:

Signed and dated Good Laboratory Practice (GLP), Quality Assurance and Data Confidentiality statements were provided. No deviations from regulatory requirements were reported which would have an impact on the validity of the study.

A. BACKGROUND INFORMATION

Tembotrione, a new herbicide with broad use against mono- and dicotyledons in selected crops such as corn, is a 4-hydroxyphenylpyruvate deoxygenase (HPPD) inhibitor (bleacher). Details of the test compounds nomenclature (tembotrione and its three metabolites) and physiochemical properties of tembotrione are given in Tables A.1 and A.2.

TABLE A.1. Test Compound Nomenclature for Tembotrione and its Metabolites AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2).

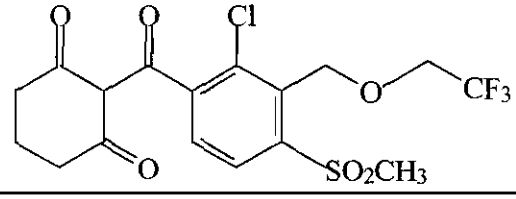
Compound: Tembotrione	Chemical Structure 
Common name	Tembotrione (Parent)
Company experimental name	AE 0172747
IUPAC name	2-{2-Chloro-4-mesyl-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl}cyclohexane-1,3-dione

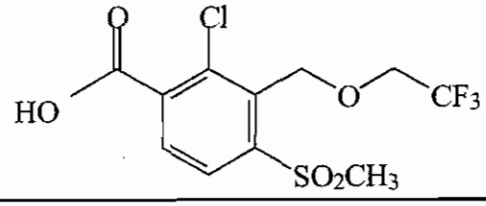
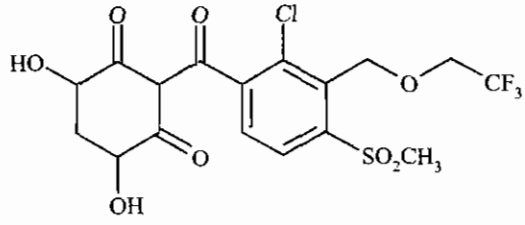
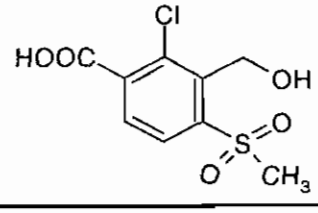
TABLE A.1. Test Compound Nomenclature for Tembotrione and its Metabolites AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2).	
CAS name	2-[2-Chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione
CAS #	335104-84-2
End-use product/EP	AE 0172747 Herbicide, EPA Reg No. 264-xxx
Compound: AE 0456148	Chemical Structure 
Common name	Metabolite M6
Company experimental name	AE 0456148
IUPAC name	None provided
CAS name	2-chloro-4-mesyl-3-[(2,2,2-trifluroethoxy)methyl]benzoic acid
CAS #	None provided
Compound: AE 1417268	Chemical Structure 
Common name	Metabolite M5
Company experimental name	AE 1417268
IUPAC name	None provided
CAS name	2-[2-chloro-4-(methylsulfonyl)-3-[2,2,2-trifluoroethoxy)methyl]benzoyl]-4,6-dihydroxycyclohexan-1,3-dione
CAS #	None provided
Compound: AE 1392936	Chemical Structure 
Common name	Metabolite M2
Company experimental name	AE 1392936
IUPAC name	None provided
CAS name	2-chloro-3-hydroxymethyl-4-mesylbenzoic acid
CAS #	None provided

TABLE A.2. Physicochemical Properties of Technical Grade Tembotrione.

Parameter	Value	Reference (MRID#)
Melting point	117 °C	46695402
pH @ 24 °C	3.63	
Density (g/mL @ 20 °C)	1.56	
Water solubility (mg/L @ 20 °C)	0.22 at pH4 28.3 at pH 7 29.7 at pH 9	
Solvent solubility (g/L at 20 °C) DMSO Methylene Chloride Acetone Ethyl Acetate Toluene Hexane Ethanol	 >600 >600 300-600 180.2 75.7 47.6 8.2	
Vapor pressure (Torr, 20 °C)	8.25×10^{-11}	
Dissociation eonstant (pK_a)	3.2	
Octanol/water partition coefficient (P_{ow} @ 23 °C) (P_{ow} @ 24 °C) (P_{ow} @ 23 °C)	 0.0430 at pH 9.0 0.0807 at pH 7.0 144.9 at pH 2.0	
UV/visible absorption spectrum (nm)	Primary: 205 Secondary: 284 Tertiary: 240	

B. EXPERIMENTAL DESIGN

Twenty-one field trials were conducted in the United States encompassing Zones 1 (PA; 1 trial), 2 (GA; 1 trial), 5 (IA, IL, IN, KS, MN, MO, NE, OH, SD, and WI; 18 trials), and 6 (TX; 1 trial) during the 2003 growing season.

AE 0172747 Herbicide is a SC formulation nominally containing 3.50 lb tembotrione ai/gallon (420 g ai/L). Each trial site included one control plot and two to four treated plots. Two foliar spray applications of AE 0172747 Herbicide were made to field corn at 24- and 36-inch height in treated plot A at a target rate of 0.082 lb ai/A/application (0.092 kg ai/ha/application). Field corn in treated plot B received one foliar spray application at the 36-inch height and one drop-nozzle (directed) spray one week later at the same target application rates. The target total application rate for both treatment plots was 0.164 lb ai/A (0.184 kg ai/ha). Applications were made using ground equipment in ~13-17 gal/A (122-161 L/ha). Both treated plots had the spray adjuvants methylated seed oil (MSO) at 1.5 pt/A and 28% or 32% urea ammonium nitrate (UAN) at 1.5 to 2 qt/A added to each tank mixture. Actual test parameters are reported in Table B.1.2.

Additional treated plots (Treatments C, D, and E) were included in some trials and these plots received applications at the same use pattern as treated plot A, but using different spray adjuvants. Six trials included an additional plot (Treatment C) using crop oil concentrate (COC) at 1 pt/A and UAN. Three trials included an additional plot (Treatment D) using MSO and

ammonium sulfate (AMS) at 1.5 to 3 lb/A as the adjuvants. Finally, three trials included an additional plot (Treatment E) using COC at 1 pt/A and AMS at 1.5 to 3 lb/A as the adjuvants.

The test crops were grown and maintained according to typical practices for each region. Irrigation, fertilizer, and maintenance pesticides were applied as needed. Trial site conditions are presented in Table B.1.1. The crop varieties grown are identified in Table C.3. Average minimum and maximum temperatures and total precipitation recordings for the residue study period were reported, along with average 30-year historical data. Weather conditions were similar to historical weather data. Irrigation amounts ranged from 2.0 to 10.6 inches.

B.1. Study Site Information

TABLE B.1.1 Trial Site Conditions.

Study Location City, State	Trial Number (RAAEX0-)	Year	*Soil Characteristics*				Meteorological Data[1]	
			Type	% OM[2]	pH	CEC[2]	Total Precip (inch)	Temp Range (°F)
Germansville, PA	10-01H	2003	Loam	3	7.1	9.9	28.42	30-100
Tifton, GA	10-02H	2003	Sand	1.86	4.8	3.01	23.79	55-95
Bagley, IA	10-03H	2003	Loam	4	6.0	20.8	8.84	27-101
Campbell, MN	10-04H	2003	Silt Loam	5	7.4	33.3	3.41	22-99
Ellendale, MN	10-05H	2003	Sandy Clay	4.2	7.8	34.2	6.65	17-99
Arkansaw, WI	10-06H	2003	Silt Loam	1.8	6.5	6.0	6.20	19-98
Britton, SD	10-07H	2003	Silt Loam	4	7.7	35.9	5.02	24-102
Springfield, NE	10-08H	2003	Silt Loam	2	6.5	10.9	5.56	47-105
York, NE	10-09H	2003	Silt Loam	2.1	7.1	11.9	6.65	34-101
Richland, IA	10-10H	2003	Silt Loam	3.5	6.8	20.7	12.27	22-102
Cunningham, KS	10-11H	2003	Sand	1.4	5.4	6.6	8.45	35-108
Seymore, IL	10-12D	2003	Silt Loam	3.1	6.5	21.0	13.19	25-97
Carlyle, IL	10-13H	2003	Silt Loam	1	6.8	12.0	13.36	32-97
Oxford, IN	10-14H	2003	Clay Loam	4.7	5.9	17.0	20.27	28-94
Noblesville, IN	10-15H	2003	Loam	2.7	6.3	15.5	23.43	30-94
New Holland, OH	10-16H	2003	Loam	1.9	7.0	11.0	19.65	30-92
Stilwell, KS	10-17D	2003	Silt Loam	2.3	5.7	14.8	16.85	37-107
Hudson, KS	10-18H	2003	Sand	2.1	6.5	9.2	8.81	38-109
Clarence, MO	10-19H	2003	Silt Loam	1.3	6.6	10.4	14.60	29-102
Dexter, MO	10-20H	2003	Silt Loam	0.9	7.0	9.7	13.24	53-98
East Bernard, TX	10-21H	2003	Sandy Loam	1	5.5	8.2	4.38	63-103

[1] Meteorological data from date of first application through date of final harvest.
[2] OM = Organic matter, CEC = Cation-exchange capacity (unit of measurement was not provided).

TABLE B.1.2. Study Use Pattern.

Location: City, State, NAFTA Zone Trial Number (RAAEX010-) Year	EP[1]	Trtmt Pattern[2]	Application						
			Method	Timing[3]	Rate lb ai/A (kg ai/ha)	RTI[4] (days)	GPA[5] (L/ha)	Total Rate lb ai/A (kg ai/ha)	Tank Mix Adjuvant[6]
Germansville, PA Zone 1 01H 2003	420 SC	A	Foliar	24	0.083 (0.093)	--	16.3 (152)	0.170 (0.191)	MSO & UAN
			Foliar	36	0.087 (0.098)	6	16.4 (153)		
	420 SC	B	Foliar	36	0.087 (0.098)	--	16.4 (153)	0.171 (0.193)	MSO & UAN
			Directed	1 wk later	0.084 (0.095)	6	16.4 (153)		
Tifton, GA Zone 2 02H 2003	420 SC	A	Foliar	24	0.083 (0.093)	--	14.1 (132)	0.165 (0.185)	MSO & UAN
			Foliar	36	0.082 (0.092)	11	13.3 (124)		
	420 SC	B	Foliar	36	0.082 (0.092)	--	13.3 (124)	0.164 (0.184)	MSO & UAN
			Directed	1 wk later	0.082 (0.092)	7	13.9 (130)		
	420 SC	C	Foliar	24	0.082 (0.092)	--	14.1 (132)	0.164 (0.184)	COC & UAN
			Foliar	36	0.082 (0.092)	11	13.3 (124)		
	420 SC	D	Foliar	24	0.082 (0.092)	--	14.1 (132)	0.164 (0.184)	MSO & AMS
			Foliar	36	0.082 (0.092)	11	13.3 (124)		
Bagley, IA Zone 5 03H 2003	420 SC	A	Foliar	24	0.082 (0.092)	--	13.5 (126)	0.164 (0.184)	MSO & UAN
			Foliar	36	0.082 (0.092)	7	13.1 (122)		
	420 SC	B	Foliar	36	0.082 (0.092)	--	13.0 (122)	0.166 (0.186)	MSO & UAN
			Directed	1 wk later	0.084 (0.094)	8	15.1 (141)		
	420 SC	C	Foliar	24	0.084 (0.095)	--	14.0 (131)	0.166 (0.187)	COC & UAN
			Foliar	36	0.082 (0.092)	7	13.1 (122)		

TABLE B.1.2. Study Use Pattern.

Location: City, State, NAFTA Zone Trial Number (RAAEX010-) Year	EP[1]	Trtmt Pattern[2]	Application						
			Method	Timing[3]	Rate lb ai/A (kg ai/ha)	RTI[4] (days)	GPA[5] (L/ha)	Total Rate lb ai/A (kg ai/ha)	Tank Mix Adjuvant[6]
Bagley, IA (continued)	420 SC	D	Foliar	24	0.083 (0.093)	--	13.7 (128)	0.167 (0.187)	MSO & AMS
			Foliar	36	0.084 (0.094)	7	13.3 (124)		
Campbell, MN Zone 5 04H 2003	420 SC	A	Foliar	24	0.083 (0.093)	--	15.1 (141)	0.165 (0.185)	MSO & UAN
			Foliar	36	0.082 (0.092)	7	15.0 (140)		
	420 SC	B	Foliar	36	0.082 (0.092)	--	15.1 (141)	0.164 (0.184)	MSO & UAN
			Directed	1 wk later	0.082 (0.092)	8	15.0 (140)		
Ellendale, MN Zone 5 05H 2003	420 SC	A	Foliar	24	0.082 (0.092)	--	15.8 (148)	0.164 (0.184)	MSO & UAN
			Foliar	36	0.082 (0.092)	10	15.5 (145)		
	420 SC	B	Foliar	36	0.082 (0.092)	--	15.6 (146)	0.165 (0.185)	MSO & UAN
			Directed	1 wk later	0.083 (0.093)	7	15.5 (145)		
Arkansaw, WI Zone 5 06H 2003	420 SC	A	Foliar	24	0.083 (0.093)	--	15.1 (141)	0.165 (0.185)	MSO & UAN
			Foliar	36	0.082 (0.092)	6	15.0 (140)		
	420 SC	B	Foliar	36	0.083 (0.093)	--	15.2 (142)	0.166 (0.186)	MSO & UAN
			Directed	1 wk later	0.083 (0.093)	8	15.2 (142)		
Britton, SD Zone 5 07H 2003	420 SC	A	Foliar	24	0.082 (0.092)	--	15.0 (140)	0.168 (0.188)	MSO & UAN
			Foliar	36	0.086 (0.096)	10	15.7 (146)		
	420 SC	B	Foliar	36	0.084 (0.094)	--	15.4 (144)	0.166 (0.186)	MSO & UAN
			Directed	1 wk later	0.082 (0.092)	7	15.0 (140)		

TABLE B.1.2. Study Use Pattern.

Location: City, State, NAFTA Zone Trial Number (RAAEX010-) Year	EP[1]	Trtmt Pattern[2]	Application						
			Method	Timing[3]	Rate lb ai/A (kg ai/ha)	RTI[4] (days)	GPA[5] (L/ha)	Total Rate lb ai/A (kg ai/ha)	Tank Mix Adjuvant[6]
Springfield, NE Zone 5 08H 2003	420 SC	A	Foliar	24	0.082 (0.092)	--	15.0 (140)	0.164 (0.184)	MSO & UAN
			Foliar	36	0.082 (0.092)	4	14.8 (138)		
	420 SC	B	Foliar	36	0.082 (0.092)	--	14.7 (137)	0.164 (0.184)	MSO & UAN
			Directed	1 wk later	0.082 (0.092)	8	14.4 (135)		
	420 SC	C	Foliar	24	0.082 (0.092)	--	15.1 (141)	0.164 (0.184)	COC & UAN
			Foliar	36	0.082 (0.092)	4	14.8 (138)		
	420 SC	D	Foliar	24	0.082 (0.092)	--	15.0 (140)	0.164 (0.184)	MSO & AMS
			Foliar	36	0.082 (0.092)	4	14.8 (138)		
York, NE Zone 5 09H 2003	420 SC	A	Foliar	24	0.084 (0.094)	--	15.1 (141)	0.166 (0.186)	MSO & UAN
			Foliar	36	0.082 (0.092)	5	15.1 (141)		
	420 SC	B	Foliar	36	0.082 (0.092)	--	15.1 (141)	0.165 (0.185)	MSO & UAN
			Directed	1 wk later	0.083 (0.093)	7	15.0 (140)		
Richland, IA Zone 5 10H 2003	420 SC	A	Foliar	24	0.080 (0.090)	--	14.8 (138)	0.164 (0.184)	MSO & UAN
			Foliar	36	0.084 (0.094)	9	15.4 (144)		
	420 SC	B	Foliar	36	0.085 (0.095)	--	15.5 (145)	0.169 (0.189)	MSO & UAN
			Directed	1 wk later	0.084 (0.094)	6	15.9 (149)		
Cunningham, KS Zone 5 11H 2003	420 SC	A	Foliar	24	0.082 (0.092)	--	14.9 (139)	0.167 (0.187)	MSO & UAN
			Foliar	36	0.085 (0.095)	13	14.6 (137)		
	420 SC	B	Foliar	36	0.085 (0.095)	--	14.5 (136)	0.167 (0.187)	MSO & UAN
			Directed	1 wk later	0.082 (0.092)	8	14.2 (133)		

TABLE B.1.2. Study Use Pattern.

Location: City, State, NAFTA Zone Trial Number (RAAEX010-) Year	EP[1]	Trtmt Pattern[2]	Application						
			Method	Timing[3]	Rate lb ai/A (kg ai/ha)	RTI[4] (days)	GPA[5] (L/ha)	Total Rate lb ai/A (kg ai/ha)	Tank Mix Adjuvant[6]
Seymour, IL Zone 5 12D 2003	420 SC	A	Foliar	24	0.083 (0.093)	--	16.2 (151)	0.166 (0.186)	MSO & UAN
			Foliar	36	0.083 (0.093)	7	16.4 (153)		
	420 SC	B	Foliar	36	0.083 (0.093)	--	16.3 (153)	0.165 (0.185)	MSO & UAN
			Directed	1 wk later	0.082 (0.092)	7	14.9 (139)		
	420 SC	C	Foliar	24	0.081 (0.091)	--	15.8 (148)	0.163 (0.183)	COC & UAN
			Foliar	36	0.082 (0.092)	7	16.2 (151)		
	420 SC	E	Foliar	24	0.081 (0.091)	--	15.8 (148)	0.164 (0.184)	COC & AMS
			Foliar	36	0.083 (0.093)	7	16.4 (153)		
Carlyle, IL Zone 5 13H 2003	420 SC	A	Foliar	24	0.084 (0.094)	--	14.1 (132)	0.164 (0.184)	MSO & UAN
			Foliar	36	0.080 (0.090)	5	16.1 (151)		
	420 SC	B	Foliar	36	0.081 (0.091)	--	16.2 (151)	0.165 (0.185)	MSO & UAN
			Directed	1 wk later	0.084 (0.094)	6	14.3 (134)		
Oxford, IL Zone 5 14H 2003	420 SC	A	Foliar	24	0.083 (0.093)	--	15.5 (145)	0.168 (0.188)	MSO & UAN
			Foliar	36	0.085 (0.095)	9	15.7 (147)		
	420 SC	B	Foliar	36	0.085 (0.095)	--	15.7 (147)	0.169 (0.189)	MSO & UAN
			Directed	1 wk later	0.084 (0.094)	6	14.4 (135)		
	420 SC	C	Foliar	24	0.084 (0.094)	--	15.6 (146)	0.168 (0.188)	COC & UAN
			Foliar	36	0.084 (0.094)	9	15.6 (146)		
	420 SC	E	Foliar	24	0.084 (0.094)	--	15.8 (148)	0.169 (0.189)	COC & AMS
			Foliar	36	0.085 (0.095)	9	15.8 (148)		

TABLE B.1.2. Study Use Pattern.

Location: City, State, NAFTA Zone Trial Number (RAAEX010-) Year	EP[1]	Trtmt Pattern[2]	Application						
			Method	Timing[3]	Rate lb ai/A (kg ai/ha)	RTI[4] (days)	GPA[5] (L/ha)	Total Rate lb ai/A (kg ai/ha)	Tank Mix Adjuvant[6]
Noblesville, IN Zone 5 15H 2003	420 SC	A	Foliar	24	0.081 (0.091)	--	14.7 (137)	0.165 (0.185)	MSO & UAN
			Foliar	36	0.084 (0.094)	6	15.9 (149)		
	420 SC	B	Foliar	36	0.083 (0.093)	--	15.7 (147)	0.165 (0.185)	MSO & UAN
			Directed	1 wk later	0.082 (0.092)	6	15.6 (146)		
New Holland, OH Zone 5 16H 2003	420 SC	A	Foliar	24	0.085 (0.095)	--	15.7 (147)	0.170 (0.190)	MSO & UAN
			Foliar	36	0.085 (0.095)	10	14.7 (137)		
	420 SC	B	Foliar	36	0.085 (0.095)	--	14.7 (137)	0.168 (0.188)	MSO & UAN
			Directed	1 wk later	0.083 (0.093)	6	16.3 (152)		
Stilwell, KS Zone 5 17D 2003	420 SC	A	Foliar	24	0.077 (0.086)	--	14.2 (133)	0.161 (0.180)	MSO & UAN
			Foliar	36	0.084 (0.094)	6	14.8 (138)		
	420 SC	B	Foliar	36	0.085 (0.095)	--	15.1 (141)	0.174 (0.195)	MSO & UAN
			Directed	1 wk later	0.089 (0.100)	6	17.2 (161)		
	420 SC	C	Foliar	24	0.076 (0.086)	--	14.1 (132)	0.160 (0.180)	COC & UAN
			Foliar	36	0.084 (0.094)	6	14.9 (139)		
	420 SC	E	Foliar	24	0.081 (0.090)	--	14.9 (139)	0.170 (0.190)	COC & AMS
			Foliar	36	0.089 (0.100)	6	15.7 (147)		
Hudson, KS Zone 5 18H 2003	420 SC	A	Foliar	24	0.081 (0.091)	--	14.7 (137)	0.163 (0.183)	MSO & UAN
			Foliar	36	0.082 (0.092)	6	15.0 (140)		
	420 SC	B	Foliar	36	0.081 (0.091)	--	14.9 (139)	0.163 (0.183)	MSO & UAN
			Directed	1 wk later	0.082 (0.092)	8	15.6 (146)		

TABLE B.1.2. Study Use Pattern.

Location: City, State, NAFTA Zone Trial Number (RAAEX010-) Year	EP[1]	Trtmt Pattern[2]	Application						
			Method	Timing[3]	Rate lb ai/A (kg ai/ha)	RTI[4] (days)	GPA[5] (L/ha)	Total Rate lb ai/A (kg ai/ha)	Tank Mix Adjuvant[6]
Clarence, MO Zone 5 19H 2003	420 SC	A	Foliar	24	0.082 (0.092)	--	14.9 (139)	0.165 (0.185)	MSO & UAN
			Foliar	36	0.083 (0.093)	11	15.1 (141)		
	420 SC	B	Foliar	36	0.083 (0.093)	--	15.3 (143)	0.166 (0.186)	MSO & UAN
			Directed	1 wk later	0.083 (0.093)	7	15.0 (140)		
Dexter, MO Zone 5 20H 2003	420 SC	A	Foliar	24	0.082 (0.092)	--	15.1 (141)	0.164 (0.184)	MSO & UAN
			Foliar	36	0.082 (0.092)	15	16.5 (154)		
	420 SC	B	Foliar	36	0.082 (0.092)	--	16.6 (155)	0.165 (0.185)	MSO & UAN
			Directed	1 wk later	0.083 (0.093)	7	15.1 (141)		
East Bernard, TX Zone 6 21H 2003	420 SC	A	Foliar	24	0.083 (0.093)	--	13.8 (129)	0.164 (0.184)	MSO & UAN
			Foliar	36	0.081 (0.091)	7	15.8 (148)		
	420 SC	B	Foliar	36	0.084 (0.094)	--	15.9 (149)	0.166 (0.186)	MSO & UAN
			Directed	1 wk later	0.082 (0.092)	8	16.4 (153)		

[1] The end-use product is a SC formulation of tembotrione and isoxadifen safener.
[2] Treatment Pattern A: two foliar spray applications at 24-inch and 36-inch corn height.
Treatment Pattern B: One foliar spray application at 36-inch corn height and one directed-spray application one week later.
Treatment Patterns C, D, and E: application at the same use pattern as Pattern A with different adjuvants added.
[3] Timing = Corn height in inches or 1 week later.
[4] RTI = Retreatment Interval.
[5] GPA = gallons per acre and L/ha = liters per hectare.
[6] Spray adjuvants methylated seed oil (MSO), urea ammonium nitrate (UAN), crop oil concentrate (COC) and ammonium sulfate (AMS).

TABLE B.1.3. Trial Numbers and Geographical Locations.

NAFTA Growing Zones	Field Corn		
	Submitted	Requested	
		Canada	U.S.
1	1		1
2	1		1
5	18		17
6	1		1
Total	21		20

B.2. Sample Handling and Preparation

In all of the trials, duplicate treated samples and a single control sample of field corn forage, grain, and stover were collected at normal harvest times. Field corn forage samples were harvested at a PHI of 44 to 53 days after the last application (DALA). The grain and stover were harvested at commercial maturity (BBCH 87 to 89) at PHIs ranging from 76 to 112 days. At two trial locations, field corn matrices were collected at various PHIs to evaluate residue decline.

All corn samples were harvested, put into labeled cloth bags in the field and transported to a freezer within 2 hours of harvest except for trial -18H, in which samples were placed in frozen storage within 6 hours of harvest. Following collection of the field corn samples, reasonable attempts were made to maintain the samples under cool conditions in the field prior to being transferred to frozen storage. Samples remained in frozen storage at the field facilities until shipment via freezer truck to Bayer Research Park (BRP; Stilwell, KS) for analysis. In preparation for analysis, the field corn RAC samples were homogenized in dry ice using a chopper. All samples remained frozen at all times except during sub-sampling for analysis.

B.3. Analytical Methodology

The harvested field corn RAC samples were analyzed for residues of the parent compound, tembotrione, and the metabolites AE 1392936 (M2), AE 1417268 (M5), and AE 0456148 (M6). The analytical method used was a liquid chromatography/mass spectroscopy (LC/MS)/MS method entitled "AE 0172747: An Analytical Method for the Determination of Residues of AE 0172747, and its major metabolites AE 0456148, AE 1417268, and AE 1392936 in Plant Matrices Using LC/MS/MS." This method quantifies all analytes from a single sample using isotopically labeled internal standards.

Briefly, residues of tembotrione and its metabolites M2, M5, and M6 were extracted from crop matrices with acetonitrile:water (1:1, v:v) using accelerated solvent extraction. Internal standards of the deuterated analytes were added to the extract. For parent, M5, and M6 analysis, an aliquot of the extract was concentrated via Turbo-Vap. For M2 analysis, an aliquot of the extract was loaded onto a strong anion exchange solid-phase extraction (SPE) cartridge and eluted with oxalic acid. The SPE eluate was concentrated. The concentrates were reconstituted in 0.1% formic acid and filtered for LC/MS/MS analysis.

For the subject field trial study, reference standards were prepared in tembotrione molar equivalents, therefore, quantitating residues as parent equivalents.

Method validation was performed prior to sample analysis with field corn forage, grain, and stover (refer to 860.1340 DER for MRID 46695537), and concurrent recoveries were performed during sample analysis to demonstrate acceptable method performance.

The LOQs for tembotrione, M2, M5, and M6 were 0.010 ppm for each analyte in field corn matrices. The LOQ was defined as the lowest fortification level of an analyte at which acceptable recovery data was achieved.

The calculated LODs were 0.001 ppm for tembotrione and 0.002 ppm for M6, M5, and M2 in corn forage. The calculated LODs were 0.001 ppm for tembotrione, 0.003 ppm for M6 and M5, and 0.002 ppm for M2 in corn grain. The calculated LODs were 0.001 ppm for tembotrione and M5, 0.004 ppm for M6, 0.002 ppm for M2 in corn stover. The LOD was calculated by multiplying the standard deviation of recovery measurements at the LOQ by $t_{0.99}$ (where $t_{0.99}$ is the one-tailed statistic at the 99% confidence level for n-1 replicates) and adding the average residue found in the untreated control samples.

HED notes that the petitioner used the highest LOD of the individual analytes in a particular matrix as the LOD for total tembotrione residues (sum of tembotrione, M6, M5, and M2 residues). For purposes of residue evaluation, HED used the aggregate LOQs of each analyte in totaling combined residues of tembotrione.

C. RESULTS AND DISCUSSION

Sample storage conditions and intervals are summarized in Table C.2. The maximum storage intervals of samples from harvest to analysis were 283 days (9.3 months) for field corn forage, 250 days (8.2 months) for field corn grain, and 260 days (8.5 months) for field corn stover. In addition, one forage from the GA trial (RAAEX010-02H) and one stover sample from the PA trial (RAAEX010-01H) were reanalyzed for tembotrione only, 490 to 512 days after the initial analysis; the maximum storage intervals of these samples were 665 days (21.9 months) for forage and 659 days (21.7 months) for stover. Results of the reanalyses were not significantly different from the original analyses; therefore, stability may be inferred for the additional storage interval. The submitted storage stability data on field corn RAC commodities (refer to 860.1380 DER for MRID 46695601) indicate that tembotrione, M2, M5, and M6 residues are stable (<30% decomposition) during frozen storage for at least 13 months prior to analysis with one exception. Residues of M5 in grain showed some apparent degradation with time; however, based on the results of the corn metabolism studies with tembotrione, M5 is not found in significant amounts in grain (<0.010 ppm). Adequate storage stability data are available to support the storage conditions and intervals of samples from the field corn trials.

The analytical method (LC/MS/MS) was successfully validated for the analysis of tembotrione residue and its metabolites M2, M5, and M6 in/on various on plant matrices (Bayer CropScience Report No. 201098, see 860.1340 DER for MRID 46695537). Recoveries of tembotrione, M6,

M5, and M2 from field corn matrices were measured concurrently with each set of samples to verify method performance. The concurrent recovery data are summarized in Table C.1. The data demonstrate acceptable method performance during sample analysis. Recoveries from field corn forage, grain, and stover controls fortified with tembotrione, M6, M5 or M2 at 0.01-1.0 ppm ranged from 70% to 123%, except for a few forage, grain and stover samples which had recoveries of M6, M5, and/or M2 at 58-69%. Apparent residues of all analytes were each nonquantifiable in/on all untreated corn forage, grain, and stover samples, except two forage and two stover samples which bore residues of the metabolites at 0.01-0.02 ppm (M2, M5, and/or M6 in forage; M2 in stover). The duplicate sample or re-analysis of these samples resulted in nonquantifiable residues, and the average residue was reported.

Individual and total tembotrione residues found in treated field corn forage, grain, and stover samples are presented in Tables C.3.1 through C.3.3, respectively. Total residues in field corn matrices are summarized in Table C.4. Following Treatment A [two foliar applications of the SC formulation totaling 0.161-0.170 lb ai/A (0.180-0.191 kg ai/ha)], the sum of residues (parent + M5 + M6 + M2, as parent equivalents) as determined by the data collection method were <0.052-<0.471 ppm in/on 42 samples of field corn forage, below the combined LOQ (<0.04 ppm) to <0.155 ppm in/on 42 samples of field corn grain, and <0.04-<0.554 ppm in/on 42 samples of field corn stover. Following Treatment B [one foliar application and one directed-spray application of the SC formulation totaling 0.164-0.174 lb ai/A (0.184-0.195 kg ai/ha)], the sum of parent + M5 + M6 + M2 residues were <0.077-<0.322 ppm in/on 42 samples of field corn forage, <0.04-<0.144 ppm in/on 42 samples of field corn grain, and <0.04-<0.525 ppm in/on 42 samples of field corn stover.

Following Treatment A, the sum of parent + M5 were <0.032-<0.375 ppm in/on 42 samples of field corn forage, below the combined LOQ (<0.02 ppm) to <0.022 ppm in/on 42 samples of field corn grain, and <0.02-<0.450 ppm in/on 42 samples of field corn stover. Following Treatment B, the sum of parent + M5 residues were <0.056-<0.290 ppm in/on 42 samples of field corn forage, <0.02-<0.025 ppm in/on 42 samples of field corn grain, and <0.02-<0.445 ppm in/on 42 samples of field corn stover.

Overall, the maximum residues of M5 were 0.860 ppm in/on field corn forage, <0.01 ppm in/on field corn grain, and 0.440 ppm in/on field corn stover; maximum residues of M6 were 0.148 ppm in/on field corn forage, 0.125 ppm in/on field corn grain, and 0.129 ppm in/on field corn stover; and maximum residues of M2 were 0.023 ppm in/on field corn forage, <0.01 ppm in/on field corn grain, and 0.042 ppm in/on field corn stover.

Based on the results of the side-by-side field trials, residues were similar in/on field corn matrices treated with two foliar applications or treated with one foliar + one directed-spray application. Residues of the parent were nonquantifiable in all field corn matrices from both treatment regimes.

Based on the two residue decline trials, total tembotrione residues do not appear to decline in stover with later sampling intervals, and residue levels in forage were inconsistent, therefore no conclusion could be made. Total residues in grain were near or below the LOQ at all sampling intervals.

The results of the bridging studies, conducted with different spray adjuvant mixtures, indicate that overall the combination of spray adjuvants used had no significant impact on the residue levels in the treated corn matrices. Similar total tembotrione residues were observed between Treatment A (MSO+UAN) and Treatments C (COC+UAN), D (MSO+AMS), or E (COC+AMS) for all field corn matrices. However, it is noted that two trials (Stillwell, KS & Tifton, GA) had low residues in forage and stover with all Treatments, which explains why the overall residue maximums differed significantly between Treatment A and Treatments C, D, and E in Table C.4.

TABLE C.1. Summary of Concurrent Recoveries of Tembotrione, M5, M6, and M2 from Field Corn Forage, Grain, and Stover.

Matrix	Analyte	Spike Level (ppm)	Sample Size (n)	Recoveries (%)	Mean Recovery (%)± std dev[1]
Forage	Tembotrione	0.01	6	73, 73, 80, 88, 91, 96	83 ± 9.6
		0.02	4	70, 83, 90, 101	86 ± 12.7
		0.05	10	77, 84, 88, 89, 92, 93, 96, 102, 106, 107	94 ± 9.7
		0.10	2	90, 103	97
		0.20	3	81, 97, 99	92 ± 9.8
		0.25	1	98	98
		0.50	5	75, 88, 90, 92, 95	88 ± 7.5
	AE 0456148 (M6)	0.01	7	78, 84, 85, 89, 94, 103, 111	92 ± 11.4
		0.02	3	75, 88, 98	87 ± 11.6
		0.05	10	64, 82, 93, 95, 96, 102, 103, 105, 106, 111	95 ± 13.7
		0.10	2	107, 117	112
		0.20	3	78, 106, 111	98 ± 17.4
		0.25	1	105	105
		0.50	5	75, 77, 97, 98, 103	90 ± 13.0
	AE 1417268 (M5)	0.01	5	76, 79, 96, 100, 112	93 ± 15.2
		0.02	3	91, 93, 94	93 ± 1.4
		0.05	8	69, 85, 100, 107, 107, 110, 117, 120	102 ± 16.9
		0.10	2	85, 107	96
		0.20	3	80, 83, 91	85 ± 5.5
		0.25	1	70	70
		0.50	3	61, 75, 102	80 ± 20.9
	AE 1392936 (M2)	0.01	7	58, 85, 86, 86, 90, 90, 96	84 ± 12.3
		0.02	4	72, 90, 90, 96	87 ± 10.4
		0.05	8	71, 94, 98, 100, 103, 105, 116, 117	101 ± 14.4
		0.10	2	99, 101	100
		0.20	1	103	103
		0.25	1	94	94
		0.50	5	89, 99, 99, 110, 112	102 ± 8.7
		1.00	1	103	103
Grain	Tembotrione	0.01	5	73, 79, 80, 82, 93	81 ± 7.3
		0.02	1	89	89
		0.05	7	77, 80, 83, 85, 89, 93, 98	86 ± 7.5
		0.10	2	76, 89	82
		0.20	3	91, 92, 103	95 ± 6.9

TABLE C.1. Summary of Concurrent Recoveries of Tembotrione, M5, M6, and M2 from Field Corn Forage, Grain, and Stover.

Matrix	Analyte	Spike Level (ppm)	Sample Size (n)	Recoveries (%)	Mean Recovery (%)± std dev[1]
		0.50	2	78, 79	78
		1.00	9	100, 100, 101, 102, 102, 104, 104, 105, 105	103 ± 2.1
	AE 0456148 (M6)	0.01	6	73, 75, 88, 94, 95, 103	88 ± 11.8
		0.05	7	92, 97, 104, 104, 106, 109, 116	104 ± 8.1
		0.10	2	82, 102	92
		0.20	3	95, 101, 108	101 ± 6.4
		0.50	2	89, 97	93
		1.00	9	97, 98, 101, 106, 106, 107, 107, 108, 113	105 ± 5.2
	AE 1417268 (M5)	0.01	6	72, 72, 72, 86, 101, 115	86 ± 18.3
		0.05	7	77, 87, 95, 111, 118, 119, 120	104 ± 17.3
		0.10	2	71, 84	77
		0.20	3	71, 72, 88	77 ± 9.6
		0.50	2	66, 72	69
		1.00	9	82, 85, 87, 88, 88, 88, 89, 89, 95	88 ± 3.6
	AE 1392936 (M2)	0.01	5	69, 71, 98, 99, 105	89 ± 17.1
		0.05	7	78, 91, 93, 96, 97, 100, 103	94 ± 8.2
		0.10	3	78, 93, 102	91 ± 12.3
		0.20	2	85, 94	90
		0.50	2	93, 105	99
Stover	Tembotrione	0.01	6	71, 72, 73, 75, 77, 78	75 ± 2.7
		0.02	1	89	89
		0.05	7	90, 90, 91, 93, 95, 100, 101	94 ± 4.7
		0.10	5	72, 77, 96, 97, 99	88 ± 12.6
		0.20	2	93, 94	93
		0.25	1	97	97
		0.30	1	94	94
		0.50	1	100	100
		1.00	1	81	81
	AE 0456148 (M6)	0.01	7	73, 77, 85, 79, 99, 112, 117	92 ± 17.7
		0.05	9	81, 85, 86, 93, 98, 99, 107, 110, 121	98 ± 13.0
		0.10	5	71, 83, 91, 104, 104	91 ± 14.1
		0.20	1	92	92
		0.25	1	108	108
		0.30	1	84	84
		0.50	1	109	109
		1.00	1	72	72
	AE 1417268 (M5)	0.01	6	70, 72, 84, 92, 99, 105	87 ± 14.0
		0.02	2	114, 120	117
		0.05	8	87, 91, 94, 105, 110, 115, 119, 123	106 ± 13.0
		0.10	5	75, 77, 79, 91, 116	88 ± 17.1
		0.20	2	81, 86	83
		0.25	1	72	72
		0.30	1	114	114

TABLE C.1. Summary of Concurrent Recoveries of Tembotrione, M5, M6, and M2 from Field Corn Forage, Grain, and Stover.

Matrix	Analyte	Spike Level (ppm)	Sample Size (n)	Recoveries (%)	Mean Recovery (%)± std dev[1]
		0.50	1	72	72
		1.00	1	65	65
	AE 1392936 (M2)	0.01	7	70, 74, 89, 92, 108, 117, 122	96 ± 20.4
		0.02	2	71, 77	74
		0.05	7	87, 91, 101, 102, 108, 108, 111	101 ± 9.1
		0.10	5	81, 88, 92, 100, 101	93 ± 8.4
		0.20	1	88	88
		0.25	1	100	100
		0.50	2	90, 101	95
		1.00	1	86	86

[1] The standard deviation is not applicable for a sample size (n) of less than three.

TABLE C.2. Summary of Storage Conditions for Field Corn.

Residue Components	Matrix (RAC or Extract)	Storage Temp. (°C)[1]	Actual Storage Duration[2]	Interval of Demonstrated Storage Stability[3]
Tembotrione AE 0456148 (M6) AE 1417268 (M5) AE 1392936 (M2)	Forage	< -15	118 – 283 days / 665 days[4] (3.9-9.3 months / 21.9 months)	Tembotrione, M6, and M2 are stable for up to 12-13 months in frozen field corn grain, forage, and fodder. M5 is stable in frozen field corn forage and fodder for up to 12 months. M5 is stable in frozen field corn grain for up to 188 days but declined by 17% after 371 days (61% average corrected recovery).
Tembotrione AE 0456148 (M6) AE 1417268 (M5) AE 1392936 (M2)	Grain	< -15	84-250 days (2.8-8.2 months)	
Tembotrione AE 0456148 (M6) AE 1417268 (M5) AE 1392936 (M2)	Stover	< -15	119-260 days / 659 days[4] (3.9-8.5 months/ 21.7 months)	

[1] Storage temperature = storage temperature from receipt at Bayer CropScience through the last sample extraction.
[2] Actual study duration = time from field sampling through the last sample analyses. Samples were analyzed within 1-9 days of extraction.
[3] Field corn storage stability data; refer to the 860.1380 DER for MRID 46695601.
[4] The analytical portion of the study was originally completed in June, 2004; however, one forage and one stover sample were reanalyzed in June 2005. The first number comprises study duration for initial analyses of all samples; the second number for the two samples reanalyzed in June, 2005.

TABLE C.3.1. Residue Data from Field Corn Forage Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX010-) Year	Treatment Pattern[1]	Crop; Variety	Commodity (% Dry Matter)	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Germansville, PA Zone 1 01H 2003	A	Field Corn; Doeblers 609XRR	Forage (24)	0.170 (0.191)	44	<LOD + 0.248 + 0.034 + *0.008* = 0.291 **(<0.302)** <LOD + 0.226 + 0.032 + *0.007* = 0.266 **(<0.278)**	<LOD + 0.248 = 0.249 **(<0.258)** <LOD + 0.226 = 0.227 **(<0.236)**
	B	Field Corn; Doeblers 609XRR	Forage (26)	0.171 (0.193)	46	<LOD + 0.210 + 0.031 + *0.008* = 0.250 **(<0.261)** <LOD + 0.236 + 0.029 + *0.007* = 0.273 **(<0.285)**	<LOD + 0.210 = 0.211 **(<0.220)** <LOD + 0.236 = 0.237 **(<0.246)**
Tifton, GA Zone 2 02H 2003	A	Field Corn; Pioneer 31G98	Forage (26)	0.165 (0.185)	45	<LOD + 0.033 + *0.007* + <LOD = 0.043 **(<0.063)** <LOD +0.051 + *0.006* + <LOD = 0.060 **(<0.081)**	<LOD + 0.033 = 0.034 **(<0.043)** <LOD +0.051 = 0.052 **(<0.061)**
	B	Field Corn; Pioneer 31G98	Forage (31)	0.164 (0.184)	45	<LOD + 0.050 + 0.015 + <LOD = 0.068 **(<0.085)** <LOD + 0.047 + 0.010 + <LOD = 0.060 **(<0.077)**	<LOD + 0.050 = 0.051 **(<0.060)** <LOD + 0.047 = 0.048 **(<0.057)**
	C	Field Corn; Pioneer 31G98	Forage (28)	0.164 (0.184)	45	<LOD + 0.036 + *0.003* + <LOD = 0.042 **(<0.066)** <LOD + *0.025* + *0.003* + <LOD = 0.031 **(<0.055)**	<LOD + 0.036 = 0.037 **(<0.046)** <LOD + *0.025* = 0.026 **(<0.035)**
	D	Field Corn; Pioneer 31G98	Forage (23)	0.164 (0.184)	45	<LOD + 0.028 + *0.006* + <LOD = 0.037 **(<0.058)** <LOD + 0.040 + *0.004* + <LOD = 0.047 **(<0.070)**	<LOD + 0.028 = 0.029 **(<0.038)** <LOD + 0.040 = 0.041 **(<0.050)**

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TABLE C.3.1. Residue Data from Field Corn Forage Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX010-) Year	Treatment Pattern[1]	Crop; Variety	Commodity (% Dry Matter)	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Bagley, IA Zone 5 03H 2003	A	Field Corn; 34M95	Forage (32)	0.164 (0.184)	46	<LOD + 0.123 +0.022 + <LOD = 0.148 (**<0.165**) <LOD + 0.084 + 0.012 + <LOD = 0.099 (**<0.116**)	<LOD + 0.123 = 0.124 (**<0.133**) <LOD + 0.084 = 0.085 (**<0.094**)
	B	Field Corn; 34M95	Forage (32)	0.166 (0.186)	45	<LOD + 0.136 + 0.022 + <LOD = 0.161 (**<0.178**) <LOD + 0.138 + 0.020 + <LOD = 0.161(**<0.178**)	<LOD + 0.136 = 0.137 (**<0.146**) <LOD + 0.138 = 0.139 (**<0.148**)
	C	Field Corn; 34M95	Forage (31)	0.166 (0.187)	46	<LOD + 0.076 + 0.014 + <LOD = 0.093 (**<0.110**) <LOD + 0.042 + 0.010 + <LOD = 0.055 (**<0.072**)	<LOD + 0.076 = 0.077 (**<0.086**) <LOD + 0.042 = 0.043 (**<0.052**)
	D	Field Corn; 34M95	Forage (25)	0.167 (0.187)	46	<LOD + 0.114 + *0.008* + <LOD = 0.125 (**<0.144**) <LOD + 0.097 + *0.008* + <LOD = 0.108 (**<0.127**)	<LOD + 0.114 = 0.115 (**<0.124**) <LOD + 0.097 = 0.098 (**<0.107**)
Campbell, MN Zone 5 04H 2003	A	Field Corn; Dekalb 39-47	Forage (33)	0.165 (0.185)	53	<LOD + 0.346 + 0.023 + <LOD = 0.372 (**<0.389**) <LOD + 0.305 + 0.022 + <LOD = 0.330 (**<0.347**)	<LOD + 0.346 = 0.347 (**<0.356**) <LOD + 0.305 = 0.306 (**<0.315**)
	B	Field Corn; Dekalb 39-47	Forage (34)	0.164 (0.184)	45	<LOD + 0.280 + 0.022 + <LOD = 0.305 (**<0.322**) <LOD + 0.243 + 0.024 + <LOD = 0.270 (**<0.287**)	<LOD + 0.280 = 0.281 (**<0.290**) <LOD + 0.243 = 0.244 (**<0.253**)

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TABLE C.3.1. Residue Data from Field Corn Forage Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX010-) Year	Treatment Pattern[1]	Crop; Variety	Commodity (% Dry Matter)	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm *in parent equivalents*)	Sum of Parent + M5 = Total[2] (ppm *in parent equivalents*)
Ellendale, MN Zone 5 05H 2003	A	Field Corn; Pioneer 3730	Forage (27)	0.164 (0.184)	44	<LOD + 0.181 + 0.016 + <LOD = 0.200 **(<0.217)** <LOD + 0.189 +0.021 + <LOD = 0.213 **(<0.230)**	<LOD + 0.181 = 0.182 **(<0.191)** <LOD + 0.189 = 0.190 **(<0.199)**
	B	Field Corn; Pioneer 3730	Forage (31)	0.165 (0.185)	45	<LOD + 0.208 + 0.020 + <LOD = 0.231 **(<0.248)** <LOD + 0.185 + 0.018 + <LOD = 0.206 **(<0.223)**	<LOD + 0.208 = 0.209 **(<0.218)** <LOD + 0.185 = 0.186 **(<0.195)**
Arkansaw, WI Zone 5 06H 2003	A	Field Corn; Dekalb DKC46-26	Forage (26)	0.165 (0.185)	46	<LOD + 0.132 + 0.034 + <LOD = 0.169 **(<0.186)** <LOD + 0.121 + 0.033 + <LOD = 0.157 **(<0.174)**	<LOD + 0.132 = 0.133 **(<0.142)** <LOD + 0.121 = 0.122 **(<0.131)**
	B	Field Corn; Dekalb DKC46-26	Forage (26)	0.166 (0.186)	45	<LOD + 0.073 + 0.036 + <LOD = 0.112 **(<0.129)** <LOD + 0.144 + 0.031 + <LOD = 0.178 **(<0.195)**	<LOD + 0.073 = 0.074 **(<0.083)** <LOD + 0.144 = 0.145 **(<0.154)**
Britton, SD Zone 5 07H 2003	A	Field Corn; Dekalb DK493	Forage (29)	0.168 (0.188)	46	<LOD + 0.078 + 0.018 + <LOD = 0.099 **(<0.116)** <LOD + 0.061 + 0.017 + <LOD = 0.081 **(<0.098)**	<LOD + 0.078 = 0.079 **(<0.088)** <LOD + 0.061 = 0.062 **(<0.071)**
	B	Field Corn; Dekalb DK493	Forage (30)	0.166 (0.186)	45	<LOD + 0.112 + 0.031 + <LOD = 0.146 **(<0.163)** <LOD + 0.108 + 0.029 + <LOD = 0.140 **(<0.157)**	<LOD + 0.112 = 0.113 **(<0.122)** <LOD + 0.108 = 0.109 **(<0.118)**

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TABLE C.3.1. Residue Data from Field Corn Forage Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX010-) Year	Treatment Pattern[1]	Crop; Variety	Commodity (% Dry Matter)	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: *Parent + M5 + M6 + M2 = Total*[2] (ppm in parent equivalents)	*Sum of Parent + M5 = Total*[2] (ppm in parent equivalents)
Springfield, NE Zone 5 08H 2003	A	Field Corn; Asgrow 741RR	Forage (25)	0.164 (0.184)	45	<LOD + 0.041 + *0.002* + <LOD = 0.046 **(<0.071)** <LOD + 0.057 + <LOD + <LOD = 0.062 **(<0.087)**	<LOD + 0.041 = 0.042 **(<0.051)** <LOD + 0.057 = 0.058 **(<0.067)**
	B	Field Corn; Asgrow 741RR	Forage (26)	0.164 (0.184)	45	<LOD + 0.133 + 0.014 + <LOD = 0.150 **(<0.167)** <LOD + 0.127 + 0.016 + <LOD = 0.146 **(<0.163)**	<LOD + 0.133 = 0.134 **(<0.143)** <LOD + 0.127 = 0.128 **(<0.137)**
	C	Field Corn; Asgrow 741RR	Forage (26)	0.164 (0.184)	45	<LOD + 0.020 + <LOD + <LOD = 0.025 **(<0.050)** <LOD + 0.020 + *0.002* + <LOD = 0.025 **(<0.050)**	<LOD + 0.020 = 0.021 **(<0.030)** <LOD + 0.020 = 0.021 **(<0.030)**
	D	Field Corn; Asgrow 741RR	Forage (25)	0.164 (0.184)	45	<LOD + 0.074 + *0.002* + <LOD = 0.079 **(<0.104)** <LOD + 0.057 + *0.003* + <LOD = 0.063 **(<0.087)**	<LOD + 0.074 =0.075 **(<0.084)** <LOD + 0.057 = 0.058 **(<0.067)**
York, NE Zone 5 09H 2003	A	Field Corn; DKC64-10RR	Forage (30)	0.166 (0.186)	51	<LOD + 0.224 + 0.022 + *0.003* = 0.250 **(<0.266)** <LOD + 0.185 + 0.026 + *0.002* = 0.214 **(<0.231)**	<LOD + 0.224 = 0.225 **(<0.234)** <LOD + 0.185 = 0.186 **(<0.195)**
	B	Field Corn; DKC64-10RR	Forage (31)	0.165 (0.185)	44	<LOD + 0.134 + 0.021 + <LOD = 0.158 **(<0.175)** <LOD + 0.221 + 0.028 + *0.003* = 0.253 **(<0.269)**	<LOD + 0.134 = 0.135 **(<0.144)** <LOD + 0.221 = 0.222 **(<0.231)**

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TABLE C.3.1. Residue Data from Field Corn Forage Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX010-) Year	Treatment Pattern[1]	Crop; Variety	Commodity (% Dry Matter)	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Richland, IA Zone 5 10H 2003	A	Field Corn; Pioneer 33G28	Forage (32)	0.164 (0.184)	50	<LOD + 0.196 + 0.018 + <LOD = 0.217 **(<0.234)** <LOD + 0.039 + 0.014 + <LOD = 0.056 **(<0.073)**	<LOD + 0.196 = 0.197 **(<0.206)** <LOD + 0.039 = 0.040 **(<0.049)**
	B	Field Corn; Pioneer 33G28	Forage (37)	0.169 (0.189)	44	<LOD + 0.208 + 0.031 + <LOD = 0.242 **(<0.259)** <LOD + 0.267 + 0.019 + <LOD = 0.289 **(<0.306)**	<LOD + 0.208 = 0.209 **(<0.218)** <LOD + 0.267 = 0.268 **(<0.277)**
Cunningham, KS Zone 5 11H 2003	A	Field Corn; 31A13	Forage (28)	0.167 (0.187)	44	*0.004* + 0.074 + 0.011 + *0.007* = 0.096 **(<0.105)** <LOD + 0.089 + 0.013 + *0.006* = 0.109 **(<0.122)**	*0.004* + 0.074 = 0.078 **(<0.084)** <LOD + 0.089 = 0.090 **(<0.099)**
	B	Field Corn; 31A13	Forage (32)	0.167 (0.187)	46	<LOD + 0.059 + *0.007* + *0.006* = 0.073 **(<0.089)** *0.005* + 0.064 + *0.008* + *0.006* = 0.083 **(<0.094)**	<LOD + 0.059 = 0.060 **(<0.069)** *0.005* + 0.064 = 0.069 **(<0.074)**
Carlyle, IL Zone 5 13H 2003	A	Field Corn; Burrus BX	Forage (27)	0.164 (0.184)	44	*0.006* + 0.142 + 0.019 + *0.008* = 0.175 **(<0.181)** *0.005* + 0.221 + 0.021 + *0.009* = 0.256 **(<0.262)**	*0.006* + 0.142 = 0.148 **(<0.152)** *0.005* + 0.221 = 0.226 **(<0.231)**
	B	Field Corn; Burrus BX	Forage (36)	0.165 (0.185)	45	*0.004* + 0.046 + 0.036 + *0.007* = 0.093 **(<0.102)** *0.007* + 0.062 + 0.039 + *0.007* = 0.115 **(<0.121)**	*0.004* + 0.046 = 0.050 **(<0.056)** *0.007* + 0.062 = 0.069 **(<0.072)**

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TABLE C.3.1. Residue Data from Field Corn Forage Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX010-) Year	Treatment Pattern[1]	Crop; Variety	Commodity (% Dry Matter)	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: *Parent + M5 + M6 + M2 = Total*[2] (ppm in parent equivalents)	*Sum of Parent + M5 = Total*[2] (ppm in parent equivalents)
Oxford, IN Zone 5 14H 2003	A	Field Corn; Beeks 5283Bt	Forage (28)	0.168 (0.188)	45	<LOD + 0.206 + 0.020 + <LOD = 0.229 (**<0.246**) <LOD + 0.239 + 0.015 + <LOD = 0.257 (**<0.274**)	<LOD + 0.206 = 0.207 (**<0.216**) <LOD + 0.239 = 0.240 (**<0.249**)
	B	Field Corn; Beeks 5283Bt	Forage (23)	0.169 (0.189)	45	<LOD + 0.179 + 0.016 + <LOD = 0.198 (**<0.215**) <LOD + 0.183 + 0.024 + <LOD = 0.210 (**<0.227**)	<LOD + 0.179 = 0.180 (**<0.189**) <LOD + 0.183 = 0.184 (**<0.193**)
	C	Field Corn; Becks 5283Bt	Forage (31)	0.168 (0.188)	45	<LOD + 0.205 + 0.017 + <LOD = 0.225 (**<0.242**) <LOD + 0.124 + *0.009* + <LOD = 0.136 (**<0.154**)	<LOD + 0.205 = 0.206 (**<0.215**) <LOD + 0.124 = 0.125 (**<0.134**)
	E	Field Corn; Beeks 5283Bt	Forage (31)	0.169 (0.189)	45	<LOD + 0.112 + 0.011 + <LOD = 0.126 (**<0.143**) <LOD + 0.154 + 0.013 + <LOD = 0.170 (**<0.187**)	<LOD + 0.112 = 0.113 (**<0.122**) <LOD + 0.154 = 0.155 (**<0.164**)
Noblesville, IN Zone 5 15H 2003	A	Field Corn; Becks 5322	Forage (30)	0.165 (0.185)	44	<LOD + 0.138 + 0.020 + *0.004* = 0.163 (**<0.178**) <LOD + 0.102 + 0.017 + <LOD = 0.122 (**<0.139**)	<LOD + 0.138 = 0.139 (**<0.148**) <LOD + 0.102 = 0.103 (**<0.112**)
	B	Field Corn; Becks 5322	Forage (23)	0.165 (0.185)	44	<LOD + 0.047 + 0.016 + <LOD = 0.066 (**<0.083**) <LOD + 0.060 + 0.015 + <LOD = 0.078 (**<0.095**)	<LOD + 0.047 = 0.048 (**<0.057**) <LOD + 0.060 = 0.061 (**<0.070**)

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TABLE C.3.1. Residue Data from Field Corn Forage Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX010-) Year	Treatment Pattern[1]	Crop; Variety	Commodity (% Dry Matter)	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
New Holland, OH Zone 5 16H 2003	A	Field Corn; Crows 8626R	Forage (34)	0.170 (0.190)	45	<LOD + 0.091 + 0.039 + <LOD = 0.133 (**<0.150**) <LOD + 0.148 + 0.036 + <LOD = 0.187 (**<0.204**)	<LOD + 0.091 = 0.092 (**<0.101**) <LOD + 0.148 = 0.149 (**<0.158**)
	B	Field Corn; Crows 8626R	Forage (41)	0.168 (0.188)	48	<LOD + 0.130 + 0.056 + *0.002* = 0.189 (**<0.206**) <LOD + 0.099 + 0.056 + <LOD = 0.158 (**<0.175**)	<LOD + 0.130 = 0.131 (**<0.140**) <LOD + 0.099 = 0.100 (**<0.109**)
Hudson, KS Zone 5 18H 2003	A	Field Corn; 32M38	Forage (23)	0.163 (0.183)	46	<LOD + 0.070 + 0.028 + *0.009* = 0.108 (**<0.118**) <LOD + 0.065 + 0.019 + *0.006* = 0.091 (**<0.104**)	<LOD + 0.070 = 0.071 (**<0.080**) <LOD + 0.065 = 0.066 (**<0.075**)
	B	Field Corn; 32M38	Forage (29)	0.163 (0.183)	44	<LOD + 0.115 + 0.029 + *0.008* = 0.153 (**<0.164**) <LOD + 0.084 + 0.025 + *0.008* = 0.118 (**<0.129**)	<LOD + 0.115 = 0.116 (**<0.125**) <LOD + 0.084 = 0.085 (**<0.094**)
Clarence, MO Zone 5 19H 2003	A	Field Corn; Pioneer 3B23	Forage (27)	0.165 (0.185)	45	<LOD + 0.053 + 0.012 + *0.003* = 0.069 (**<0.085**) <LOD + 0.098 + 0.013 + *0.005* = 0.117 (**<0.131**)	<LOD + 0.053 = 0.054 (**<0.063**) <LOD + 0.098 = 0.099 (**<0.108**)
	B	Field Corn; Pioneer 3B23	Forage (36)	0.166 (0.186)	45	<LOD + 0.147 + 0.043 + *0.002* = 0.193 (**<0.210**) <LOD + 0.103 + 0.042 + *0.002* = 0.148 (**<0.165**)	<LOD + 0.147 = 0.148 (**<0.157**) <LOD + 0.103 = 0.104 (**<0.113**)

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TABLE C.3.1. Residue Data from Field Corn Forage Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX010-) Year	Treatment Pattern[1]	Crop; Variety	Commodity (% Dry Matter)	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (*ppm in parent equivalents*)	Sum of Parent + M5 = Total[2] (*ppm in parent equivalents*)
Dexter, MO Zone 5 20H 2003	A	Field Corn; Pioneer 3394	Forage (40)	0.164 (0.184)	46	<LOD + 0.318 + 0.101 + *0.008* = 0.428 **(<0.439)** <LOD + 0.346 + 0.105 + *0.008* = 0.460 **(<0.471)**	<LOD + 0.318 = 0.319 **(<0.328)** <LOD + 0.346 = 0.347 **(<0.356)**
	B	Field Corn; Pioneer 3394	Forage (39)	0.165 (0.185)	46	<LOD + 0.100 + 0.048 + *0.006* = 0.155 **(<0.168)** <LOD + 0.093 + 0.036 + <LOD = 0.132 **(<0.149)**	<LOD + 0.100 = 0.101 **(<0.110)** <LOD + 0.093 = 0.094 **(<0.103)**
East Bernard, TX Zone 6 21H 2003	A	Field Corn; Golden Acres 2850 R	Forage (37)	0.164 (0.184)	45	<LOD + 0.150 + 0.059 + *0.008* = 0.218 **(<0.229)** <LOD + 0.163 + 0.092 + *0.009* = 0.265 **(<0.275)**	<LOD + 0.150 = 0.151 **(<0.160)** <LOD + 0.163 = 0.164 **(<0.173)**
	B	Field Corn; Golden Acres 2850 RR	Forage (48)	0.166 (0.186)	45	<LOD + 0.129 + 0.079 + *0.009* = 0.218 **(<0.228)** <LOD + 0.109 + 0.071 + *0.008* = 0.189 **(<0.200)**	<LOD + 0.129 = 0.130 **(<0.139)** <LOD + 0.109 = 0.110 **(<0.119)**

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TABLE C.3.1. Residue Data from Field Corn Forage Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX010-) Year	Treatment Pattern[1]	Crop; Variety	Commodity (% Dry Matter)	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Seymore, IL Zone 5 12D 2003	A	Field Corn; Pioneer 33G28	Forage (19)	0.166 (0.186)	35	<LOD + 0.018 + *0.006* + 0.023 = 0.048 **(<0.061)** <LOD + 0.078 + *0.008* + *0.004* = 0.091 **(<0.108)**	<LOD + 0.018 = 0.019 **(<0.028)** <LOD + 0.078 = 0.079 **(<0.088)**
			Forage (23)		40	<LOD + 0.133 + 0.010 + 0.020 = 0.164 **(<0.173)** <LOD + 0.060 + *0.008* + 0.015 = 0.084 **(<0.095)**	<LOD + 0.133 = 0.134 **(<0.143)** <LOD + 0.060 = 0.061 **(<0.070)**
			Forage (24)		45	<LOD + 0.064 + 0.010 + *0.002* = 0.077 **(<0.094)** <LOD + 0.022 + *0.008* + *0.003* = 0.034 **(<0.052)**	<LOD + 0.064 = 0.065 **(<0.074)** <LOD + 0.022 = 0.023 **(<0.032)**
			Forage (29)		50	<LOD + 0.075 + 0.015 + <LOD = 0.093 **(<0.110)** <LOD +0.113 + 0.022 + <LOD = 0.138 **(<0.155)**	<LOD + 0.075 = 0.076 **(<0.085)** <LOD + 0.113 = 0.114 **(<0.123)**
			Forage (33)		55	<LOD + 0.088 + 0.022 + <LOD = 0.113 **(<0.130)** <LOD + 0.107 + 0.020 + <LOD = 0.130 **(<0.147)**	<LOD + 0.088 = 0.089 **(<0.098)** <LOD + 0.107 = 0.108 **(<0.117)**

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TABLE C.3.1. Residue Data from Field Corn Forage Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX010-) Year	Treatment Pattern[1]	Crop; Variety	Commodity (% Dry Matter)	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Seymore, IL (continued)	B	Field Corn; Pioneer 33G28	Forage (23)	0.165 (0.185)	35	<LOD + 0.084 + *0.008* + <LOD = 0.095 **(<0.114)** <LOD + 0.120 + 0.010 + *0.003* = 0.134 **(<0.150)**	<LOD + 0.084 = 0.085 **(<0.094)** <LOD + 0.120 = 0.121 **(<0.130)**
			Forage (26)		41	<LOD + 0.071 + 0.010 + *0.005* = 0.087 **(<0.101)** <LOD + 0.071 + 0.010 + <LOD = 0.084 **(<0.101)**	<LOD + 0.071 = 0.072 **(<0.081)** <LOD + 0.071 = 0.072 **(<0.081)**
			Forage (30)		45	<LOD + 0.077 + 0.014 + *0.006* = 0.098 **(<0.111)** <LOD + 0.073 + 0.014 + *0.007* = 0.095 **(<0.107)**	<LOD + 0.077 = 0.078 **(<0.087)** <LOD + 0.073 = 0.074 **(<0.083)**
			Forage (36)		50	<LOD + 0.145 + 0.030 + *0.002* = 0.178 **(<0.195)** <LOD + 0.143 + 0.026 + <LOD = 0.172 **(<0.189)**	<LOD + 0.145 = 0.146 **(<0.155)** <LOD + 0.143 = 0.144 **(<0.153)**
			Forage (41)		56	<LOD + 0.055 + 0.017 + <LOD = 0.075 **(<0.092)** <LOD + 0.064 + 0.024 + <LOD = 0.091 **(<0.108)**	<LOD + 0.055 = 0.056 **(<0.065)** <LOD + 0.064 = 0.065 **(<0.074)**
	C	Field Corn; Pioneer 33G28	Forage (22)	0.163 (0.183)	45	<LOD + 0.049 + *0.006* + <LOD = 0.058 **(<0.079)** <LOD + 0.063 + *0.008* + <LOD = 0.074 **(<0.093)**	<LOD + 0.049 = 0.050 **(<0.059)** <LOD + 0.063 = 0.064 **(<0.073)**

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TABLE C.3.1. Residue Data from Field Corn Forage Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX010-) Year	Treatment Pattern[1]	Crop; Variety	Commodity (% Dry Matter)	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Seymore, IL (continued)	E	Field Corn; Pioneer 33G28	Forage (22)	0.164 (0.184)	45	<LOD + 0.042 + *0.006* + <LOD = 0.051 **(<0.072)** <LOD + 0.028 + *0.005* + 0.011 = 0.045 **(<0.059)**	<LOD + 0.042 = 0.043 **(<0.052)** <LOD + 0.028 = 0.029 **(<0.038)**
Stilwell, KS Zone 5 17D 2003	A	Field Corn; Pioneer 33G26	Forage (22)	0.161 (0.180)	35	<LOD + 0.212 + 0.018 + *0.003* = 0.234 **(<0.250)** <LOD + 0.284 + 0.027 + *0.005* = 0.317 **(<0.331)**	<LOD + 0.212 = 0.213 **(<0.222)** <LOD + 0.284 =0.285 **(<0.294)**
			Forage (27)		39	<LOD + 0.416 + 0.031 + *0.005* = 0.453 **(<0.467)** <LOD + 0.383 + 0.048 + 0.006 = 0.438 **(<0.451)**	<LOD + 0.416 = 0.417 **(<0.426)** <LOD + 0.383 = 0.384 **(<0.393)**
			Forage (29)		45	<LOD + 0.365 +0.052 + *0.005* = 0.423 **(<0.437)** <LOD + 0.269 + 0.031 + <LOD = 0.303 **(<0.320)**	<LOD + 0.365 = 0.366 **(<0.375)** <LOD + 0.269 = 0.270 **(<0.279)**
			Forage (37)		50	<LOD + 0.201 + 0.044 + <LOD = 0.248 **(<0.265)** <LOD + 0.201 + 0.032 +<LOD = 0.236 **(<0.253)**	<LOD + 0.201 = 0.202 **(<0.211)** <LOD + 0.201 = 0.202 **(<0.211)**
			Forage (43)		56	*0.003* + 0.185 + 0.138 + 0.013 = 0.339 **(<0.346)** *0.004* + 0.201 + 0.148 + 0.010 = 0.363 **(<0.369)**	*0.003* + 0.185 = 0.188 **(<0.195)** *0.004* + 0.201 = 0.205 **(<0.211)**

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TABLE C.3.1. Residue Data from Field Corn Forage Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX010-) Year	Treatment Pattern[1]	Crop; Variety	Commodity (% Dry Matter)	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Stilwell, KS (continued)	B	Field Corn; Pioneer 33G26	Forage (26)	0.174 (0.195)	35	<LOD + 0.581 + 0.069 + *0.007* = 0.658 **(<0.670)** <LOD + 0.797 + 0.061 + *0.005* = 0.864 **(<0.868)**	<LOD + 0.581 = 0.582 **(<0.591)** <LOD + 0.797 = 0.798 **(<0.807)**
			Forage (28)		39	<LOD + 0.467 + 0.041 + *0.005* = 0.514 **(<0.528)** <LOD + 0.860 + 0.089 + *0.005* = 0.955 **(<0.969)**	<LOD + 0.467 = 0.468 **(<0.477)** <LOD + 0.860 = 0.861 **(<0.870)**
			Forage (37)		44	<LOD + 0.175 + 0.044 + *0.007* = 0.227 **(<0.239)** <LOD + 0.195 + 0.040 + *0.006* = 0.242 **(<0.255)**	<LOD + 0.175 = 0.176 **(<0.185)** <LOD + 0.195 = 0.196 **(<0.205)**
			Forage (40)		50	<LOD + 0.257 + 0.075 + <LOD = 0.335 **(<0.352)** <LOD + 0.340 + 0.082 + <LOD = 0.0425 **(<0.442)**	<LOD + 0.257 = 0.258 **(<0.267)** <LOD + 0.340 = 0.341 **(<0.350)**
			Forage (43)		56	*0.004* + 0.021 + 0.049 + *0.007* = 0.081 **(<0.090)** *0.004* + 0.024 + 0.070 + *0.008* = 0.106 **(<0.114)**	*0.004* + 0.021 = 0.025 **(<0.031)** *0.004* + 0.024 = 0.028 **(<0.034)**
	C	Field Corn; Pioneer 33G26	Forage (29)	0.160 (0.180)	45	<LOD + 0.154 + 0.017 + <LOD = 0.174 **(<0.191)** <LOD + 0.197 + 0.018 + <LOD = 0.218 **(<0.235)**	<LOD + 0.154 = 0.155 **(<0.164)** <LOD + 0.197 = 0.198 **(<0.207)**

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TABLE C.3.1. Residue Data from Field Corn Forage Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX010-) Year	Treatment Pattern[1]	Crop; Variety	Commodity (% Dry Matter)	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Stilwell, KS (continued)	E	Field Corn; Pioneer 33G26	Forage (29)	0.170 (0.190)	45	<LOD + 0.166 + 0.018 + <LOD = 0.187 **(<0.204)** <LOD + 0.098 + *0.007* + <LOD = 0.108 **(<0.128)**	<LOD + 0.166 = 0.167 **(<0.176)** <LOD + 0.098 = 0.099 **(<0.108)**

[1] Treatment Pattern A: two foliar spray applications at 24-inch and 36-inch corn height, with adjuvants methylated seed oil (MSO) and urea ammonium nitrate (UAN)
Treatment Pattern B: One foliar spray application at 36-inch corn height and one directed-spray application one week later.
Treatment Pattern C: application at the same use pattern as Pattern A except adjuvants added were crop oil concentrate (COC) and UAN.
Treatment Pattern D: application at the same use pattern as Pattern A except adjuvants added were MSO and ammonium sulfate (AMS).
Treatment Pattern E: application at the same use pattern as Pattern A except adjuvants added were COC and AMS.
[2] The LOD values for tembotrione (parent), M5, M6, and M2 in field corn forage were 0.001 ppm, 0.002 ppm, 0.002 ppm, and 0.002 ppm, respectively. Residues below the LOQ (<0.01 ppm each analyte) but above the respective LOD are *italicized*. Total residues based on the LOQ of each analyte are **bolded** in parentheses.

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TABLE C.3.2. Residue Data from Field Corn Grain Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX010-) Year	Treatment Pattern[1]	Crop; Variety	Commodity	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Germansville, PA Zone 1 01H 2003	A	Field Corn; Doeblers 609XRR	Grain	0.170 (0.191)	108	<LOD + <LOD + 0.036 + <LOD = 0.042 **(<0.066)** <LOD + <LOD + 0.036 + <LOD = 0.042 **(<0.066)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**
	B	Field Corn; Doeblers 609XRR	Grain	0.171 (0.193)	102	<LOD + <LOD + 0.043 + <LOD = 0.049 **(<0.073)** <LOD + <LOD + 0.042 + <LOD = 0.048 **(<0.072)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**
Tifton, GA Zone 2 02H 2003	A	Field Corn; Pioneer 31G98	Grain	0.165 (0.185)	107	<LOD + <LOD + <LOD + *0.004* = 0.011 **(<0.04)** <LOD + <LOD + *0.004* + *0.004* = 0.012 **(<0.04)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**
	B	Field Corn; Pioneer 31G98	Grain	0.164 (0.184)	100	<LOD + <LOD + *0.005* + *0.002* = 0.011 **(<0.04)** <LOD + <LOD + 0.010 + *0.003* = 0.017 **(<0.04)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**
	C	Field Corn; Pioneer 31G98	Grain	0.164 (0.184)	107	<LOD + <LOD + <LOD + *0.002* = 0.009 **(<0.04)** <LOD + <LOD + <LOD + *0.004* = 0.011 **(<0.04)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**
	D	Field Corn; Pioneer 31G98	Grain	0.164 (0.184)	107	<LOD + <LOD + *0.004* + *0.003* = 0.011 **(<0.04)** <LOD + <LOD + *0.005* + *0.003* = 0.012 **(<0.04)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**

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TABLE C.3.2. Residue Data from Field Corn Grain Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX010-) Year	Treatment Pattern[1]	Crop; Variety	Commodity	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Bagley, IA Zone 5 03H 2003	A	Field Corn; 34M95	Grain	0.164 (0.184)	104	<LOD + *0.007* + 0.039 + <LOD = 0.049 **(<0.069)** <LOD + *0.004* + 0.026+ <LOD = 0.033 **(<0.056)**	<LOD + *0.007* = 0.008 **(<0.02)** <LOD + *0.004* = 0.005 **(<0.02)**
	B	Field Corn; 34M95	Grain	0.166 (0.186)	96	<LOD + *0.004* + 0.043 + <LOD = 0.050 **(<0.073)** <LOD + *0.004* + 0.037 + <LOD = 0.044 **(<0.067)**	<LOD + *0.004* = 0.005 **(<0.02)** <LOD + *0.004* = 0.005 **(<0.02)**
	C	Field Corn; 34M95	Grain	0.166 (0.187)	104	<LOD + *0.003* + 0.019 + <LOD = 0.025 **(<0.049)** <LOD + *0.003* + 0.024 + <LOD = 0.030 **(<0.054)**	<LOD + *0.003* = 0.004 **(<0.02)** <LOD + *0.003* = 0.004 **(<0.02)**
	D	Field Corn; 34M95	Grain	0.167 (0.187)	104	<LOD + *0.004* + 0.027 + <LOD = 0.034 **(<0.057)** <LOD + *0.006* + 0.043 + <LOD = 0.052 **(<0.073)**	<LOD + *0.004* = 0.005 **(<0.02)** <LOD + *0.006* = 0.007 **(<0.02)**
Campbell, MN Zone 5 04H 2003	A	Field Corn; Dekalb 39-47	Grain	0.165 (0.185)	97	<LOD + <LOD + 0.025 + <LOD = 0.031 **(<0.055)** <LOD + <LOD + 0.027 + <LOD = 0.033 **(<0.057)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**
	B	Field Corn; Dekalb 39-47	Grain	0.164 (0.184)	89	<LOD + <LOD + 0.035 + <LOD = 0.041 **(<0.065)** <LOD + <LOD + 0.037 + <LOD = 0.043 **(<0.067)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**

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TABLE C.3.2. Residue Data from Field Corn Grain Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX010-) Year	Treatment Pattern[1]	Crop; Variety	Commodity	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: *Parent* + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Ellendale, MN Zone 5 05H 2003	A	Field Corn; Pioneer 3730	Grain	0.164 (0.184)	94	<LOD + *0.004* + 0.018 + <LOD = 0.025 **(<0.048)** <LOD + *0.003* + 0.019 + <LOD = 0.025 **(<0.049)**	<LOD + *0.004* = 0.005 **(<0.02)** <LOD + *0.003* = 0.004 **(<0.02)**
	B	Field Corn; Pioneer 3730	Grain	0.165 (0.185)	87	<LOD + *0.006* + 0.018 + <LOD = 0.027 **(<0.048)** <LOD + *0.004* + 0.022 + <LOD = 0.029 **(<0.052)**	<LOD + *0.006* = 0.007 **(<0.02)** <LOD + *0.004* = 0.005 **(<0.02)**
Arkansaw, WI Zone 5 06H 2003	A	Field Corn; Dekalb DKC46-26	Grain	0.165 (0.185)	95	<LOD + <LOD + 0.045 + <LOD = 0.051 **(<0.075)** <LOD + <LOD + 0.047 + <LOD = 0.053 **(<0.077)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**
	B	Field Corn; Dekalb DKC46-26	Grain	0.166 (0.186)	87	<LOD + <LOD + 0.041+ <LOD = 0.047 **(<0.071)** <LOD + <LOD + 0.042 + <LOD = 0.048 **(<0.072)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**
Britton, SD *Zone 5* 07H 2003	A	Field Corn; Dekalb DK493	Grain	0.168 (0.188)	97	<LOD + <LOD + *0.009* + <LOD = 0.015 **(<0.04)** <LOD + <LOD + *0.006* + *0.002* = 0.012 **(<0.04)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**
	B	Field Corn; Dekalb DK493	Grain	0.166 (0.186)	90	<LOD + <LOD + 0.017 + *0.002* = 0.023 **(<0.047)** <LOD + <LOD + 0.023 + *0.003* = 0.030 **(<0.053)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**

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TABLE C.3.2. Residue Data from Field Corn Grain Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX010-) Year	Treatment Pattern[1]	Crop; Variety	Commodity	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Springfield, NE Zone 5 08H 2003	A	Field Corn; Asgrow 741RR	Grain	0.164 (0.184)	91	<LOD + <LOD + 0.013 + <LOD = 0.019 **(<0.043)** <LOD + <LOD + 0.013 + <LOD = 0.019 **(<0.043)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**
	B	Field Corn; Asgrow 741RR	Grain	0.164 (0.184)	83	<LOD + <LOD + *0.008* + <LOD = 0.014 **(<0.04)** <LOD + <LOD + 0.010 + <LOD = 0.016 **(<0.04)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**
	C	Field Corn; Asgrow 741RR	Grain	0.164 (0.184)	91	<LOD + <LOD + *0.009*+ <LOD = 0.015 **(<0.04)** <LOD + <LOD + *0.007* + <LOD = 0.013 **(<0.04)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**
	D	Field Corn; Asgrow 741RR	Grain	0.164 (0.184)	91	<LOD + <LOD + 0.011+ <LOD = 0.017 **(<0.041)** <LOD + <LOD + 0.010 + <LOD = 0.016 **(<0.040)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**
York, NE Zone 5 09H 2003	A	Field Corn; DKC64-10RR	Grain	0.166 (0.186)	83	<LOD + <LOD + 0.024 + <LOD = 0.030 **(<0.054)** <LOD + <LOD + 0.021 + <LOD = 0.027 **(<0.051)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**
	B	Field Corn; DKC64-10RR	Grain	0.165 (0.185)	76	<LOD + <LOD + 0.023 + <LOD = 0.029 **(<0.053)** <LOD + <LOD + 0.023 + <LOD = 0.029 **(<0.053)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**

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TABLE C.3.2. Residue Data from Field Corn Grain Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX010-) Year	Treatment Pattern[1]	Crop; Variety	Commodity	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Richland, IA Zone 5 10H 2003	A	Field Corn; Pioneer 33G28	Grain	0.164 (0.184)	97	<LOD + <LOD + *0.005* + <LOD = 0.011 **(<0.04)** <LOD + <LOD + *0.009* + <LOD = 0.015 **(<0.04)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**
	B	Field Corn; Pioneer 33G28	Grain	0.169 (0.189)	90	<LOD + <LOD + 0.016 + <LOD = 0.022 **(<0.046)** <LOD + *0.003* + 0.020 + <LOD = 0.026 **(<0.050)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + *0.003* = 0.004 **(<0.02)**
Cunningham, KS Zone 5 11H 2003	A	Field Corn; 31A13	Grain	0.167 (0.187)	96	<LOD + <LOD + 0.012 + *0.002* = 0.018 **(<0.042)** <LOD + <LOD + <LOD + <LOD = 0.009 **(<0.04)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**
	B	Field Corn; 31A13	Grain	0.167 (0.187)	88	<LOD + *0.003* + 0.012 + <LOD = 0.018**(<0.042)** <LOD + <LOD + *0.007* + <LOD = 0.013 **(<0.04)**	<LOD + *0.003* = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**
Carlyle, IL Zone 5 13H 2003	A	Field Corn; Burrus BX	Grain	0.164 (0.184)	107	<LOD + <LOD + 0.040 + <LOD = 0.046 **(<0.070)** <LOD + *0.003* + 0.042 + <LOD = 0.048 **(<0.072)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + *0.003* = 0.004 **(<0.02)**
	B	Field Corn; Burrus BX	Grain	0.165 (0.185)	101	<LOD + *0.003* + 0.070 + <LOD = 0.076 **(<0.100)** <LOD + *0.003* + 0.062 + <LOD = 0.068 **(<0.092)**	<LOD + *0.003* = 0.004 **(<0.02)** <LOD + *0.003* = 0.004 **(<0.02)**

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TABLE C.3.2. Residue Data from Field Corn Grain Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX010-) Year	Treatment Pattern[1]	Crop; Variety	Commodity	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Oxford, IN Zone 5 14H 2003	A	Field Corn; Becks 5283Bt	Grain	0.168 (0.188)	93	<LOD + <LOD + 0.020 + <LOD = 0.026 (**<0.050**) <LOD + <LOD + 0.017 + <LOD = 0.023 (**<0.047**)	<LOD + <LOD = 0.004 (**<0.02**) <LOD + <LOD = 0.004 (**<0.02**)
	B	Field Corn; Becks 5283Bt	Grain	0.169 (0.189)	87	<LOD + <LOD + 0.020 + <LOD = 0.026 (**<0.050**) <LOD + *0.003* + 0.019 + <LOD = 0.025 (**<0.049**)	<LOD + <LOD = 0.004 (**<0.02**) <LOD + *0.003* = 0.004 (**<0.02**)
	C	Field Corn; Becks 5283Bt	Grain	0.168 (0.188)	93	<LOD + <LOD + 0.013 + <LOD = 0.019 (**<0.043**) <LOD + <LOD + 0.016 + <LOD = 0.022 (**<0.046**)	<LOD + <LOD = 0.004 (**<0.02**) <LOD + <LOD = 0.004 (**<0.02**)
	E	Field Corn; Becks 5283Bt	Grain	0.169 (0.189)	93	<LOD + <LOD + 0.018 + <LOD = 0.024 (**<0.048**) <LOD + <LOD + 0.020 + <LOD = 0.026 (**<0.050**)	<LOD + <LOD = 0.004 (**<0.02**) <LOD + <LOD = 0.004 (**<0.02**)
Noblesville, IN Zone 5 15H 2003	A	Field Corn; Becks 5322	Grain	0.165 (0.185)	105	<LOD + <LOD + *0.009* + *0.002* = 0.015 (**<0.04**) <LOD + <LOD + *0.007* + <LOD = 0.013 (**<0.04**)	<LOD + <LOD = 0.004 (**<0.02**) <LOD + <LOD = 0.004 (**<0.02**)
	B	Field Corn; Becks 5322	Grain	0.165 (0.185)	99	<LOD + <LOD + 0.010 + <LOD = 0.016 (**<0.04**) <LOD + <LOD + *0.008* + <LOD = 0.014 (**<0.04**)	<LOD + <LOD = 0.004 (**<0.02**) <LOD + <LOD = 0.004 (**<0.02**)

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TABLE C.3.2. Residue Data from Field Corn Grain Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX010-) Year	Treatment Pattern[1]	Crop; Variety	Commodity	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
New Holland, OH Zone 5 16H 2003	A	Field Corn; Crows 8626R	Grain	0.170 (0.190)	89	<LOD + *0.004* + 0.037 + *0.002* = 0.044 (**<0.067**) <LOD + 0.012 + 0.096 + *0.002* = 0.111 (**<0.128**)	<LOD + *0.004* = 0.005 (**<0.02**) <LOD + 0.012 = 0.013 (**<0.022**)
	B	Field Corn; Crows 8626R	Grain	0.168 (0.188)	83	<LOD + *0.005* + 0.039 + <LOD = 0.047 (**<0.069**) <LOD + 0.015 + 0.109 + *0.005* = 0.130 (**<0.144**)	<LOD + *0.005* = 0.006 (**0.02**) <LOD + 0.015= 0.016 (**<0.025**)
Hudson, KS Zone 5 18H 2003	A	Field Corn; 32M38	Grain	0.163 (0.183)	100	<LOD + <LOD + *0.009* + <LOD = 0.015 (**<0.04**) <LOD + <LOD + *0.009* + <LOD = 0.015 (**<0.04**)	<LOD + <LOD = 0.004 (**<0.02**) <LOD + <LOD = 0.004 (**<0.02**)
	B	Field Corn; 32M38	Grain	0.163 (0.183)	92	<LOD + <LOD + 0.011 + <LOD = 0.017 (**<0.041**) <LOD + <LOD + 0.015 + <LOD = 0.021 (**<0.045**)	<LOD + <LOD = 0.004 (**<0.02**) <LOD + <LOD = 0.004 (**<0.02**)
Clarence, MO Zone 5 19H 2003	A	Field Corn; Pioneer 3B23	Grain	0.165 (0.185)	112	<LOD + <LOD + *0.009* + <LOD = 0.015 (**<0.04**) <LOD + <LOD + 0.012 + <LOD = 0.018 (**<0.042**)	<LOD + <LOD = 0.004 (**<0.02**) <LOD + <LOD = 0.004 (**<0.02**)
	B	Field Corn; Pioneer 3B23	Grain	0.166 (0.186)	105	<LOD + <LOD + 0.019 + <LOD = 0.025 (**<0.049**) <LOD + <LOD + 0.020 + <LOD = 0.026 (**<0.050**)	<LOD + <LOD = 0.004 (**<0.02**) <LOD + <LOD = 0.004 (**<0.02**)

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TABLE C.3.2. Residue Data from Field Corn Grain Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX010-) Year	Treatment Pattern[1]	Crop; Variety	Commodity	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] *(ppm in parent equivalents)*	Sum of Parent + M5 = Total[2] *(ppm in parent equivalents)*
Dexter, MO Zone 5 20H 2003	A	Field Corn; Pioneer 3394	Grain	0.164 (0.184)	84	<LOD + *0.003* + 0.043 + <LOD = 0.049 **(<0.073)** <LOD + *0.004* + 0.050 + <LOD = 0.057 **(<0.080)**	<LOD + *0.003* = 0.004 **(<0.02)** <LOD + *0.004* = 0.005 **(<0.02)**
	B	Field Corn; Pioneer 3394	Grain	0.165 (0.185)	77	<LOD + *0.003* + 0.047 + <LOD = 0.053 **(<0.077)** <LOD + <LOD + 0.025 + <LOD = 0.031 **(<0.055)**	<LOD + *0.003* = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**
East Bernard, TX Zone 6 21H 2003	A	Field Corn; Golden Acres 2850 R	Grain	0.164 (0.184)	98	<LOD + <LOD + 0.125 + <LOD = 0.131 **(<0.155)** <LOD + <LOD + 0.122 + <LOD = 0.128 **(<0.152)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**
	B	Field Corn; Golden Acres 2850 R	Grain	0.166 (0.186)	90	<LOD + <LOD + 0.111 + <LOD = 0.117 **(<0.141)** <LOD + <LOD + 0.113 + <LOD = 0.119 **(<0.143)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**

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TABLE C.3.2. Residue Data from Field Corn Grain Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX010-) Year	Treatment Pattern[1]	Crop; Variety	Commodity	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Seymore, IL Zone 5 12D 2003	A	Field Corn; Pioneer 33G28	Grain	0.166 (0.186)	85	<LOD + *0.003* + 0.020 + <LOD = 0.026 **(<0.050)** <LOD + <LOD + 0.016 + <LOD = 0.022 **(<0.046)**	<LOD + *0.003* = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**
					91	<LOD + <LOD + 0.018 + <LOD = 0.024 **(<0.048)** <LOD + <LOD + 0.017 + <LOD = 0.023 **(<0.047)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**
					99	<LOD + <LOD + 0.018 + <LOD = 0.024 **(<0.048)** <LOD + *0.003* + 0.017 + <LOD = 0.023 **(<0.047)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + *0.003* = 0.004 **(<0.02)**
					106	<LOD + <LOD + 0.016 + <LOD = 0.022 **(<0.046)** <LOD + <LOD + 0.017 + <LOD = 0.023 **(<0.047)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**
					112	<LOD + <LOD + 0.020 + <LOD = 0.026 **(<0.050)** <LOD + <LOD + 0.020 + <LOD = 0.026 **(<0.050)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**

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TABLE C.3.2. Residue Data from Field Corn Grain Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX010-) Year	Treatment Pattern[1]	Crop; Variety	Commodity	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: *Parent + M5 + M6 + M2 = Total*[2] (ppm in parent equivalents)	*Sum of Parent + M5 = Total*[2] (ppm in parent equivalents)
Seymore, IL (continued)	B	Field Corn; Pioneer 33G28	Grain	0.165 (0.185)	78	<LOD + *0.003* + 0.019 + <LOD = 0.025 **(<0.049)** <LOD + *0.003* + 0.018 + <LOD = 0.024 **(<0.048)**	<LOD + *0.003* = 0.004 **(<0.02)** <LOD + *0.003* = 0.004 **(<0.02)**
					84	<LOD + *0.003* + 0.019 + <LOD = 0.025 **(<0.049)** <LOD + *0.003* + 0.024 + *0.002* = 0.030 **(<0.054)**	<LOD + *0.003* = 0.004 **(<0.02)** <LOD + *0.003* = 0.004 **(<0.02)**
					92	<LOD + *0.003* + 0.025 + <LOD = 0.031 **(<0.055)** <LOD + *0.003* + 0.022 + <LOD = 0.028 **(<0.052)**	<LOD + *0.003* = 0.004 **(<0.02)** <LOD + *0.003* = 0.004 **(<0.02)**
					99	<LOD + <LOD + 0.023 + <LOD = 0.029 **(<0.053)** <LOD + <LOD + 0.020 + <LOD = 0.026 **(<0.050)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**
					105	<LOD + <LOD + 0.023 + <LOD = 0.029 **(<0.053)** <LOD + <LOD + 0.019 + <LOD = 0.025 **(<0.049)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**
	C	Field Corn; Pioneer 33G28	Grain	0.163 (0.183)	99	<LOD + <LOD + 0.019 + <LOD = 0.025 **(<0.049)** <LOD + <LOD + 0.018 + <LOD = 0.024 **(<0.048)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**

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TABLE C.3.2. Residue Data from Field Corn Grain Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX010-) Year	Treatment Pattern[1]	Crop; Variety	Commodity	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Seymore, IL (continued)	E	Field Corn; Pioneer 33G28	Grain	0.164 (0.184)	99	<LOD + <LOD + 0.015 + <LOD = 0.021 **(<0.045)** <LOD + <LOD + 0.015 + <LOD = 0.021 **(<0.045)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**
Stilwell, KS Zone 5 17D 2003	A	Field Corn; Pioneer 33G26	Grain	0.161 (0.180)	83	<LOD + <LOD + 0.022 + <LOD = 0.028 **(<0.052)** <LOD + <LOD + 0.020 + <LOD = 0.026 **(<0.050)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**
					90	<LOD + <LOD + 0.024 + <LOD = 0.030 **(<0.054)** <LOD + <LOD + 0.026 + <LOD = 0.032 **(<0.056)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**
					97	<LOD + <LOD + 0.026 + <LOD = 0.032 **(<0.056)** <LOD + <LOD + 0.030 + <LOD = 0.036 **(<0.060)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**
					104	<LOD + <LOD + 0.020 + *0.002* = 0.026 **(<0.050)** <LOD + <LOD + 0.021 + *0.002* = 0.027 **(<0.051)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**
					111	<LOD + <LOD + 0.016 + *0.003* = 0.023 **(<0.046)** <LOD + <LOD + 0.021 + *0.003* = 0.028 **(<0.051)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**

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TABLE C.3.2. Residue Data from Field Corn Grain Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX010-) Year	Treatment Pattern[1]	Crop; Variety	Commodity	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Stilwell, KS (continued)	B	Field Corn; Pioneer 33G26	Grain	0.174 (0.195)	77	<LOD + *0.004* + 0.044 + <LOD = 0.051 **(<0.074)** <LOD + *0.003* + 0.034 + <LOD = 0.040 **(<0.064)**	<LOD + *0.004* = 0.005 **(<0.02)** <LOD + *0.003* = 0.004 **(<0.02)**
					84	<LOD + *0.003* + 0.032 + <LOD = 0.038 **(<0.062)** <LOD + <LOD + 0.032 + <LOD = 0.038 **(<0.062)**	<LOD + *0.003* = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**
					91	<LOD + *0.004* + 0.036 + <LOD = 0.043 **(<0.066)** <LOD + *0.003* + 0.019 + <LOD = 0.025 **(<0.049)**	<LOD + *0.004* = 0.005 **(<0.02)** <LOD + *0.003* = 0.004 **(<0.02)**
					98	<LOD + *0.003* + 0.037 + *0.002* = 0.043 **(<0.067)** <LOD + *0.003* + 0.042 + *0.002* = 0.048 **(<0.072)**	<LOD + *0.003* = 0.004 **(<0.02)** <LOD + *0.003* = 0.004 **(<0.02)**
					105	<LOD + *0.003* + 0.033 + <LOD = 0.039 **(<0.063)** <LOD + *0.004* + 0.041 + <LOD = 0.048 **(0.071)**	<LOD + *0.003* = 0.004 **(<0.02)** <LOD + *0.004* = 0.005 **(<0.02)**
	C	Field Corn; Pioneer 33G26	Grain	0.160 (0.180)	97	<LOD + <LOD + *0.009* + *0.002* = 0.015 **(<0.04)** <LOD + <LOD + *0.009* + <LOD = 0.015 **(<0.04)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**

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TABLE C.3.2. Residue Data from Field Corn Grain Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX010-) Year	Treatment Pattern[1]	Crop; Variety	Commodity	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Stilwell, KS (continued)	E	Field Corn; Pioneer 33G26	Grain	0.170 (0.190)	97	<LOD + <LOD + *0.005* + *0.002* = 0.011 (**<0.04**) <LOD + <LOD + *0.006* + <LOD = 0.012 (**<0.04**)	<LOD + <LOD = 0.004 (**<0.02**) <LOD + <LOD = 0.004 (**<0.02**)

[1] Treatment Pattern A: two foliar spray applications at 24-inch and 36-inch corn height, with adjuvants methylated seed oil (MSO) and urea ammonium nitrate (UAN)
Treatment Pattern B: One foliar spray application at 36-inch corn height and one directed-spray application one week later.
Treatment Pattern C: application at the same use pattern as Pattern A except adjuvants added were crop oil concentrate (COC) and UAN.
Treatment Pattern D: application at the same use pattern as Pattern A except adjuvants added were MSO and ammonium sulfate (AMS).
Treatment Pattern E: application at the same use pattern as Pattern A except adjuvants added were COC and AMS.
[2] The LOD values for tembotrione (parent), M5, M6, and M2 in field corn grain were 0.001 ppm, 0.003 ppm, 0.003 ppm, and 0.002 ppm, respeetively. Residues below the LOQ (<0.01 ppm each analyte) but above the respective LOD are *italicized*. Total residues based on the LOQ of each analyte are **bolded** in parentheses.

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TABLE C.3.3. Residue Data from Field Corn Stover Field Trials with Tembotrione.

Location (City, State) Trial Number (RAAEX010-) Year	Treatment Pattern[1]	Crop; Variety	Commodity (% Dry Matter)	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Germansville, PA Zone 1 01H 2003	A	Field Corn; Doeblers 609XRR	Stover (35)	0.170 (0.191)	108	<LOD + 0.013 + 0.015 + <LOD = 0.031 **(<0.048)** <LOD + 0.018 + 0.034 + <LOD = 0.055 **(<0.072)**	<LOD + 0.013 = 0.014 **(<0.023)** <LOD + 0.018 = 0.019 **(<0.028)**
	B	Field Corn; Doeblers 609XRR	Stover (41)	0.171 (0.193)	102	<LOD + 0.016 + 0.025 + <LOD = 0.044 **(<0.061)** <LOD + 0.031 + 0.078 + <LOD = 0.112 **(<0.129)**	<LOD + 0.016 = 0.017 **(<0.026)** <LOD + 0.031 = 0.032 **(<0.041)**
Tifton, GA Zone 2 02H 2003	A	Field Corn; Pioneer 31G98	Stover (83)	0.165 (0.185)	107	<LOD + <LOD + <LOD + 0.019 = 0.025 **(<0.049)** <LOD + <LOD + <LOD + 0.030 = 0.036 **(<0.060)**	<LOD + <LOD = 0.002 **(<0.02)** <LOD + <LOD = 0.002 **(<0.02)**
	B	Field Corn; Pioneer 31G98	Stover (83)	0.164 (0.184)	100	<LOD + *0.005* + <LOD + 0.033 = 0.043 **(<0.063)** <LOD + *0.002* + <LOD + 0.019 = 0.026 **(<0.049)**	<LOD + *0.005* = 0.006 **(<0.02)** <LOD + *0.002* = 0.003 **(<0.02)**
	C	Field Corn; Pioneer 31G98	Stover (79)	0.164 (0.184)	107	<LOD + <LOD + <LOD + 0.017 = 0.023 **(<0.047)** <LOD + <LOD + <LOD + 0.021 = 0.027 **(<0.051)**	<LOD + <LOD = 0.002 **(<0.02)** <LOD + <LOD = 0.002 **(<0.02)**
	D	Field Corn; Pioneer 31G98	Stover (84)	0.164 (0.184)	107	<LOD + <LOD + 0.015 + 0.010 = 0.027 **(<0.045)** <LOD + <LOD + 0.024 + 0.025 = 0.051 **(<0.069)**	<LOD + <LOD = 0.002 **(<0.02)** <LOD + <LOD = 0.002 **(<0.02)**

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TABLE C.3.3. Residue Data from Field Corn Stover Field Trials with Tembotrione.

Location (City, State) Trial Number (RAAEX010-) Year	Treatment Pattern[1]	Crop; Variety	Commodity (% Dry Matter)	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Bagley, IA Zone 5 03H 2003	A	Field Corn; 34M95	Stover (77)	0.164 (0.184)	104	<LOD + 0.117 + 0.058 + <LOD = 0.178 **(<0.195)** <LOD + 0.153 + 0.039 + *0.003* = 0.196 **(<0.212)**	<LOD + 0.117 = 0.118 **(<0.127)** <LOD + 0.153 = 0.154 **(<0.163)**
	B	Field Corn; 34M95	Stover (70)	0.166 (0.186)	96	<LOD + 0.092 + 0.054 + <LOD = 0.149 **(<0.166)** <LOD + 0.059 + 0.032 + <LOD = 0.094 **(<0.111)**	<LOD + 0.092 = 0.093 **(<0.102)** <LOD + 0.059 = 0.060 **(<0.069)**
	C	Field Corn; 34M95	Stover (66)	0.166 (0.187)	104	<LOD + 0.067 + 0.025 + <LOD = 0.095 **(<0.112)** <LOD + 0.060 + 0.027 + <LOD = 0.090 **(<0.107)**	<LOD + 0.067 = 0.068 **(<0.077)** <LOD + 0.060 = 0.061 **(<0.070)**
	D	Field Corn; 34M95	Stover (57)	0.167 (0.187)	104	<LOD + 0.056 + 0.032 + <LOD = 0.091 **(<0.108)** <LOD + 0.042 + 0.023 + <LOD = 0.068 **(<0.085)**	<LOD + 0.056 = 0.057 **(<0.066)** <LOD + 0.042 = 0.043 **(<0.052)**
Campbell, MN Zone 5 04H 2003	A	Field Corn; Dekalb 39-47	Stover (51)	0.165 (0.185)	97	<LOD + 0.253 + 0.068 + <LOD = 0.324 **(<0.341)** <LOD + 0.367 + 0.085 + <LOD = 0.455 **(<0.472)**	<LOD + 0.253 = 0.254 **(<0.263)** <LOD + 0.367 = 0.368 **(<0.377)**
	B	Field Corn; Dekalb 39-47	Stover (75)	0.164 (0.184)	89	<LOD + 0.277 + 0.103 + <LOD = 0.383 **(<0.400)** <LOD + 0.217 + 0.077 + <LOD = 0.297 **(<0.314)**	<LOD + 0.277 = 0.278 **(<0.287)** <LOD + 0.217 = 0.218 **(<0.227)**

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TABLE C.3.3. Residue Data from Field Corn Stover Field Trials with Tembotrione.

Location (City, State) Trial Number (RAAEX010-) Year	Treatment Pattern[1]	Crop; Variety	Commodity (% Dry Matter)	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Ellendale, MN Zone 5 05H 2003	A	Field Corn; Pioneer 3730	Stover (52)	0.164 (0.184)	94	<LOD + 0.090 + 0.023 + *0.003* ≈ 0.117 (**<0.133**) <LOD + 0.071 + 0.028 + <LOD = 0.102 (**<0.119**)	<LOD + 0.090 = 0.091 (**<0.100**) <LOD + 0.071 = 0.072 (**<0.081**)
	B	Field Corn; Pioneer 3730	Stover (43)	0.165 (0.185)	87	<LOD + 0.114 + 0.031 + <LOD = 0.148 (**<0.165**) <LOD + 0.168 + 0.045 + <LOD = 0.216 (**<0.233**)	<LOD + 0.114 = 0.115 (**<0.124**) <LOD + 0.168 = 0.169 (**<0.178**)
Arkansaw, WI Zone 5 06H 2003	A	Field Corn; Dekalb DKC46-26	Stover (43)	0.165 (0.185)	95	<LOD + 0.440 + 0.094 + *0.009* = 0.544 (**<0.554**) <LOD + 0.320 + 0.064 + *0.006* = 0.391 (**<0.404**)	<LOD + 0.440 = 0.441 (**<0.450**) <LOD + 0.320 = 0.321 (**<0.330**)
	B	Field Corn; Dekalb DKC46-26	Stover (32)	0.166 (0.186)	87	<LOD + 0.435 + 0.070 + <LOD = 0.508 (**<0.525**) <LOD + 0.401 + 0.055 + *0.004* = 0.461 (**<0.476**)	<LOD + 0.435 = 0.436 (**<0.445**) <LOD + 0.401 = 0.402 (**<0.411**)
Britton, SD Zone 5 07H 2003	A	Field Corn; Dekalb DK493	Stover (53)	0.168 (0.188)	97	<LOD + 0.040 + 0.018 + <LOD = 0.061 (**<0.078**) <LOD + 0.040 + 0.017 + <LOD = 0.060 (**<0.077**)	<LOD + 0.040 = 0.041 (**<0.050**) <LOD + 0.040 = 0.041 (**<0.050**)
	B	Field Corn; Dekalb DK493	Stover (62)	0.166 (0.186)	90	<LOD + 0.085 + 0.053 + <LOD = 0.141 (**<0.158**) <LOD + 0.123 + 0.066 + <LOD = 0.192 (**<0.209**)	<LOD + 0.085 = 0.086 (**<0.095**) <LOD + 0.123 = 0.124 (**<0.133**)

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TABLE C.3.3. Residue Data from Field Corn Stover Field Trials with Tembotrione.

Location (City, State) Trial Number (RAAEX010-) Year	Treatment Pattern[1]	Crop; Variety	Commodity (% Dry Matter)	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Springfield, NE Zone 5 08H 2003	A	Field Corn; Asgrow 741RR	Stover (58)	0.164 (0.184)	91	<LOD + 0.055 + 0.031+ *0.005* = 0.092 **(<0.106)** <LOD + 0.048 + 0.036 + <LOD = 0.087 **(<0.104)**	<LOD + 0.055 = 0.056 **(<0.065)** <LOD + 0.048 = 0.049 **(<0.058)**
	B	Field Corn; Asgrow 741RR	Stover (57)	0.164 (0.184)	83	<LOD + 0.056 + 0.043 + <LOD = 0.102 **(<0.119)** <LOD + 0.047 + 0.025 + <LOD = 0.075 **(0.092)**	<LOD + 0.056 = 0.057 **(<0.066)** <LOD + 0.047 = 0.048 **(<0.057)**
	C	Field Corn; Asgrow 741RR	Stover (30)	0.164 (0.184)	91	<LOD + *0.005* + *0.005* + <LOD = 0.013 **(<0.04)** <LOD + 0.016 + 0.016 + <LOD = 0.035 **(<0.052)**	<LOD + *0.005* = 0.006 **(<0.02)** <LOD + 0.016 = 0.017 **(<0.026)**
	D	Field Corn; Asgrow 741RR	Stover (53)	0.164 (0.184)	91	<LOD + 0.033 + 0.030 + <LOD = 0.066 **(<0.083)** <LOD + 0.067 + 0.058 + <LOD = 0.128 **(<0.145)**	<LOD + 0.033 = 0.034 **(<0.043)** <LOD + 0.067 = 0.068 **(<0.077)**
York, NE Zone 5 09H 2003	A	Field Corn; DKC64-10RR	Stover (51)	0.166 (0.186)	83	<LOD + 0.105 + 0.058 + *0.007* = 0.171 **(<0.183)** <LOD + 0.084 + 0.046 + *0.005* = 0.136 **(<0.150)**	<LOD + 0.105 = 0.106 **(<0.115)** <LOD + 0.084 = 0.085 **(<0.094)**
	B	Field Corn; DKC64-10RR	Stover (49)	0.165 (0.185)	76	<LOD + 0.088 + 0.056 + *0.005* = 0.150 **(<0.164)** <LOD + 0.084 + 0.064 + *0.005* = 0.154 **(<0.168)**	<LOD + 0.088 = 0.089 **(<0.098)** <LOD + 0.084 = 0.085 **(<0.094)**

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TABLE C.3.3. Residue Data from Field Corn Stover Field Trials with Tembotrione.

Location (City, State) Trial Number (RAAEX010-) Year	Treatment Pattern[1]	Crop; Variety	Commodity (% Dry Matter)	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Richland, IA Zone 5 10H 2003	A	Field Corn; Pioneer 33G28	Stover (57)	0.164 (0.184)	97	<LOD + 0.024 + *0.016* + <LOD = 0.043 **(<0.060)** <LOD + 0.039 + 0.031 + *0.002* = 0.073 **(<0.090)**	<LOD + 0.024 = 0.025 **(<0.034)** <LOD + 0.039 = 0.040 **(<0.049)**
	B	Field Corn; Pioneer 33G28	Stover (51)	0.169 (0.189)	90	<LOD + 0.092 + 0.043 + *0.003* = 0.139 **(<0.155)** <LOD + 0.073 + 0.034 + <LOD = 0.110 **(<0.127)**	<LOD + 0.092 = 0.093 **(<0.102)** <LOD + 0.073 = 0.074 **(<0.083)**
Cunningham, KS Zone 5 11H 2003	A	Field Corn; 31A13	Stover (45)	0.167 (0.187)	96	<LOD + 0.019 + 0.018 + 0.010 = 0.048 **(<0.057)** <LOD + 0.015 + 0.018 + *0.009* = 0.043 **(<0.053)**	<LOD + 0.019 = 0.020 **(<0.029)** <LOD + 0.015 = 0.016 **(<0.025)**
	B	Field Corn; 31A13	Stover (46)	0.167 (0.187)	88	<LOD + 0.013 + 0.010 + *0.006* = 0.030 **(<0.043)** <LOD + *0.009* + *0.009* + *0.006* = *0.025* **(<0.04)**	<LOD + 0.013 = 0.014 **(<0.023)** <LOD + *0.009* = 0.010 **(<0.02)**
Carlyle, IL Zone 5 13H 2003	A	Field Corn; Burrus BX	Stover (49)	0.164 (0.184)	107	<LOD + 0.017 + 0.022 + *0.003* = 0.043 **(<0.059)** <LOD + 0.024 + 0.026 + *0.007* = 0.058 **(<0.070)**	<LOD + 0.017 = 0.018 **(<0.027)** <LOD + 0.024 = 0.025 **(<0.034)**
	B	Field Corn; Burrus BX	Stover (46)	0.165 (0.185)	101	<LOD + 0.031 + 0.036 + *0.007* = 0.075 **(<0.087)** <LOD + 0.071 + 0.042 + *0.007* = 0.121 **(<0.133)**	<LOD + 0.031 = 0.032 **(<0.041)** <LOD + 0.071 = 0.072 **(<0.081)**

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TABLE C.3.3. Residue Data from Field Corn Stover Field Trials with Tembotrione.

Location (City, State) Trial Number (RAAEX010-) Year	Treatment Pattern[1]	Crop; Variety	Commodity (% Dry Matter)	Total Rate lb ai/A (kg ai/ha)	PHI (days)	*Sum of Residues as determined by the data-collection method:* Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Oxford, IN Zone 5 14H 2003	A	Field Corn; Becks 5283Bt	Stover (49)	0.168 (0.188)	93	<LOD + 0.039 + 0.020 + <LOD = 0.062 **(<0.079)** <LOD + 0.014 + *0.009* + <LOD = 0.026 **(<0.044)**	<LOD + 0.039 = 0.040 **(<0.049)** <LOD + 0.014 = 0.015 **(<0.024)**
	B	Field Corn; Becks 5283Bt	Stover (38)	0.169 (0.189)	87	<LOD + 0.070 + 0.032 + <LOD = 0.105 **(<0.122)** <LOD + 0.089 + 0.037 + <LOD = 0.129 **(<0.146)**	<LOD + 0.070 = 0.071 **(<0.080)** <LOD + *0.089* = *0.090* **(<0.099)**
	C	Field Corn; Becks 5283Bt	Stover (39)	0.168 (0.188)	93	<LOD + 0.034 + 0.017 + <LOD = 0.054 **(<0.071)** <LOD + 0.035 + 0.020 + <LOD = 0.058 **(<0.075)**	<LOD + 0.034 = 0.035 **(<0.044)** <LOD + 0.035 = 0.036 **(<0.045)**
	E	Field Corn; Becks 5283Bt	Stover (48)	0.169 (0.189)	93	<LOD + 0.033 + 0.017 + *0.003* = 0.054 **(<0.070)** <LOD + 0.054 + 0.033 + <LOD = 0.090 **(<0.107)**	<LOD + 0.033 = 0.034 **(<0.043)** <LOD + 0.054 = 0.055 **(<0.064)**
Noblesville, IN Zone 5 15H 2003	A	Field Corn; Becks 5322	Stover (40)	0.165 (0.185)	105	<LOD + *0.002* + <LOD + *0.008* = 0.015 **(<0.04)** <LOD + *0.002* + *0.007* + 0.011 = 0.021 **(<0.041)**	<LOD + *0.002* = 0.003 **(<0.02)** <LOD + *0.002* = 0.003 **(<0.02)**
	B	Field Corn; Becks 5322	Stover (26)	0.165 (0.185)	99	<LOD + <LOD + <LOD + *0.009* = 0.015 **(<0.04)** <LOD + *0.002* + *0.008* + *0.009* = 0.020 **(<0.04)**	<LOD + <LOD = 0.002 **(<0.02)** <LOD + *0.002* = 0.003 **(<0.02)**

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TABLE C.3.3. Residue Data from Field Corn Stover Field Trials with Tembotrione.

Location (City, State) Trial Number (RAAEX010-) Year	Treatment Pattern[1]	Crop; Variety	Commodity (% Dry Matter)	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
New Holland, OH Zone 5 16H 2003	A	Field Corn; Crows 8626R	Stover (46)	0.170 (0.190)	89	<LOD + 0.035 + 0.025 + *0.006* = 0.067 **(<0.080)** <LOD + 0.088 + 0.050 + *0.005* = 0.144 **(<0.158)**	<LOD + 0.035 = 0.036 **(<0.045)** <LOD + 0.088 = 0.089 **(<0.098)**
	B	Field Corn; Crows 8626R	Stover (59)	0.168 (0.188)	83	<LOD + 0.044 + 0.033 + *0.004* = 0.082 **(<0.097)** <LOD + 0.158 + 0.080 + 0.013 = 0.252 **(<0.261)**	<LOD + 0.044 = 0.045 **(<0.054)** <LOD + 0.158 = 0.159 **(<0.168)**
Hudson, KS Zone 5 18H 2003	A	Field Corn; 32M38	Stover (33)	0.163 (0.183)	100	<LOD + 0.023 + 0.028 + *0.009* = 0.061 **(<0.071)** <LOD + 0.015 + 0.030 + *0.006* = 0.052 **(<0.065)**	<LOD + 0.023 = 0.024 **(<0.033)** <LOD + 0.015 = 0.016 **(<0.025)**
	B	Field Corn; 32M38	Stover (38)	0.163 (0.183)	92	<LOD + 0.024 + 0.026 + 0.011 = 0.062 **(<0.071)** <LOD + 0.017 + 0.033 + 0.012 = 0.063 **(<0.072)**	<LOD + 0.024 = 0.025 **(<0.034)** <LOD + 0.017 = 0.018 **(<0.027)**
Clarence, MO Zone 5 19H 2003	A	Field Corn; Pioneer 3B23	Stover (75)	0.165 (0.185)	112	<LOD + *0.004* + *0.008* + <LOD = 0.015 **(<0.04)** <LOD + *0.002* + *0.006* + <LOD = 0.011 **(<0.04)**	<LOD + *0.004* = 0.005 **(<0.02)** <LOD + *0.002* = 0.003 **(<0.02)**
	B	Field Corn; Pioneer 3B23	Stover (75)	0.166 (0.186)	105	<LOD + *0.008* + 0.018 + <LOD = 0.029 **(<0.048)** <LOD + *0.005* + 0.011 + <LOD = 0.019 **(<0.041)**	<LOD + *0.008* = 0.009 **(<0.02)** <LOD + *0.005* = 0.006 **(<0.02)**

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TABLE C.3.3. Residue Data from Field Corn Stover Field Trials with Tembotrione.

Location (City, State) Trial Number (RAAEX010-) Year	Treatment Pattern[1]	Crop; Variety	Commodity (% Dry Matter)	Total Rate lb ai/A (kg ai/ha)	*PHI* (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Dexter, MO Zone 5 20H 2003	A	Field Corn; Pioneer 3394	Stover (48)	0.164 (0.184)	84	<LOD + 0.016 + 0.033 + <LOD = 0.052 **(<0.069)** <LOD + 0.024 + 0.042 + <LOD = 0.069 **(<0.086)**	<LOD + 0.016 = 0.017 **(<0.026)** <LOD + 0.024 = 0.025 **(<0.034)**
	B	Field Corn; Pioneer 3394	Stover (51)	0.165 (0.185)	77	<LOD + 0.015 + 0.031 + <LOD = 0.049 **(<0.066)** <LOD + 0.016 + 0.017 + <LOD = 0.036 **(<0.053)**	<LOD + 0.015 = 0.016 **(<0.025)** <LOD + 0.016 = 0.017 **(<0.026)**
East Bernard, TX Zone 6 21H 2003	A	Field Corn; Golden Acres 2850 R	Stover (87)	0.164 (0.184)	98	<LOD + 0.057 + 0.129 + 0.013 = 0.200 **(<0.209)** <LOD + 0.062 + 0.107 + *0.009* = 0.179 **(<0.189)**	<LOD + 0.057 = 0.058 **(<0.067)** <LOD + 0.062 = 0.063 **(<0.072)**
	B	Field Corn; Golden Acres 2850 R	Stover (91)	0.166 (0.186)	90	<LOD + 0.032 + 0.080 + *0.005* = 0.118 **(<0.132)** <LOD + 0.052 + 0.109 + *0.005* = 0.167 **(<0.181)**	<LOD + 0.032 = 0.033 **(<0.042)** <LOD + 0.052 = 0.053 **(<0.062)**

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TABLE C.3.3. Residue Data from Field Corn Stover Field Trials with Tembotrione.

Location (City, State) Trial Number (RAAEX010-) Year	Treatment Pattern[1]	Crop; Variety	Commodity (% Dry Matter)	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Seymore, IL Zone 5 12D 2003	A	Field Corn; Pioneer 33G28	Stover (36)	0.166 (0.186)	85	<LOD + 0.048 + 0.018 + *0.005* = 0.072 **(<0.086)** <LOD + 0.070 + 0.036 + *0.007* = 0.114 **(<0.126)**	<LOD + 0.048 = 0.049 **(<0.058)** <LOD + 0.070 = 0.071 **(<0.080)**
			Stover (41)		91	<LOD + 0.023 + 0.016 + *0.006* = 0.046 **(<0.059)** <LOD + *0.034* + *0.017* + *0.011* = 0.063 **(<0.072)**	<LOD + 0.023 = 0.024 **(<0.033)** <LOD + *0.034* = 0.035 **(<0.044)**
			Stover (69)		99	<LOD + 0.023 + 0.028 + *0.009* = 0.061 **(<0.071)** <LOD + 0.015 + 0.030 + *0.006* = 0.052 **(<0.065)**	<LOD + 0.023 = 0.024 **(<0.033)** <LOD + 0.015 = 0.016 **(<0.025)**
			Stover (57)		106	<LOD + 0.048 + 0.028 + <LOD = 0.079 **(<0.096)** <LOD + 0.038 + 0.025 + <LOD = 0.066 **(<0.083)**	<LOD + 0.048 = 0.049 **(<0.058)** <LOD + 0.038 = 0.039 **(<0.048)**
			Stover (81)		112	<LOD + 0.044 + 0.027 + <LOD = 0.074 **(<0.091)** <LOD + 0.045 + 0.031 + <LOD = 0.079 **(<0.096)**	<LOD + 0.044 = 0.045 **(<0.054)** <LOD + 0.045 = 0.046 **(<0.055)**

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TABLE C.3.3. Residue Data from Field Corn Stover Field Trials with Tembotrione.

Location (City, State) Trial Number (RAAEX010-) Year	Treatment Pattern[1]	Crop; Variety	Commodity (% Dry Matter)	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Seymore, IL (continued)	B	Field Corn; Pioneer 33G28	Stover (53)	0.165 (0.185)	78	<LOD + 0.093 + 0.047 + 0.015 = 0.156 (**<0.165**) <LOD + 0.066 + 0.035 + 0.017 = 0.119 (**<0.128**)	<LOD + 0.093 = 0.094 (**<0.103**) <LOD + 0.066 = 0.067 (**<0.076**)
			Stover (54)		84	<LOD + 0.041 + 0.019 + 0.015 = 0.076 (**<0.085**) <LOD + 0.037 + 0.028 + 0.021 = 0.087 (**<0.096**)	<LOD + 0.041 = 0.042 (**<0.051**) <LOD + 0.037 = 0.038 (**<0.047**)
			Stover (89)		92	<LOD + 0.040 + 0.034 + 0.042 = 0.117 (**<0.126**) <LOD + 0.056 + 0.046 + 0.038 = 0.141 (**<0.150**)	<LOD + 0.040 = 0.041 (**<0.050**) <LOD + 0.056 = 0.057 (**<0.066**)
			Stover (89)		99	<LOD + 0.055 + 0.034 + <LOD = 0.092 (**<0.109**) <LOD + 0.058 + 0.039 + <LOD = 0.100 (**<0.117**)	<LOD + 0.055 = 0.056 (**<0.065**) <LOD + 0.058 = 0.059 (**<0.068**)
			Stover (87)		105	<LOD + 0.044 + 0.040 + <LOD = 0.087 (**<0.104**) <LOD + 0.077 + 0.058 + <LOD = 0.138 (**<0.155**)	<LOD + 0.044 = 0.045 (**<0.054**) <LOD + 0.077 = 0.078 (**<0.087**)
	C	Field Corn; Pioneer 33G28	Stover (73)	0.163 (0.183)	99	<LOD + 0.049 + *0.006* + <LOD = 0.058 (**<0.079**) <LOD + 0.063 + *0.008* + <LOD = 0.074 (**<0.093**)	<LOD + 0.049 = 0.050 (**<0.059**) <LOD + 0.063 = 0.064 (**<0.073**)
	E	Field Corn; Pioneer 33G28	Stover (83)	0.164 (0.184)	99	<LOD + 0.033 + 0.028 + 0.022 = 0.084 (**<0.093**) <LOD + 0.031 + 0.029 + 0.017 = 0.078 (**<0.087**)	<LOD + 0.033 = 0.034 (**<0.043**) <LOD + 0.031 = 0.032 (**<0.041**)

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TABLE C.3.3. Residue Data from Field Corn Stover Field Trials with Tembotrione.

Location (City, State) Trial Number (RAAEX010-) Year	Treatment Pattern[1]	Crop; Variety	Commodity (% Dry Matter)	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Stilwell, KS Zone 5 17D 2003	A	Field Corn; Pioneer 33G26	Stover (33)	0.161 (0.180)	83	*0.003* + 0.013 + 0.023 + *0.003* = 0.042 **(<0.056)** *0.003* + 0.014 + 0.042 + *0.002* = 0.061 **(<0.076)**	*0.003* + 0.013 = 0.016 **(<0.023)** *0.003* + 0.014 = 0.017 **(<0.024)**
			Stover (42)		90	*0.003* + 0.010 + 0.029 + <LOD = 0.044 **(<0.059)** *0.003* + 0.011 + 0.029 + *0.003* = 0.046 **(<0.060)**	*0.003* + 0.010 = 0.013 **(<0.020)** *0.003* + 0.011 = 0.014 **(<0.021)**
			Stover (50)		97	<LOD + *0.009* + 0.027 + <LOD = 0.039 **(<0.057)** <LOD + 0.020 + 0.060 + *0.003* = 0.084 **(<0.100)**	<LOD + *0.009* = 0.010 **(<0.02)** <LOD + 0.020 = 0.021 **(<0.030)**
			Stover (57)		104	<LOD + 0.010 + 0.032 + 0.015 = 0.058 **(<0.067)** <LOD + 0.012 + 0.026 + 0.013 = 0.052 **(<0.061)**	<LOD + 0.010 = 0.011 **(<0.020)** <LOD + 0.012 = 0.013 **(<0.021)**
			Stover (42)		111	<LOD + *0.008* + 0.016 + *0.004* = 0.029 **(<0.046)** <LOD + *0.009* + 0.020 + *0.008* = 0.038 **(<0.050)**	<LOD + *0.008* = 0.009 **(<0.02)** <LOD + *0.009* = 0.010 **(<0.02)**

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TABLE C.3.3. Residue Data from Field Corn Stover Field Trials with Tembotrione.

Location (City, State) Trial Number (RAAEX010-) Year	Treatment Pattern[1]	Crop; Variety	Commodity (% Dry Matter)	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Stillwell, KS (continued)	B	Field Corn; Pioneer 33G26	Stover (31)	0.174 (0.195)	77	*0.003* + 0.016 + 0.035 + *0.004* = 0.058 **(<0.071)** *0.003* + 0.063 + 0.093 + *0.007* = 0.166 **(<0.176)**	*0.003* + 0.016 = 0.019 **(<0.026)** *0.003* + 0.063 = 0.066 **(<0.073)**
			Stover (44)		84	*0.003* + 0.024 + 0.064 + *0.006* = 0.097 **(<0.108)** *0.003* + 0.026 + 0.069 + *0.005* = 0.103 **(<0.115)**	*0.003* + 0.024 = 0.027 **(<0.034)** *0.003* + 0.026 = 0.029 **(<0.036)**
			Stover (57)		91	<LOD + 0.031 + 0.062 + *0.005* = 0.099 **(<0.113)** <LOD + 0.029 + 0.084 + *0.007* = 0.121 **(<0.133)**	<LOD + 0.031 = 0.032 **(<0.041)** <LOD + 0.029 = 0.031 **(<0.039)**
			Stover (66)		98	<LOD + 0.044 + 0.065 + 0.020 = 0.130 **(<0.139)** <LOD + 0.022 + 0.064 + 0.011 = 0.098 **(<0.107)**	<LOD + 0.044 = 0.045 **(<0.054)** <LOD + 0.022 = 0.023 **(<0.032)**
			Stover (48)		105	<LOD + 0.020 + 0.042 + 0.010 = 0.073 **(<0.082)** <LOD + 0.019 + 0.042 + 0.011 = 0.073 **(<0.082)**	<LOD + 0.020 = 0.021 **(<0.030)** <LOD + 0.019 = 0.020 **(<0.029)**
	C	Field Corn; Pioneer 33G26	Stover (66)	0.160 (0.180)	97	*0.003* + *0.007* + 0.029 + 0.019 = 0.058 **(<0.068)** *0.003* + *0.008* + 0.014 + 0.010 = 0.035 **(<0.044)**	*0.003* + *0.007* = 0.010 **(<0.02)** *0.003* + *0.008* = 0.011 **(<0.02)**

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TABLE C.3.3. Residue Data from Field Corn Stover Field Trials with Tembotrione.

Location (City, State) Trial Number (RAAEX010-) Year	Treatment Pattern[1]	Crop; Variety	Commodity (% Dry Matter)	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Stillwell, KS (continued)	E	Field Corn; Pioneer 33G26	Stover (39)	0.170 (0.190)	97	*0.003* + *0.005* + 0.011 + *0.009* = 0.028 **(<0.041)** *0.003* + *0.008* + 0.016 + *0.005* = 0.032 **(<0.046)**	*0.003* + *0.005* = 0.008 **(<0.02)** *0.003* + *0.008* = 0.011 **(<0.02)**

[1] Treatment Pattern A: two foliar spray applications at 24-inch and 36-inch corn height, with adjuvants methylated seed oil (MSO) and urea ammonium nitrate (UAN)
Treatment Pattern B: One foliar spray application at 36-inch corn height and one directed-spray application one week later.
Treatment Pattern C: application at the same use pattern as Pattern A except adjuvants added were crop oil concentrate (COC) and UAN.
Treatment Pattern D: application at the same use pattern as Pattern A except adjuvants added were MSO and ammonium sulfate (AMS).
Treatment Pattern E: application at the same use pattern as Pattern A except adjuvants added were COC and AMS.
[2] The LOD values for tembotrione (parent), M5, M6, and M2 in field corn stover were 0.001 ppm, 0.001 ppm, 0.004 ppm, and 0.002 ppm, respectively. Residues below the LOQ (<0.01 ppm each analyte) but above the respective LOD are *italicized*. Total residues based on the LOQ of each analyte are **bolded** in parentheses.

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TABLE C.4. Summary of Residue Data from Field Corn Field Trials with Tembotrione.

Commodity	Treated[1]	PHI (days)	Sum of Residues: Parent + M5 + M6 + M2 (ppm in parent equivalents) [2]						
			n	Min	Max	HAFT	Median	Mean	Std. Dev.
Forage	A	44-53	42	<0.052	<0.471	<0.455	0.170	0.188	0.111
	B	44-48	42	<0.077	<0.322	<0.305	0.165	0.172	0.067
	C	45-46	12	<0.050	<0.242	<0.213	0.071	0.104	0.073
	D	45-46	6	<0.058	<0.144	<0.136	0.081	0.083	0.033
	E	45	6	<0.059	<0.204	<0.166	0.123	0.121	0.060
Grain	A	83-112	42	<0.04	<0.155	<0.154	0.035	0.043	0.029
	B	76-105	42	<0.04	<0.144	<0.142	0.038	0.046	0.028
	C	91-107	12	<0.04	<0.054	<0.052	0.024	0.027	0.007
	D	91-107	6	<0.04	<0.073	<0.065	0.026	0.032	0.015
	E	93-99	6	<0.04	<0.05	<0.049	0.030	0.028	0.006
Stover (fodder)	A	83-112	42	<0.04	<0.554	<0.479	0.068	0.114	0.119
	B	76-105	42	<0.04	<0.525	<0.501	0.118	0.134	0.112
	C	91-107	12	<0.04	<0.112	<0.110	0.052	0.055	0.027
	D	91-107	6	<0.045	<0.145	<0.114	0.074	0.075	0.039
	E	93-99	6	<0.041	<0.107	<0.090	0.071	0.064	0.030
Commodity	Treated[1]	PHI (days)	Sum of Residues: Parent + M5 (ppm in parent equivalents)[2]						
			n	Min	Max	HAFT	Median	Mean	Std. Dev.
Forage	A	44-53	42	<0.032	<0.375	<0.342	0.140	0.156	0.095
	B	44-48	42	<0.056	<0.290	<0.272	0.133	0.139	0.065
	C	45-46	12	<0.030	<0.215	<0.186	0.061	0.089	0.068
	D	45-46	6	<0.038	<0.124	<0.116	0.071	0.073	0.033
	E	45	6	<0.038	<0.176	<0.143	0.110	0.105	0.057
Grain	A	83-112	42	<0.02	<0.022	<0.021	0.010	0.010	0.001
	B	76-105	42	<0.02	<0.025	<0.023	0.010	0.010	0.002
	C	91-107	12	<0.02	<0.02	<0.02	0.010	0.010	0.000
	D	91-107	6	<0.02	<0.02	<0.02	0.010	0.010	0.000
	E	93-99	6	<0.02	<0.02	<0.02	0.010	0.010	0.000
Stover (fodder)	A	83-112	42	<0.02	<0.450	<0.390	0.029	0.072	0.100
	B	76-105	42	<0.02	<0.445	<0.428	0.055	0.083	0.097
	C	91-107	12	<0.02	<0.077	<0.074	0.030	0.034	0.025
	D	91-107	6	<0.02	<0.077	<0.060	0.043	0.040	0.026
	E	93-99	6	<0.02	<0.064	<0.054	0.037	0.032	0.019

[1] Treatment Pattern A: two foliar spray applications at 24-inch and 36-inch corn height for a total rate of 0.161-0.170 lb ai/A (with adjuvants MSO & UAN).
Treatment Pattern B: one foliar spray application at 36-inch corn height and one directed-spray application one week later for a total rate of 0.164-0.174 lb ai/A.
Treatment Pattern C: same use pattern as Pattern A except adjuvants added were COC & UAN.
Treatment Pattern D: same use pattern as Pattern A except adjuvants added were MSO & AMS.
Treatment Pattern E: same use pattern as Pattern A except adjuvants added were COC & AMS.

[2] The LOQ (0.01 ppm for each analyte) was used to determine the minimum, maximum, and highest-average field trial (HAFT). For the calculation of the median, mean and standard deviation ½ the LOQ (0.005 ppm for each analyte) was used for residues reported below the LOQ (or <LOD) in Tables C.3.1-C.3.3.

D. CONCLUSION

The submitted field corn field trial data are adequate and reflect the use of the SC formulation nominally containing 3.50 lb tembotrione ai/gallon (420 g ai/L) as two foliar applications made to field corn at 24- and 36-inch height (Treatment A) or one foliar spray application at 36-inch height plus one drop-nozzle (directed) spray one week later (Treatment B) at a target rate of 0.082 lb ai/A/application (0.092 kg ai/ha/application). Additional treated plots (C, D, and E) were included in some trials which received applications at the same use pattern as the treated plot A, but using different spray adjuvants. Field corn forage samples were harvested at a PHI of 44 to 53 days following total applications at 0.161-0.174 lb ai/A (0.180-0.195 kg ai/ha), and grain and stover samples were harvested at commercial maturity (BBCH 87 to 89) at PHIs ranging from 76 to 112 days. Two trials collected additional samples at various PHIs to monitor residue decline. An acceptable method was used for quantitation of residues in/on field corn forage, grain, and stover. Adequate data are available to support sample storage intervals and conditions.

Following Treatment B (one foliar application and one directed-spray application totaling 0.164-0.174 lb ai/A), the maximum combined residues of parent and its metabolites (M5 + M6 + M2), as parent equivalents, were <0.322 ppm in/on field corn forage, <0.144 ppm in/on field corn grain, and <0.525 ppm in/on field corn stover. When only residues of the parent and Metabolite M5 are summed, the maximum combined residues following Treatment A were <0.375 ppm in/on field corn forage, <0.022 ppm in/on field corn grain, and <0.450 ppm in/on field corn stover. Following Treatment B, the maximum combined residues were <0.290 ppm in/on field corn forage, <0.025 ppm in/on field corn grain, and <0.445 ppm in/on field corn stover.

E. REFERENCES

46695537.der.doc
46695601.der.doc

F. DOCUMENT TRACKING

RDI: RAB1 Chemists (1/10/07)
Petition Number: PP#5F7009
DP#s: 325349, 325663, and 331222
PC Code: 012801

Template Version June 2005

Tembotrione/AE 0172747/PC Code 012801/Bayer CropScience/264
DACO 7.5.1/OPPTS 860.1480/OECD IIA 6.4.1, 6.4.2 and IIIA 8.2, 8.4.1, 8.4.2
Livestock Feeding Study – Dairy Cows

Primary Evaluator	George F. Kramer, Ph.D., Senior Chemist Registration Action Branch (RAB1) Health Effects Division (HED) (7509P)	Date: 18-JUL-2007
Approved by	P.V. Shah, Ph.D., Branch Senior Scientist RAB1/HED (7509P)	Date: 18-JUL-2007

This DER was originally prepared under contract by Dynamac Corporation (2275 Research Boulevard, Suite 300; Rockville, MD 20850; submitted 11/30/2006). The DER has been reviewed by HED and revised to reflect current Office of Pesticide Programs (OPP) policies.

STUDY REPORT:

46695604 Mackie, S. (2005) AE 0172747 - Magnitude of the Residue in Lactating Cows. Project Number: RAAEX040, 205/010/10, 03RAAEX040. Unpublished study prepared by Bayer Corp. and Genesis Midwest Laboratories. 298 p.

The petitioner has submitted an evaluation template for the study (Bayer CropScience DER to Study RAAEX040), which was used to generate this DER; selected sections were copied without alteration or were modified to more specifically reflect the Agency's data evaluation requirements.

EXECUTIVE SUMMARY:

Bayer CropScience has submitted a cattle feeding study with tembotrione. Three treatment groups of three dairy cows each were dosed orally with gelatin capsules containing tembotrione at target dose rates approximating 3.2, 9.6, and 32 ppm in the diet (dry feed weight basis) for 29 consecutive days. Cows were milked twice daily, and samples were composited daily for each cow. All cows were sacrificed within 8 hours of the final dose on day 29. Samples of liver (portions of each lobe), kidney (center and ends), fat (composite of available omental, renal, and subcutaneous), and skeletal muscle (composite of loin, round and shank) were collected from each cow. Samples of milk collected on study days 0, 1, 3, 7, 10, 14, 17, 21, 24, 26 and 28, and samples of cream (milk fat) and skim milk collected on day 26 were retained for analysis.

Milk and tissue samples were analyzed for residues of tembotrione using the proposed liquid chromatography/mass spectroscopy (LC/MS)/MS enforcement method, Method AE-003-A04-01 (refer to 46695536.der.doc for a complete description of the method). The validated limit of quantitation (LOQ) for tembotrione was 0.01 ppm in milk and tissues, and the estimated limits of detection (LODs) ranged 0.0011-0.0024 ppm. The method is adequate for data collection based on acceptable concurrent recovery and method validation data. No storage stability data are required because all milk and tissue samples were stored frozen from collection to analysis and were analyzed within 20 days of collection.

In whole milk, cream, and skim milk, residues of tembotrione were below the LOQ (<0.01 ppm) in all samples from all dose groups. In fat and muscle, residues of tembotrione were below the LOQ (<0.01 ppm) in all samples from the 3.2-, 9.6-, and 32-ppm dose groups, with the exception of samples from one cow from the 32-ppm group which bore quantifiable tembotrione residues

of 0.025 ppm in fat and 0.014 ppm in muscle. Maximum residues of tembotrione were 0.454 ppm, 0.486 ppm, and 1.37 ppm in samples of kidney from the 3.2-, 9.6-, and 32-ppm dose groups, respectively, and 2.89 ppm, 2.96 ppm, and 3.35 ppm in samples of liver from the 3.2-, 9.6-, and 32-ppm dose groups, respectively. There appeared to be a slight residue-level dose dependence in kidney samples, but no residue-level dose dependence in liver.

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the data depicting residues in livestock are classified as scientifically acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document [DP# 325349].

COMPLIANCE:

Signed and dated Good Laboratory Practice (GLP), Quality Assurance and Data Confidentiality statements were provided. No GLP deviations were reported which would impact the study results or their interpretation.

A. BACKGROUND INFORMATION

Tembotrione, a new herbicide with broad use against mono- and dicotyledons in selected crops such as corn, is a 4-hydroxyphenylpyruvate deoxygenase (HPPD) inhibitor (bleacher). The test compound nomenclature and physiochemical properties of the test compound are presented in Tables A.1 and A.2, respectively.

TABLE A.1. Test Compound Nomenclature for Tembotrione.

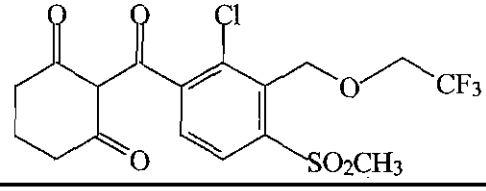
Compound: Tembotrione	Chemical Structure 
Proposed common name	Tembotrione
Company experimental name	AE 0172747
IUPAC name	2-{2-chloro-4-mesyl-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl}cyclohexane-1,3-dione
CAS name	2-[2-chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione
CAS #	335104-84-2
End-use product/EP	AE 0172747 Herbicide, EPA Reg No. 264-xxx

TABLE A.2. Physicochemical Properties of Technical Grade Tembotrione.

Parameter	Value	Reference (MRID#)
Melting point	117 °C	46695402
pH @ 24 °C	3.63	
Density (g/mL @ 20 °C)	1.56	
Water solubility (mg/L @ 20 °C)	0.22 at pH4 28.3 at pH 7 29.7 at pH 9	
Solvent solubility (g/L at 20 °C) DMSO Methylene Chloride Acetone Ethyl Acetate Toluene Hexane Ethanol	 >600 >600 300-600 180.2 75.7 47.6 8.2	
Vapor pressure (Torr, 20 °C)	8.25×10^{-11}	
Dissociation constant (pK_a)	3.2	
Octanol/water partition coefficient (P_{ow} @ 23 °C) (P_{ow} @ 24 °C) (P_{ow} @ 23 °C)	 0.0430 at pH 9.0 0.0807 at pH 7.0 144.9 at pH 2.0	
UV/visible absorption spectrum (nm)	Primary: 205 Secondary: 284 Tertiary: 240	

B. EXPERIMENTAL DESIGN

The in-life phase of the feeding study was conducted at Genesis Midwest Laboratories (GML; Neillsville, WI). Ten mature lactating dairy cattle were divided into four treatment groups (three cows/treatment group and one control cow). Three groups of three cows each were dosed orally with gelatin capsules containing tembotrione at average levels of 3.2, 9.6, and 32.0 ppm in the feed (dry weight basis). Tembotrione was weighed directly into gelatin capsules. Capsules were administered using a balling gun, once per day after the morning milking once a day for 29 consecutive days.

Cows were milked twice daily; the evening and following morning milk samples were composited for each cow. All cows were sacrificed within eight hours after the final dose on Day 29. Following termination, each animal was examined macroscopically, and representative samples totaling approximately 500 g were taken of liver (portions of each lobe), kidney (center and ends), fat (composite of available omental, renal, and subcutaneous), and skeletal muscle (composite of loin, round and shank). Descriptions of the test animals used and the dietary regime are presented in Tables B.1.1 and B.1.2; the dosing regime and sample collection procedures are summarized in Tables B.1.3 and B.1.4.

B.1. Livestock

TABLE B.1.1. Description of Livestock Used in the Feeding Study.

Species	Breed	Age	Weight at study initiation (kg)	Health status	Description of housing/holding area
Dairy cows (*Bos taurus*)	Holstein	~3-7 years	461-730	All animals clinically healthy and lactating at start of study. During study, one animal (9.6-ppm dose group) had a displaced left abomasum which was corrected surgically. A second animal (32-ppm dose group) exhibited decreased feed consumption; no physical abnormality was noted (may have been in heat).	Housed in individual stalls with stanchions in a dairy barn maintained at 54-72 °F, RH = 75%

TABLE B.1.2. Test Animal Dietary Regime.

Composition of Diet	Feed consumption (average, kg/day)	Water	Acclimation period	Predosing
Dairy ration, 8 kg Alfalfa cubes, 16 kg Baled hay, 2 kg	3.2-ppm dose group: 19.9 9.6-ppm dose group: 21.5 32-ppm dose group: 20.6 (20 kg nominal individual daily feed consumption on dry weight basis)	*Ad libitum*	15 days	None

TABLE B.1.3. Dosing Regime.

Treatment group	Treatment Type	Level of administered dose (mg/day)	Residue intake in diet (ppm)[1]	Vehicle	*Timing*/ Duration (days)
3.2 ppm	Oral	60.5 – 64.6	3.2 – 3.6	Gelatin capsule	29
9.6 ppm		190.1 – 206.4	9.2 – 11.5		
32 ppm		624.0 – 684.8	31.9 – 37.5		

[1] Based on dry weight.

TABLE B.1.4. Sample Collection.

Milk collected	Amount of milk produced during normal production (kg/cow/day)	Urine, feces and cage wash collected	Interval from last dose to sacrifice	Tissues harvested and analyzed
Milk collected twice daily; evening milk combined with the following morning milk sample for each time point; samples collected on days 0, 1, 3, 7, 10, 14, 17, 21, 24, 26, and 28 were used for the study. Skim milk (whey) and cream (milk fat) were collected on Study Day 26.	Average daily milk production: 3.2-ppm dose group: 17.5-31.1 9.6-ppm dose group: 20.4-27.0 32-ppm dose group: 18.5-24.4	Not collected	8 hours	Liver (each lobe), kidney (center and ends), fat (composite of omental, renal, and subcutaneous), and muscle (composite of loin, round, and flank)

B.2. Sampling Handling and Preparation

Milk was collected twice daily, and milk samples were retained on Days 0, 1, 3, 7, 10, 14, 17, 21, 24, 26, and 28. The evening milk for each study time point was refrigerated overnight and combined with the following morning milk samples collected predosing. Extra milk samples

from the control group animal and each cow in the high-dose (32 ppm) group were collected on Study Day 26 and centrifuged to create separate cream (milk fat) and skim milk samples. Samples of milk, cream, and skim milk were frozen and shipped weekly on dry ice to Bayer CropScience (Stillwell, KS) for analysis. The milk, cream, and skim milk samples remained in frozen (<-15 °C) storage at all times except during analysis.

After sample collection and weighing, tissue samples (liver, kidney, and muscle) were individually cubed prior to freezing; fat samples were allowed to freeze prior to cubing. The frozen tissue samples were subsequently homogenized in the presence of dry ice using a commercial food processor. Samples were shipped within 2 weeks of collection on dry ice to Bayer CropScience (Stillwell, KS), where samples were placed in frozen storage (<-15 °C) at all times except during analysis.

B.3. Analytical Methodology

Milk and tissue samples were analyzed for residues of tembotrione using the proposed LC/MS/MS enforcement method, Method AE-003-A04-01 (refer to 46695536.der.doc for a complete description of the method). A brief summary of the method, which uses an isotopically labeled internal standard of deuterated tembotrione for quantification of the analyte, was included in the submission.

Briefly, residues were extracted with acetonitrile:water (1:1, v:v) using accelerated solvent extraction. The internal standard was added, and the sample was filtered, concentrated, and reconstituted in dilute formic acid prior to quantitation by. The validated LOQ, determined as the lowest level of method validation (LLMV), for tembotrione was 0.01 ppm in milk and tissues, and the estimated LODs were 0.0019 ppm in milk, 0.002 ppm in cream (milk fat), 0.0016 ppm in skim milk, 0.0011 ppm in fat, 0.0014 ppm in kidney, 0.0020 ppm in muscle, and 0.0024 ppm in liver. The LODs were determined by multiplying the standard deviation of recovery measurements at the LOQ by $t_{0.99}$ (where $t_{0.99}$ is the one-tailed t-statistic at the 99% confidence level for n-1 replicates) and adding average residue found in the untreated control samples.

The results of method validation conducted prior to sample analysis and concurrent method validation were included in the submission.

C. RESULTS AND DISCUSSION

Sample storage conditions and intervals are summarized in Table C.2. The petitioner submitted extraction and analysis dates indicating that milk samples were stored frozen for up to 15 days, and tissue samples were stored frozen for up to 20 days prior to analysis. No storage stability data are required because all samples from the ruminant feeding study were stored frozen from collection to analysis and were analyzed within 20 days of collection.

Method validation and concurrent recovery data are presented in Table C.1. The LC/MS/MS method, Method AE-003-A04-01, was adequate for data collection based on acceptable concurrent recovery and method validation data. The fortification levels encompassed the

residues found in cattle tissues, and the recoveries were generally within the acceptable range of 70-120%, except for one sample of milk fortified at 0.010 ppm, with a recovery of 55%, and two samples of fat fortified at 0.010 ppm, with recoveries of 69%. Apparent residues of tembotrione were below the LOQ (<0.01 ppm) in 18 samples of untreated milk, one sample each of untreated cream and skim milk, and two samples each of kidney, liver, muscle, and fat. Adequate sample calculations and chromatograms were provided.

The results of the dairy cow feeding study are reported in Table C.3 and a summary of the residues of tembotrione in milk and cattle tissues is presented in Table C.4. In whole milk, cream, and skim milk, residues of tembotrione were below the LOQ (<0.01 ppm) in all samples from all dose groups. In fat and muscle, residues of tembotrione were below the LOQ (<0.01 ppm) in all samples from the 3.2-, 9.6-, and 32-ppm dose groups, with the exception of samples from one cow from the 32-ppm group which bore quantifiable tembotrione residues of 0.025 ppm in fat and 0.014 ppm in muscle. Maximum residues of tembotrione were 0.454 ppm, 0.486 ppm, and 1.37 ppm in samples of kidney from the 3.2-, 9.6-, and 32-ppm dose groups, respectively, and 2.89 ppm, 2.96 ppm, and 3.35 ppm in samples of liver from the 3.2-, 9.6-, and 32-ppm dose groups, respectively. There appeared to be a slight residue-level dose dependence in kidney samples, but no residue-level dose dependence in liver. Graphical presentations of feeding level versus residues found in kidney and liver are presented in Figures C.2.1 and C.2.2.

TABLE C.1. Summary of Concurrent and Method Validation Recoveries of Tembotrione from Dairy Cattle Milk and Tissues.

Matrix	Analyte	Spike level (ppm)	Sample size (*n*)	Recoveries (%)	Mean ± std dev[1]
Concurrent Recoveries					
Milk	Tembotrione	0.010	13	55, 74, 77, 83, 83, 86, 90, 91, 91, 92, 97, 100, 103	86 ± 13
		0.020	3	94, 100, 106	100 ± 6
		0.050	2	86, 102	94
Cream (milk fat)		0.010	1	107	107
Skim milk		0.010	1	95	95
Fat		0.010	1	90	90
		0.020	1	100	100
		0.500	1	96	96
Kidney		0.010	1	95	95
		0.500	1	99	99
		2.00	1	101	101
Muscle		0.010	1	96	96
		0.020	1	92	92
		0.500	1	99	99
Liver		0.010	1	102	102
		0.500	1	100	100
		4.00	1	100	100
Method Validation Recoveries					
Milk	Tembotrione	0.010	9	80, 82, 82, 92, 92, 94, 95, 96, 96	90 ± 7
		0.050	5	85, 86, 96, 99, 99	93 ± 7
		0.200	2	91, 96	94

TABLE C.1. Summary of Concurrent and Method Validation Recoveries of Tembotrione from Dairy Cattle Milk and Tissues.

Matrix	Analyte	Spike level (ppm)	Sample size (n)	Recoveries (%)	Mean ± std dev[1]
Cream (milk fat)		0.010	9	72, 81, 86, 88, 88, 90, 91, 92, 94	87 ± 7
		0.050	5	93, 96, 97, 99, 100	97 ± 3
		0.200	2	98, 98	98
Skim Milk		0.010	9	83, 84, 84, 85, 86, 87, 87, 96, 99	88 ± 6
		0.050	5	86, 88, 90, 90, 97	90 ± 4
		0.200	2	90, 91	91
Liver		0.010	7	83, 86, 88, 96, 97, 100, 103	93 ± 8
		0.050	3	88, 89, 90	89 ± 1
		0.200	2	85, 87	86
Kidney		0.010	7	70, 70, 75, 75, 76, 79, 82	75 ± 4
		0.050	3	78, 78, 79	78 ± 1
		0.200	2	83, 83	83
Muscle		0.010	7	81, 84, 89, 95, 95, 96, 97	91 ± 6
		0.050	3	94, 97, 99	97 ± 3
		0.200	2	95, 96	96
Fat		0.010	7	69, 69, 72, 72, 76, 76, 77	73 ± 3
		0.050	3	84, 85, 88	86 ± 2
		0.200	2	79, 80	80

[1] The standard deviation is not applicable for a sample size (n) of less than three.

TABLE C.2. Summary of Storage Conditions.

Matrix (RAC)	Storage Temperature (°C)	Actual Storage Duration[1]	Interval of Demonstrated Storage Stability
Milk	<-15	2-15 days	None submitted or required
Cream (milk fat)		4 days	
Skim milk		4 days	
Fat		17-20 days	
Kidney		15-18 days	
Muscle		17-20 days	
Liver		18 days	

[1] Interval from sample collection to analysis. All samples were analyzed within 1-2 days of extraction.

TABLE C.3. Residue Data from Ruminant Feeding Study with Tembotrione.

Collection time	Feeding Level (ppm)	Residues of Tembotrione (ppm)[1]		
Milk		**REP02**[2]	**REP03**	**REP04**
Day 10	3.2	<LOD[3]	<LOD	<LOD
Day 14		<LOD[3]	<LOD	<LOD
Day 17		<LOD	<LOD	<LOD
Day 21		<LOD	<LOD	<LOD
Milk		**REP05**	**REP06**	**REP07**
Day 0	9.6	<LOD	<LOD	<LOD
Day 1		<LOD	<LOD	<LOD
Day 3		<LOD	<LOD	<LOD
Day 7		<LOD	<LOD	<LOD[3]

TABLE C.3. Residue Data from Ruminant Feeding Study with Tembotrione.

Collection time	Feeding Level (ppm)	*Residues of Tembotrione (ppm)*[1]		
Day 10		<LOD	<LOD	<LOD
Day 14		<LOD	<LOD	(0.00585)
Day 17		<LOD	<LOD	<LOD
Day 21		<LOD	<LOD	<LOD
Milk		**REP08**	**REP09**	**REP10**
Day 0	32	<LOD	<LOD	<LOD
Day 1		<LOD	<LOD	<LOD[3]
Day 3		<LOD	<LOD	<LOD
Day 7		<LOD[3]	(0.00420)[3]	<LOD
Day 10		<LOD	<LOD	(0.00588)
Day 14		(0.00305)	<LOD	<LOD
Day 17		<LOD	<LOD	<LOD
Day 21		<LOD	(0.00374)	<LOD
Day 24		<LOD	(0.00581)	<LOD
Day 26		<LOD	(0.00484)	<LOD
Day 28		<LOD	<LOD	(0.00896)
Cream (milk fat)		**REP08**	**REP09**	**REP10**
Day 26	32 (10x)	<LOD	(0.00284)	<LOD
Skim milk		**REP08**	**REP09**	**REP10**
Day 26	32 (10x)	<LOD	(0.00407)	<LOD
Fat				
Day 29	3.2	**REP02**	**REP03**	**REP04**
		(0.00112)	(0.00809)	(0.00197)
	9.6	**REP05**	**REP06**	**REP07**
		<LOD	(0.00566)	<LOD
	32	**REP08**	**REP09**	**REP10**
		<LOD	0.02547[3]	(0.00353)
Kidney				
Day 29	3.2	**REP02**	**REP03**	**REP04**
		0.45358	0.44647	0.39372
	9.6	**REP05**	**REP06**	**REP07**
		0.47673	0.48567	0.21311
	32	**REP08**	**REP09**	**REP10**
		0.85580[3]	1.36824[3]	0.78760[3]
Muscle				
Day 29	3.2	**REP02**	**REP03**	**REP04**
		<LOD	<LOD	<LOD
	9.6	**REP05**	**REP06**	**REP07**
		<LOD	(0.00243)	<LOD
	32	**REP08**	**REP09**	**REP10**
		(0.00408)	0.01418[3]	(0.00327)

TABLE C.3. Residue Data from Ruminant Feeding Study with Tembotrione.				
Collection time	Feeding Level (ppm)	Residues of Tembotrione (ppm)[1]		
Liver				
Day 29	3.2	**REP02**	**REP03**	**REP04**
		2.46412[3]	2.89052[3]	1.99541[3]
	9.6	**REP05**	**REP06**	**REP07**
		2.95544[3]	2.64125[3]	1.39628[3]
	32	**REP08**	**REP09**	**REP10**
		3.08321[3]	2.93306[3]	3.34707[3]

[1] LOQ = 0.01 ppm in milk and tissues. The estimated LOD for tembotrione is 0.0019 ppm in milk, 0.0016 ppm in skim milk, 0.0011 ppm in fat, 0.0014 ppm in kidney, 0.0020 ppm in muscle, and 0.0024 ppm in liver. Values >LOD and <LOQ are reported in parentheses.
[2] Animal identification numbers = REPXX.
[3] Replicate analyses of a single sample; maximum residues are reported.

Table C.4. Summary of Residue Data from Ruminant Feeding Study with Tembotrione.

Matrix	Feeding Level (ppm)	Residue Levels (ppm)[1]					
		n	Min	Max	Median	Mean	Std. Dev.
Milk Days 10, 14, 17, and 21	3.2	11	<0.010	<0.010	<0.005	<0.005	N/A
Milk Days 0, 1, 3, 7, 10, 14, 17, and 21	9.6	24	<0.010	<0.010	<0.005	<0.005	N/A
Milk Days 0, 1, 3, 7, 10, 14, 17, 21, 24, 26, and 28	32	33	<0.010	<0.010	<0.005	<0.005	N/A
Cream (milk fat) Day 26	32	3	<0.010	<0.010	<0.005	<0.005	N/A
Skim milk Day 26	32	3	<0.010	<0.010	<0.005	<0.005	N/A
Fat Day 29	3.2	3	<0.010	<0.010	<0.005	<0.005	N/A
	9.6	3	<0.010	<0.010	<0.005	<0.005	N/A
	32	3	<0.010	0.025	0.005	0.012	0.012
Kidney Day 29	3.2	3	0.394	0.454	0.446	0.431	0.033
	9.6	3	0.213	0.486	0.477	0.392	0.155
	32	3	0.788	1.37	0.856	1.004	0.317
Muscle Day 29	3.2	3	<0.010	<0.010	<0.005	<0.005	N/A
	9.6	3	<0.010	<0.010	<0.005	<0.005	N/A
	32	3	<0.010	0.014	0.005	0.008	0.005
Liver Day 29	3.2	3	2.00	2.89	2.46	2.45	0.448
	9.6	3	1.40	2.96	2.64	2.33	0.825
	32	3	2.93	3.35	3.08	3.12	0.210

[1] For calculation of the minimum and maximum, the LOQ (0.01 ppm) was used for residues reported below the LOQ (or <LOD) in Table C.3. In the calculation of the median, mean, and standard deviation, 0.005 ppm (half the LOQ) was used for residues reported as less than the LOD and for residues reported between the LOD and LOQ.

FIGURE C.2.1. Linear Regression of Residues on Feeding Level in Kidney

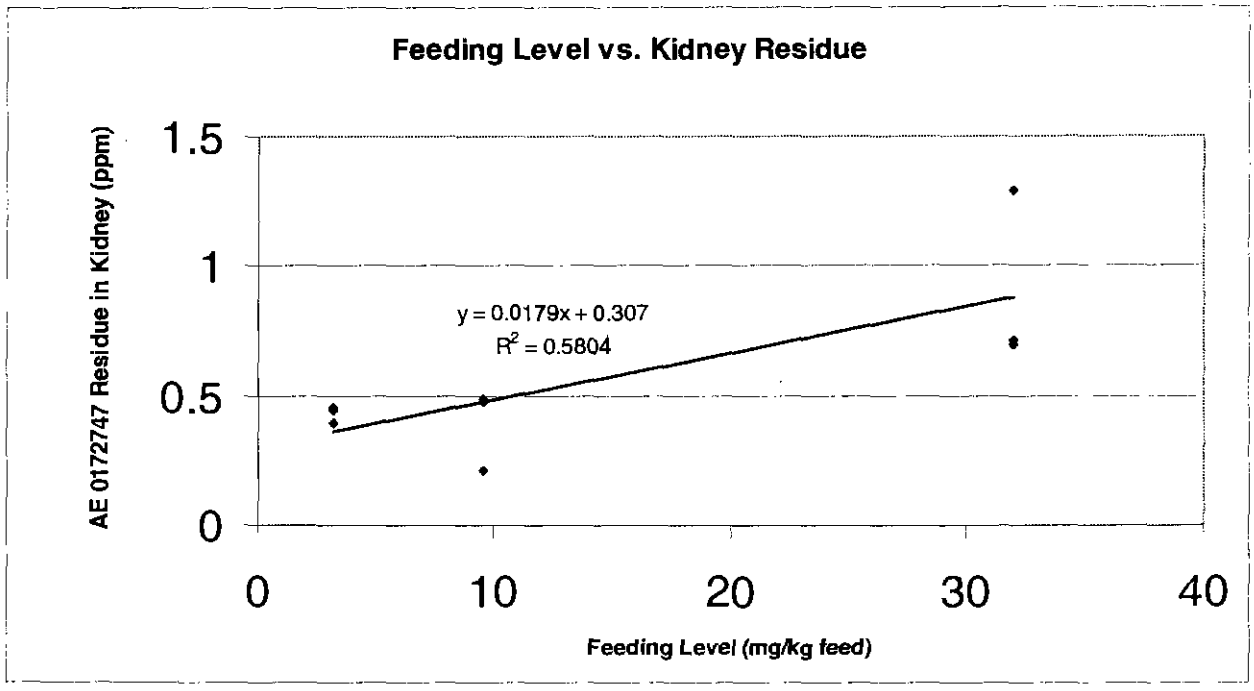
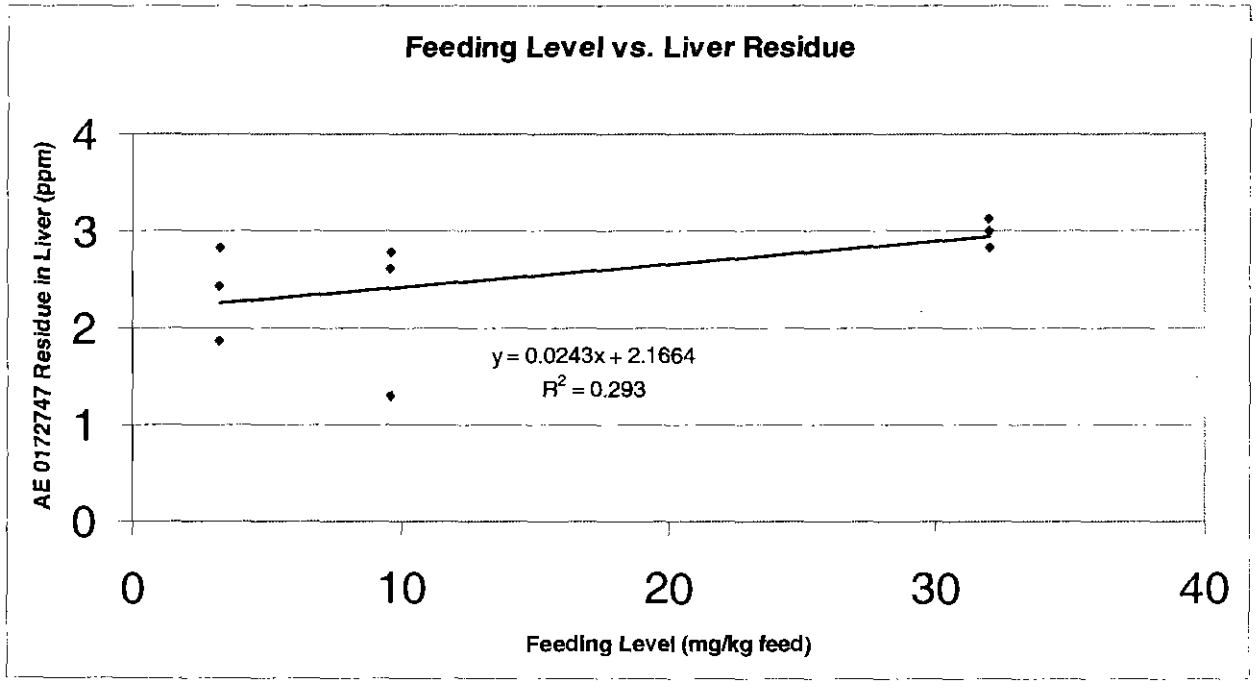


FIGURE C.2.2. Linear Regression of Residues on Feeding Level in Liver



D. CONCLUSION

The submitted dairy cattle feeding study is adequate to demonstrate the magnitude of residues of tembotrione in cattle commodities. The feeding study reflects dietary levels of tembotrione at 3.2, 9.6, and 32 ppm. No residues of tembotrione greater than the LOQ of 0.010 ppm were detected in untreated or treated bovine whole milk, skim milk or cream at any dose level. No residues of tembotrione were detected in any of the treated fat or muscle samples with the exception of one high-dose (32 ppm) cow that had residues of 0.025 ppm in the fat and 0.014 ppm in the muscle. Residues of tembotrione were found in significant amounts in the excretory organs of kidney and liver in all treated cows regardless of dose level. The petitioner noted that there appeared to be a slight residue-level dose dependence in kidney samples, but no residue-level dose dependence in liver. Residues were determined using an acceptable method, and no storage stability data were required to support the study.

E. REFERENCES

46695536.der.doc

F. DOCUMENT TRACKING

RDI: RAB1 Chemists (1/10/07)
Petition Number: PP#5F7009
DP#s: 325349, 325663, and 331222
PC Code: 012801

Template Version June 2005

Tembotrione/AE 0172747/PC Code 012801/Bayer CropScience/264
DACO 7.2.4/OPPTS 860.1360/OECD IIIA 5.3.1
Multiresidue Analytical Methods

Primary Evaluator	George F. Kramer, Ph.D., Senior Chemist Registration Action Branch (RAB1) Health Effects Division (HED) (7509P)	Date: 18-JUL-2007
Approved by	P.V. Shah, Ph.D., Branch Senior Scientist RAB1/HED (7509P)	Date: 18-JUL-2007

This DER was originally prepared under contract by Dynamac Corporation (2275 Research Boulevard, Suite 300; Rockville, MD 20850; submitted 11/10/2006). The DER has been reviewed by HED and revised to reflect current Office of Pesticide Programs (OPP) policies.

STUDY REPORT:

46695546 Perez, R. (2005) Evaluation of AE 0172747 and Relevant Metabolites FDA Multiresidue Method (MRM) Testing. Project Number: RAAEX013, ADPEN/982/2K5/0502, ADPEN/982/2K5/0502/001. Unpublished study prepared by Adpen Labs. 112 p.

EXECUTIVE SUMMARY:

The usefulness of the multiresidue method (MRM) Protocols A, B, C, D, E, and F, as described in the Food and Drug Administration (FDA) Pesticide Analytical Manual (PAM) Vol. I, was evaluated for measuring residues of tembotrione and its metabolites AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2). The decision tree for multiresidue testing (PAM Vol. I, Appendix II-2) was followed as a technical guide for testing the various Protocols.

The parent and its metabolites did not provide a response or viable chromatography under the conditions required for Protocol A. Protocol B is not applicable for tembotrione, AE 0456148, and AE 1417268 because they are not phenols. However, the metabolites AE 0456148 and AE 1392936 are acids and were tested using Protocol B; testing on these two metabolites were terminated because they were not soluble in acetone, the solvent required by Protocol B. Protocol G was not considered for testing because tembotrione and its metabolites are not substituted ureas. Tembotrione was not recovered with Florisil column cleanup and was not further tested through Protocols D, E, and F. Protocols D, E, and F, may be used for screening of metabolite AE 0456148 in corn grain and oil, if residues are at high levels, but these methods are not adequate for quantitation of AE 0456148. In summary, the MRMs are not suitable for the analysis of tembotrione or its metabolites.

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the MRM testing data are classified as scientifically acceptable and will be forwarded to FDA for further evaluation. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document [DP# 325349].

COMPLIANCE:

Signed and dated Good Laboratory Practice (GLP), Quality Assurance and Data Confidentiality statements were provided. No deviations from regulatory requirements were reported which would have an impact on the validity of the study.

A. BACKGROUND INFORMATION

Tembotrione, a new herbicide with broad use against mono- and dicotyledons in selected crops such as corn, is a 4-hydroxyphenylpyruvate deoxygenase (HPPD) inhibitor (bleacher). Details of the test compounds nomenclature (tembotrione and its three metabolites) and physiochemical properties of tembotrione are given in Tables A.1 and A.2.

TABLE A.1. Test Compound Nomenclature for Tembotrione and its Metabolites AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2).

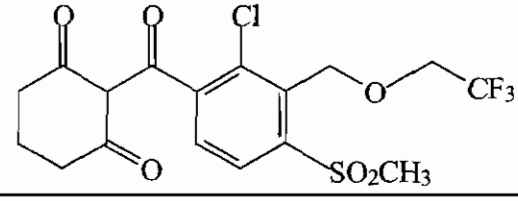
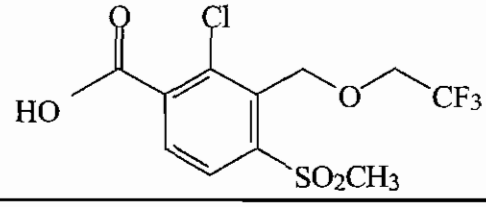
Compound: Tembotrione	Chemical Structure 
Common name	Tembotrione (Parent)
Company experimental name	AE 0172747
IUPAC name	2-{2-Chloro-4-mesyl-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl}cyclohexane-1,3-dione
CAS name	2-[2-Chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione
CAS #	335104-84-2
End-use product/EP	AE 0172747 Herbicide, EPA Reg No. 264-xxx
Compound: AE 0456148	Chemical Structure 
Common name	Metabolite M6
Company experimental name	AE 0456148
IUPAC name	None provided
CAS name	2-chloro-4-mesyl-3-[(2,2,2-trifluroethoxy)methyl]benzoic acid
CAS #	None provided

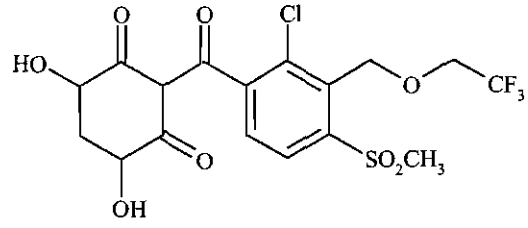
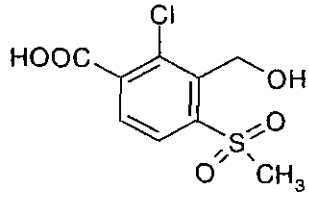
TABLE A.1. Test Compound Nomenclature for Tembotrione and its Metabolites AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2).	
Compound: AE 1417268	Chemical Structure 
Common name	Metabolite M5
Company experimental name	AE 1417268
IUPAC name	None provided
CAS name	2-[2-chloro-4-(methylsulfonyl)-3-[2,2,2-trifluoroethoxy)methyl]benzoyl]-4,6-dihydroxycyclohexan-1,3-dione
CAS #	None provided
Compound: AE 1392936	Chemical Structure 
Common name	Metabolite M2
Company experimental name	AE 1392936
IUPAC name	None provided
CAS name	2-chloro-3-hydroxymethyl-4-mesylbenzoic acid
CAS #	None provided

TABLE A.2. Physicochemical Properties of Technical Grade Tembotrione.		
Parameter	Value	Reference (MRID#)
Melting point	117 °C	46695402
pH @ 24 °C	3.63	
Density (g/mL @ 20 °C)	1.56	
Water solubility (mg/L @ 20 °C)	0.22 at pH4 28.3 at pH 7 29.7 at pH 9	
Solvent solubility (g/L at 20 °C) DMSO Methylene Chloride Acetone Ethyl Acetate Toluene Hexane Ethanol	 >600 >600 300-600 180.2 75.7 47.6 8.2	
Vapor pressure (Torr, 20 °C)	8.25×10^{-11}	
Dissociation constant (pK_a)	3.2	

TABLE A.2. Physicochemical Properties of Technical Grade Tembotrione.

Parameter	Value	Reference (MRID#)
Octanol/water partition coefficient (P_{ow} @ 23 °C) (P_{ow} @ 24 °C) (P_{ow} @ 23 °C)	 0.0430 at pH 9.0 0.0807 at pH 7.0 144.9 at pH 2.0	
UV/visible absorption spectrum (nm)	Primary: 205 Secondary: 284 Tertiary: 240	

B. MATERIALS AND METHODS

Tembotrione and its metabolites AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2) were screened through MRMs, PAM Vol. I (1/94), Protocols A, B, C, D, E, and F. Tembotrione and its metabolites are not substituted ureas and were not tested through Protocol G.

C. RESULTS AND DISCUSSION

Using Protocol A, tembotrione and its metabolites were determined not to be naturally fluorescent. Protocol B testing was terminated because tembotrione and its metabolites were not soluble in the specified solvent and, therefore, could not be derivatized. Metabolites AE 1417268 and AE 1392936 were not recovered under Protocol C. Tembotrione and metabolite AE 0456148 produced a single broad peak or two symmetric peaks, respectively, at 50% full-scale deflection (FSD). Tembotrione was not recovered with Florisil column cleanup and was not further tested through Protocols D, E, and F.

AE 0456148 was recovered with Florisil column cleanup and because of poor sensitivity with gas chromatography/electron-capture detection (GC/ECD), higher fortification levels were chosen for further testing with corn meal (non-fatty matrix) and corn oil (fatty matrix). Recoveries of AE 0456148 from corn meal under Protocol D (Module E1; C1 eluant) were inconsistent (119% or 0%) due to matrix interference. Under Protocol E, acceptable recoveries of AE 0456148 from corn meal were obtained at the 5-ppm fortification level (72 and 107%), and at the 10-ppm fortification level (73 and 74%) using the C2-2 eluant. Under Protocol F, recoveries >30% were achieved for AE 0456148 from corn oil using C1 (15%) eluant (46.4 and 47.3% at 81-ppm level and 61.3 and 66.8% at 121-ppm level); using C1 (50%) eluant (34.2 and 35.1% at 81-ppm level and 29.1 and 35.6% at 121-ppm level); and using C2-2 eluant (64.6 and 70.4% at 81-ppm level and 67.2 and 71.6% at 121-ppm level).

Results of the multi-residue methods testing are presented in Table C.1.

TABLE C.1. Results of MRM Testing with Tembotrione and Its Metabolites AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2).

PAM I Protocol	Results	Comments
A	Tembotrione and its metabolites are not N-methylcarbamates, and no response was noted for these compounds using high-performance liquid chromatography (HPLC) and fluorescence parameters in Module DL2.	Tembotrione and its metabolites are not naturally fluorescent; further work was terminated.
B	Tembotrione and its metabolites are not phenols, but metabolites AE 0456148 and AE 1392936 are acids. Metabolites AE 0456148 and AE 1392936 could not be dissolved in acetone as per the protocol, and no other conditions to derivatize these compounds that would work with the procedure were available.	Tembotrione and its metabolites could not be derivatized; further work was terminated.
C	The chromatographic system (GC/ECD) was unsuitable for metabolites AE 1417268 and AE 1392936; inconsistent results were obtained using Modules DG 10 and DG 13. Tembotrione fragmented into three peaks with Module DG 13 (DB-17 column) and produced a tailing single broad peak at 50% FSD (100 ng) using Module DG 10 (DB-1 column). AE 0456148 (M6) fragmented into several peaks with Module DG 13 (DB-17 column) and produced two symmetric peaks at 50% FSD (1007 ng) using Module DG 7 (DB-1 column).	
D	Tembotrione was not recovered through Florisil columns (Section 302, C1 and C5 eluants); not further tested. AE 0456148 (M6) was recovered from Florisil columns at 112% using C1 eluants, and at 116% for 15% ethyl ether/petroleum ether (EE/PE) and 11% for 50% EE/PE using C5 eluants. Because of poor sensitivity, higher fortification levels (3 and 6 ppm) were chosen for AE 045148 testing with corn meal (non-fatty matrix); using Module E1 (C1 eluant) recovery for one corn meal sample fortified at 6 ppm was 119%, but the remaining 6-ppm fortified sample and the 3-ppm fortified samples were not recovered due to matrix interference.	Not conducted with metabolites AE 1417268 and AE 1392936, because of Protocol C results.
E	AE 0456148 (M6) was recovered with Florisil column cleanup using C1 (6%) eluant at 97.6-103%; sporadic recoveries were obtained with C1 (15% and 50%) eluants and C2 eluants. Because of poor sensitivity, higher fortification levels (5 and 10 ppm) were chosen for AE 0456148 testing with corn meal (non-fatty matrix); recoveries were 72 and 107% at the 5-ppm fortification level, and 73 and 74% at the 10-ppm fortification level using the C2-2 eluant. Poor or inconsistent recoveries (0-244%) from fortified corn meal were obtained using C1 eluants and the other C2 eluants.	Not conducted with metabolites AE 1417268 and AE 1392936, because of Protocol C results; not conducted for tembotrione because not recovered with Florisil column cleanup.
F	AE 0456148 (M6) was recovered with Florisil column cleanup using C1 (6%) eluant at 97.6-103; sporadic recoveries were obtained with the other C1-C4 eluants. Because of poor sensitivity, higher fortification levels (81 and 121 ppm) were chosen for AE 0456148 testing with corn oil (fatty matrix). Recoveries were: 0% with C1 (6%), C2-1, and C2-3 eluants; 46.4 and 47.3% at 81-ppm level and 61.3 and 66.8% at 121-ppm level using C1 (15%) eluant; 34.2 and 35.1% at 81-ppm level and 29.1 and 35.6% at 121-ppm level using C1 (50%) eluant; and 64.6 and 70.4% at 81-ppm level and 67.2 and 71.6% at 121-ppm level using C2-2 eluant.	Not conducted with metabolites AE 1417268 and AE 1392936, because of Protocol C results; not conducted for tembotrione because not recovered with Florisil column cleanup.
G	Tembotrione and its metabolites are not substituted ureas.	Not conducted.
H		Not included in the report.

D. CONCLUSION

The MRMs are not suitable for the analysis of tembotrione or its metabolites. The MRMs, Protocols D, E, and F may be used for screening of metabolite AE 0456148 in corn grain and oil, if residues are at high levels, but these methods are not adequate for quantitation of AE 0456148. These data will be forwarded to the U.S. FDA for further evaluation.

E. REFERENCES

None.

F. DOCUMENT TRACKING

RDI: RAB1 Chemists (1/3/07)
Petition Number: PP#5F7009
DP#s: 325349, 325663, and 331222
PC Code: 012801

Template Version June 2005

Primary Evaluator	George F. Kramer, Ph.D., Senior Chemist Registration Action Branch (RAB1) Health Effects Division (HED) (7509P)	Date: 18-JUL-2007
Approved by	P.V. Shah, Ph.D., Branch Senior Scientist RAB1/HED (7509P)	Date: 18-JUL-2007

This DER was originally prepared under contract by Dynamac Corporation (2275 Research Boulevard, Suite 300; Rockville, MD 20850; submitted 11/30/2006). The DER has been reviewed by HED and revised to reflect current Office of Pesticide Programs (OPP) policies.

STUDY REPORT:

46695601 Coopersmith, H. (2005) Storage Stability of AE 0172747, AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2) in Corn Grain, Forage and Fodder. Project Number RAAEX034. Unpublished study prepared by Bayer CropScience. 154 pages.

The petitioner has submitted an evaluation template for the study (Bayer CropScience DER for Study RAAEX034), which was used to generate this DER; several sections were copied without alteration or modified to more specifically reflect the Agency's data evaluation requirements.

EXECUTIVE SUMMARY:

Bayer CropScience has submitted the results of a storage stability study with tembotrione and its metabolites AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2) in/on corn matrices. Untreated samples of corn grain, forage and stover (fodder) were fortified with tembotrione, AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2), each at a level of 0.2 ppm. The fortified as well as control samples were then stored frozen (≤-10 °C) and analyzed at intervals of 0, 91-99 days (~3 months), 181-188 days (~6 months), and 369-398 days (~12-13 months).

The results indicate that under these conditions, residues of the parent, tembotrione, and metabolites M6 and M2 appear to be stable in/on corn grain, forage, and stover for up to 396-398 days (~13 months). M5 was shown to be stable in corn grain for up to 188 days (~6 months) but declined by 17% after 371 days (61% average corrected recovery). M5 appeared reasonably stable in/on corn forage and stover for up to 369-371 days (~12 months) if the 35% recovery from samples of corn forage at storage interval of 188 days is deemed an outlier.

Samples of corn grain, forage and stover were analyzed for residues of tembotrione, AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2) using liquid chromatography/mass spectroscopy (LC/MS)/MS Method No. AE/03/01. This method is adequate for data collection based on acceptable method recoveries. The validated limit of quantitation (LOQ) is 0.010 ppm for each analyte in crops. The calculated limits of detection (LODs) for the parent and its metabolites were each ≤0.004 ppm in corn matrices.

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the storage stability data are classified as scientifically acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document [DP# 325349].

COMPLIANCE:

Signed and dated Good Laboratory Practice (GLP), Quality Assurance and Data Confidentiality statements were provided. No deviations from regulatory requirements were reported which would have an impact on the validity of the study.

A. BACKGROUND INFORMATION

Tembotrione, a new herbicide with broad use against mono- and dicotyledons in selected crops such as corn, is a 4-hydroxyphenylpyruvate deoxygenase (HPPD) inhibitor (bleacher). Details of the test compounds nomenclature (tembotrione and its three metabolites) and physiochemical properties of tembotrione are given in Tables A.1 and A.2.

TABLE A.1. Test Compound Nomenclature for Tembotrione and its Metabolites AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2).

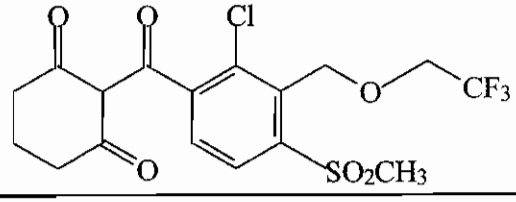
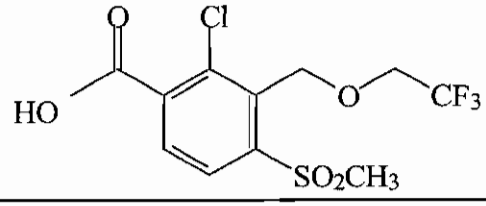
Compound: Tembotrione	Chemical Structure 
Common name	Tembotrione (Parent)
Company experimental name	AE 0172747
IUPAC name	2-{2-Chloro-4-mesyl-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl}cyclohexane-1,3-dione
CAS name	2-[2-Chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione
CAS #	335104-84-2
End-use product/EP	AE 0172747 Herbicide, EPA Reg No. 264-xxx
Compound: AE 0456148	Chemical Structure 
Common name	Metabolite M6
Company experimental name	AE 0456148

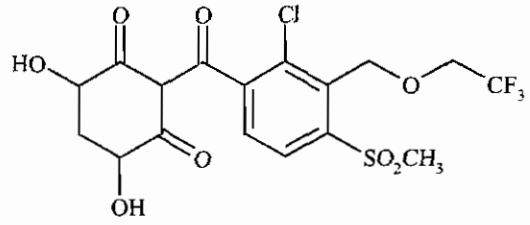
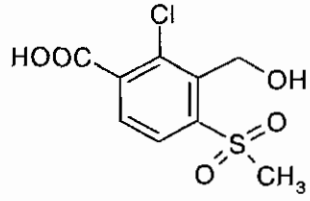
TABLE A.1. Test Compound Nomenclature for Tembotrione and its Metabolites AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2).	
IUPAC name	None provided
CAS name	2-chloro-4-mesyl-3-[(2,2,2-trifluroethoxy)methyl]benzoic acid
CAS #	None provided
Compound: AE 1417268	Chemical Structure 
Common name	Metabolite M5
Company experimental name	AE 1417268
IUPAC name	None provided
CAS name	2-[2-chloro-4-(methylsulfonyl)-3-[2,2,2-trifluoroethoxy)methyl]benzoyl]-4,6-dihydroxycyclohexan-1,3-dione
CAS #	None provided
Compound: AE 1392936	Chemical Structure 
Common name	Metabolite M2
Company experimental name	AE 1392936
IUPAC name	None provided
CAS name	2-chloro-3-hydroxymethyl-4-mesylbenzoic acid
CAS #	None provided

TABLE A.2. Physicochemical Properties of Technical Grade Tembotrione.		
Parameter	Value	Reference (MRID#)
Melting point	117 °C	46695402
pH @ 24 °C	3.63	
Density (g/mL @ 20 °C)	1.56	
Water solubility (mg/L @ 20 °C)	0.22 at pH 4 28.3 at pH 7 29.7 at pH 9	

TABLE A.2. Physicochemical Properties of Technical Grade Tembotrione.		
Parameter	Value	Reference (MRID#)
Solvent solubility (g/L at 20 °C)		
DMSO	>600	
Methylene Chloride	>600	
Acetone	300-600	
Ethyl Acetate	180.2	
Toluene	75.7	
Hexane	47.6	
Ethanol	8.2	
Vapor pressure (Torr, 20 °C)	8.25×10^{-11}	
Dissociation constant (pK_a)	3.2	
Octanol/water partition coefficient		
(P_{ow} @ 23 °C)	0.0430 at pH 9.0	
(P_{ow} @ 24 °C)	0.0807 at pH 7.0	
(P_{ow} @ 23 °C)	144.9 at pH 2.0	
UV/visible absorption spectrum (nm)	Primary: 205 Secondary: 284 Tertiary: 240	

B. EXPERIMENTAL DESIGN

B.1. Sample Handling and Preparation

Untreated samples of corn grain, forage and stover were obtained from crop field trial studies. Homogenized samples were weighed into vials and fortified with a mixed fortification standard of tembotrione, AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2), each at a level of 0.2 ppm. The mixed fortification standard was prepared in acetonitrile (ACN). The stability of the fortification standards was not reported. Fortified and unfortified samples were stored frozen (≤-10 EC) and analyzed at 0-, 91- to 99-, 181- to 188- and 369- to 398- day storage intervals.

B.2. Analytical Methodology

Samples of corn grain, forage, and stover were analyzed for residues of the parent compound, tembotrione, and the metabolites AE 1392936 (M2), AE 1417268 (M5), and AE 0456148 (M6) using LC/MS/MS Method No. AE/03/01. This method quantifies all analytes from a single sample using isotopically labeled internal standards.

Briefly, residues of tembotrione and its metabolites M2, M5, and M6 were extracted from crop matrices with acetonitrile:water (1:1, v/v) using accelerated solvent extraction (Dionex Corporation, Sunnyvale, CA). Internal standards of the deuterated analytes were added to the extract. For parent, M5, and M6 analysis, an aliquot of the extract was concentrated via Turbo-Vap. For M2 analysis, an aliquot of the extract was loaded onto a strong-anion exchange (SAX) solid-phase extraction (SPE) cartridge and eluted with oxalic acid. The SPE eluate was concentrated. The concentrates were reconstituted in 0.1% formic acid and filtered through a nylon syringe filter. The total tembotrione residue was quantitated by high-performance LC/MS/MS. Concurrent recoveries were performed during sample analysis to demonstrate acceptable method performance.

The validated LOQ reported in the method is 0.010 ppm for each analyte in crops. The reported LODs for tembotrione, AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2) in corn grain are 0.0011 ppm, 0.0029 ppm, 0.0025 ppm, and 0.0017 ppm, respectively. The reported LODs for tembotrione, AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2) in corn forage are 0.0014 ppm, 0.0021 ppm, 0.0023 ppm, and 0.0021 ppm, respectively. The reported LODs for tembotrione, AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2) in corn stover are 0.0009 ppm, 0.0040 ppm, 0.0013 ppm, and 0.0024 ppm, respectively.

C. RESULTS AND DISCUSSION

Based on the concurrent method recovery data (see Table C.1), LC/MS/MS Method AE/03/01 is adequate for the determination of residues of tembotrione, AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2) in corn matrices. Method recoveries from concurrent analysis of samples were generally within the acceptable range of 70-120%, except for one corn forage sample fortified with AE 01727747 at 0.2 ppm, which resulted in a recovery of 66%, one corn forage sample fortified with M6 at 0.2 ppm, which resulted in a recovery of 57%, one corn forage sample fortified with M2 at 0.2 ppm, which resulted in a recovery of 67%, and one corn stover sample fortified with M2 at 0.2 ppm, which resulted in a recovery or 129%. HED notes that the mean concurrent recovery for each analyte ranged 71-106% in corn forage and 81-114% in corn stover. Apparent residues of tembotrione, AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2) were less than the LOQ (<0.01 ppm) in all control samples for corn. HED notes that apparent residues above the LOD were found ranging from 0.003-0.009 ppm for tembotrione, AE 0456148 (M6), and AE 1392936 (M2). The petitioner used these results to correct the residue levels in the fortified samples.

The results of the storage stability studies are presented in Table C.2. Based on the reported results, residues of the parent, tembotrione, and metabolites M6 and M2 appear to be stable in/on corn grain, forage, and stover for up to 396-398 days (~13 months). M5 was shown to be stable in corn grain for up to 188 days (~6 months) but declined by 17% after 371 days (61% average corrected recovery). M5 appeared reasonably stable in/on corn forage and stover for up to 369-371 days (~12 months) if the 35% recovery from corn forage at storage interval of 188 days is deemed an outlier.

TABLE C.1. Summary of Concurrent Recoveries of Tembotrione and Metabolites in Corn Matrices

Matrix	Spike level (ppm)	Storage Interval (days)[1]	Sample size (n)	Recoveries (%)	Mean ± std dev[2]
Tembotrione (parent)					
Corn, grain	0.200	0(1)	3	81, 83, 86	84±2.5
	0.200	91(0)	2	94, 96	95
	0.200	182(1)	2	81, 85	83
	0.200	396(1)	2	90, 93	92
Corn, forage	0.200	0(1)	3	84, 85, 87	85±1.5
	0.200	91(0)	2	66, 102	84
	0.200	182(1)	2	86, 91	88
	0.200	396(1)	2	88, 92	90
Corn, stover	0.200	0(1)	3	72, 84, 87	81±7.9
	0.200	91(0)	2	79, 82	81
	0.200	182(1)	2	87, 91	89
	0.200	398(1)	2	92, 96	94
AE 0456148 (M6)					
Corn, grain	0.200	0(1)	3	99, 104, 106	103±3.6
	0.200	91(0)	2	93, 101	97
	0.200	186(1)	2	100, 102	101
	0.200	396(1)	2	90, 90	90
Corn, forage	0.200	0(1)	3	103, 103, 107	104±2.3
	0.200	91(0)	2	57, 94	76
	0.200	182(1)	2	92, 93	93
	0.200	396(1)	2	90, 90	90
Corn, stover	0.200	0(1)	3	110, 112, 119	114±4.7
	0.200	91(0)	2	80, 84	82
	0.200	182(1)	2	93, 94	94
	0.200	398(1)	2	92, 96	94
AE 1417268 (M5)					
Corn, grain	0.200	0(1)	3	73, 79, 80	77±3.8
	0.200	99(1)	2	89, 90	90
	0.200	188(1)	2	78, 86	82
	0.200	371(1)	2	82, 86	84
Corn, forage	0.200	0(1)	3	83, 83, 89	85±3.5
	0.200	99(1)	2	70, 72	71
	0.200	188(1)	2	90, 104	97
	0.200	369(1)/371(1)	4	91, 94, 95, 95	94±1.9
Corn, stover	0.200	0(1)	3	82, 84, 87	84±2.5
	0.200	99(1)	2	89, 91	90
	0.200	188(1)	2	83, 88	86
	0.200	371(1)	2	86, 87	87

TABLE C.1. Summary of Concurrent Recoveries of Tembotrione and Metabolites in Corn Matrices

Matrix	Spike level (ppm)	Storage Interval (days)[1]	Sample size (n)	Recoveries (%)	Mean ± std dev[2]
AE 1392936 (M2)					
Corn, grain	0.200	0(1)	3	79, 84, 88	84±4.5
	0.200	91(1)	2	94, 100	97
	0.200	187(3)	2	86, 96	91
	0.200	396(2)	2	100, 110	105
Corn, forage	0.200	0(1)	3	100, 108, 110	106±5.3
	0.200	91(1)	2	67, 98	83
	0.200	187(3)	2	95, 101	98
	0.200	396(2)	2	94, 104	99
Corn, stover	0.200	0(1)	3	102, 105, 116	108±7.4
	0.200	91(1)	2	89, 129	109
	0.200	187(3)	2	98, 105	102
	0.200	398(2)	2	102, 106	104

[1] The storage interval from fortification to extraction; the days from extraction to analysis are reported in parentheses.
[2] If sample size (n=2), then a standard deviation was not calculated, only the mean was reported.

The following graphs (Figures C.1 through C.4) were copied without alteration from the study profile prepared by the petitioner for MRID 46695601.

Figure C.1. Storage Stability of Tembotrione in Corn Matrices

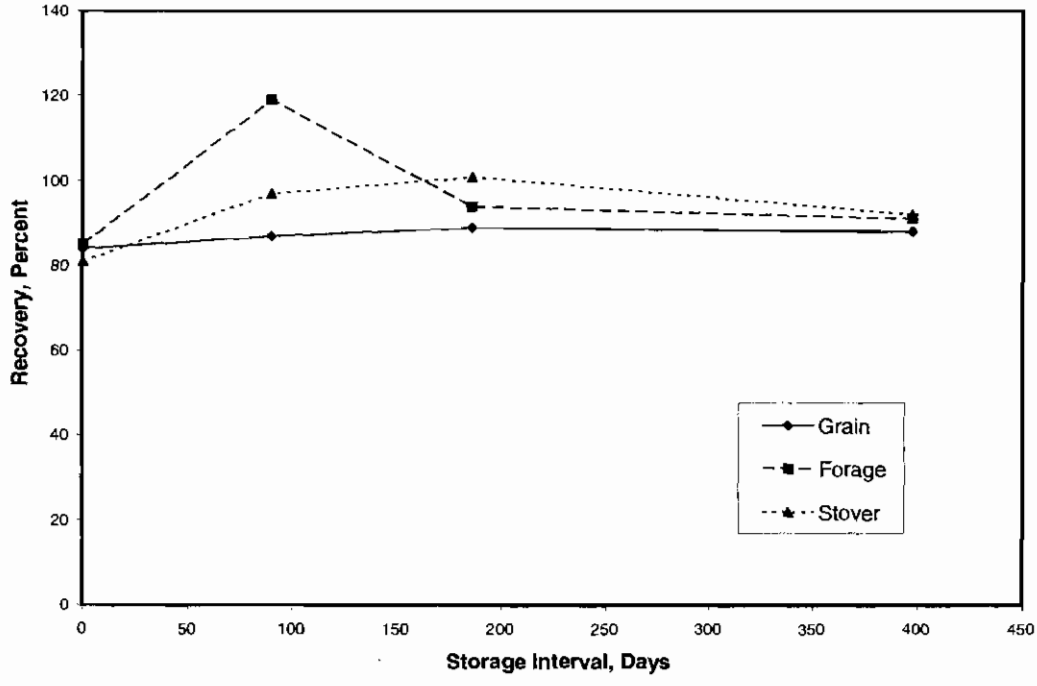


Figure C.2. Storage Stability of AE 0456148 (M6) in Corn Matrices

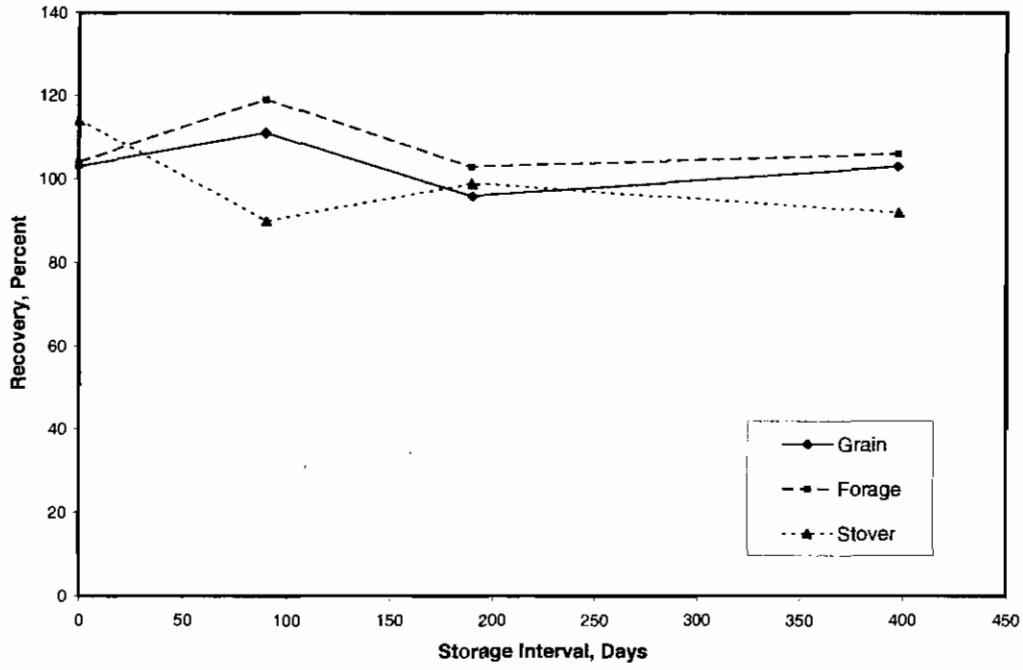


Figure C.3. Storage Stability of AE 1417268 (M5) in Corn Matrices

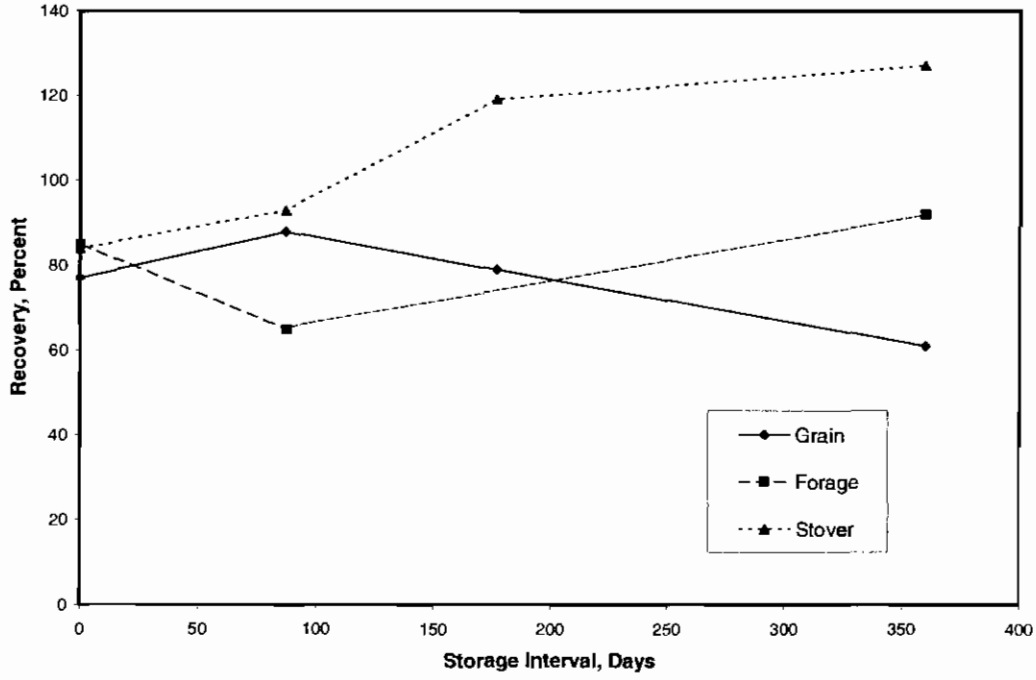


Figure C.4. Storage Stability of AE 1392936 (M2) in Corn Matrices

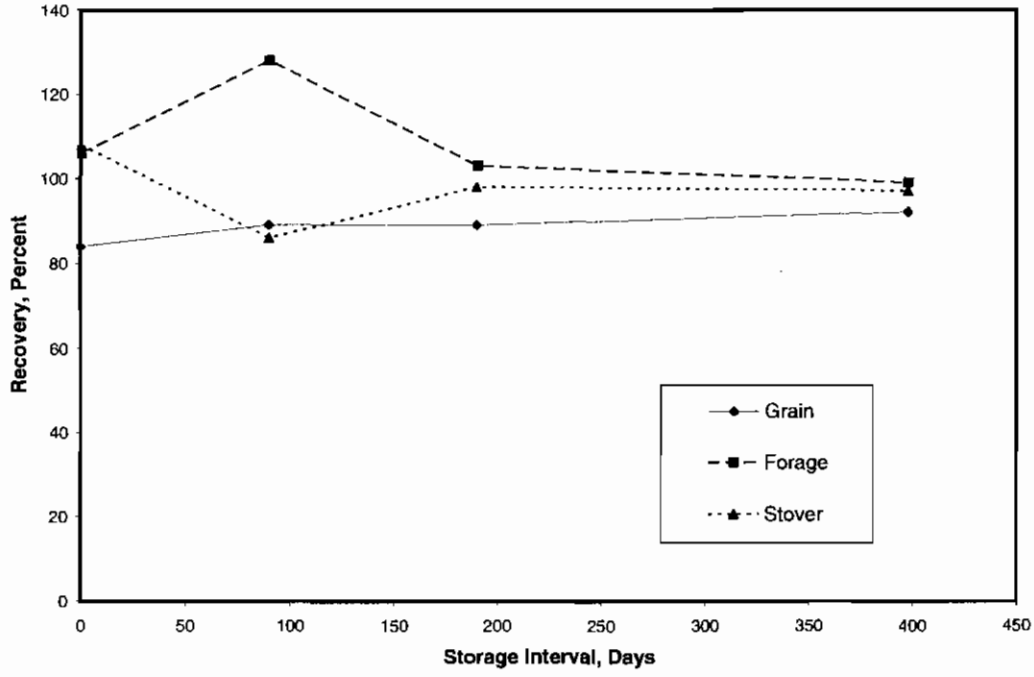


TABLE C.2. Stability of Tembotrione Residues in Selected Corn Matrices Following Storage at ≤10° C.

Matrix	Spike level (ppm)	Storage Interval[1] (days)	Recovered residues (ppm)	Mean Recovered Residues (ppm)	Mean Recovery (%)	Corrected % Recovery[2]
Tembotrione (parent)						
Corn, grain	0.200	0(1)	0.162, 0.166, 0.172	0.167	83	---
	0.200	91(0)	0.134, 0.194	0.164	82	86
	0.200	182(1)	0.156, 0.157	0.157	78	94
	0.200	396(1)	0.153, 0.169	0.161	81	88
Corn, forage	0.200	0(1)	0.168, 0.170, 0.174	0.171	85	---
	0.200	91(0)	0.194, 0.209	0.202	101	120
	0.200	182(1)	0.170, 0.171	0.171	85	97
	0.200	396(1)	0.161, 0.165	0.163	82	91
Corn, stover	0.200	0(1)	0.145, 0.173, 0.174	0.164	82	---
	0.200	91(0)	0.148, 0.162	0.155	78	96
	0.200	182(1)	0.178, 0.180	0.179	90	101
	0.200	398(1)	0.171, 0.174	0.173	86	92
AE 0456148 (M6)						
Corn, grain	0.200	0(1)	0.197, 0.207, 0.212	0.205	103	---
	0.200	91(0)	0.160, 0.192	0.176	88	91
	0.200	186(1)	0.177, 0.208	0.193	96	96
	0.200	396(1)	0.184, 0.186	0.185	93	103

TABLE C.2. Stability of Tembotrione Residues in Selected Corn Matrices Following Storage at ≤10° C.

Matrix	Spike level (ppm)	Storage Interval[1] (days)	Recovered residues (ppm)	Mean Recovered Residues (ppm)	Mean Reeovery (%)	Corrected % Recovery[2]
Corn, forage	0.200	0(1)	0.206, 0.207, 0.215	0.209	104	---
	0.200	91(0)	0.177, 0.185	0.181	91	119
	0.200	182(1)	0.189, 0.191	0.190	95	102
	0.200	396(1)	0.184, 0.197	0.191	95	106
Corn, stover	0.200	0(1)	0.221, 0.225, 0.238	0.228	114	---
	0.200	91(0)	0.146, 0.150	0.148	74	90
	0.200	182(1)	0.177, 0.192	0.185	92	98
	0.200	398(1)	0.189, 0.196	0.193	96	102
AE 1417268 (M5)						
Corn, grain	0.200	0(1)	0.145, 0.158, 0.160	0.154	77	---
	0.200	99(1)	0.149, 0.166	0.158	79	88
	0.200	188(1)	0.105, 0.152	0.129	64	78
	0.200	371(1)	0.078, 0.127	0.103	51	61
Corn, forage	0.200	0(1)	0.165, 0.166, 0.178	0.170	85	---
	0.200	99(1)	0.076, 0.106	0.091	45	64
	0.200	188(1)	0.048, 0.087	0.068	34	35[3]
	0.200	369(1) 371(1)	0.131, 0.167 0.130, 0.262	0.173	86	92
Corn, stover	0.200	0(1)	0.163, 0.167, 0.174	0.168	84	---
	0.200	99(1)	0.166, 0.170	0.168	84	93
	0.200	188(1)	0.197, 0.215	0.206	103	120
	0.200	371(1)	0.214, 0.227	0.221	110	127
AE 1392936 (M2)						
Corn, grain	0.200	0(1)	0.163, 0.171, 0.179	0.171	86	---
	0.200	91(1)	0.160, 0.186	0.173	87	89
	0.200	187(3)	0.158, 0.166	0.162	81	89
	0.200	396(2)	0.171, 0.198	0.185	92	88
Corn, forage	0.200	0(1)	0.200, 0.215, 0.220	0.212	106	---
	0.200	91(1)	0.204, 0.217	0.211	105	127
	0.200	187(3)	0.200, 0.204	0.202	101	103
	0.200	396(2)	0.190, 0.201	0.196	98	99
Corn, stover	0.200	0(1)	0.205, 0.211, 0.232	0.216	108	---
	0.200	91(1)	0.167, 0.177	0.172	86	79
	0.200	187(3)	0.193, 0.197	0.195	98	96
	0.200	398(2)	0.192, 0.197	0.195	97	94

[1] The storage interval from fortification to extraction; the days from extraction to analysis are reported in parentheses.
[2] Corrected for control interferences and mean concurrent recovery (see TABLE C.1.).
[3] These data were considered anomalous due to the recovery of this analyte, M5, at a later interval. This data point was not entered into Figure C.3.

D. CONCLUSION

The submitted storage stability results adequately demonstrate the stability of tembotrione and metabolites AE 0456148 (M6) and AE 1392936 (M2) residues in/on corn grain, forage, and stover stored frozen for up to ~13 months. AE 1417268 (M5) residues appear to be reasonably stable in/on corn grain for up to ~6 months but declined by 17% after ~12 months of frozen storage. M5 residues appear to be reasonably stable in/on corn forage and stover for up to ~12 months if the 35% recovery from corn forage from the 188-day storage interval is deemed an outlier. An acceptable method was used for the quantitation of residues in corn grain, forage, and stover.

E. REFERENCES

None.

F. DOCUMENT TRACKING

RDI: RAB1 Chemists (1/10/07)
Petition Number: PP#5F7009
DP#s: 325349, 325663, and 331222
PC Code: 012801

Template Version June 2005

Tembotrione/AE 0172747/PC Code 012801/Bayer CropScience/264
DACO 7.4.1/7.4.2/OPPTS 860.1500/OECD IIA 6.3.1, 6.3.2, 6.3.3 and IIIA 8.3.1, 8.3.2, 8.3.3
Crop Field Trial/Residue Decline – Popcorn

Primary Evaluator	George F. Kramer, Ph.D., Senior Chemist Registration Action Branch (RAB1) Health Effects Division (HED) (7509P)	Date: 18-JUL-2007
Approved by	P.V. Shah, Ph.D., Branch Senior Scientist RAB1/HED (7509P)	Date: 18-JUL-2007

This DER was originally prepared under contract by Dynamac Corporation (2275 Research Boulevard, Suite 300; Rockville, MD 20850; submitted 11/30/2006). The DER has been reviewed by HED and revised to reflect current Offiee of Pesticide Programs (OPP) policies.

STUDY REPORT:

46695609 Pither, K.; Mackie, S. (2005) AE 0172747: Magnitude of Residues in Popcorn Resulting from Foliar Applications of AE 0172747 02 SC52 A1 under Maximum Proposed Label Specifications (2003). Project Number: 03RAAEX015, RAAEX015, RAAEX015-01H. Unpublished study prepared by Bayer Corp., Bayer Research Farm and Bayer CropScience Midwest Field Technology Station. 240 p.

The petitioner has submitted an evaluation template for the study (Bayer CropScience DER for Study RAAEX015), which was used to generate this DER; selected sections were copied without alteration or were copied and modified to more specifically reflect the Agency's data evaluation requirements.

EXECUTIVE SUMMARY:

Bayer CropScience has submitted field trial data for tembotrione on popcorn. Four field trials were conducted in the United States encompassing Zones 5 (IL, KS, and NE; 3 trials) and 8 (TX; 1 trial) during the 2003 growing season.

Each trial site consisted of one control plot and two treated plots. Two foliar spray applications of a suspension-concentrate (SC) formulation (AE 0172747 Herbicide) nominally containing 3.50 lb tembotrione ai/gallon (420 g ai/L), were made to popcorn at 24-inch and 36-inch height in treated plot A at a target rate of 0.082 lb ai/A/application (0.092 kg ai/ha/application). Popcorn in treated plot B received one foliar spray application at the 36-inch height and one drop-nozzle (directed) spray one week later using the same target application rates. Applications were made using ground equipment in ~14-17 gal/A (132-154 L/ha). An adjuvant was added to the spray mixture for all applications. The achieved total seasonal rates ranged from 0.164-0.172 lb ai/A (0.184-0.193 kg ai/ha) for all treated plots at all trial sites.

Popcorn grain and stover samples were harvested at a preharvest interval (PHI) of 72 to 93 days after the last application. At one trial location, popcorn corn matrices were collected at additional sampling intervals to evaluate residue decline: popcorn grain and stover were collected 69, 77, 83, 90, and 97 days following the last application of Treatment A and collected 63, 71, 77, 84, and 91 days following the last application of Treatment B.

The harvested popcorn raw agricultural commodity (RAC) samples were analyzed for residues of the parent compound, tembotrione, and the metabolites AE 1392936 (M2), AE 1417268 (M5), and AE 0456148 (M6) using a method entitled "AE 0172747: An Analytical Method for the Determination of Residues of AE 0172747, and its major metabolites AE 0456148, AE 1417268, and AE 1392936 in Plant Matrices Using LC/MS/MS." This method is acceptable for data collection based on adequate method validation and concurrent method recovery data. The limits of quantitation (LOQs) for tembotrione, M2, M5, and M6 were each 0.010 ppm based on field corn validation data; the estimated method limits of detection (LODs) were ≤0.004 ppm for each analyte in corn grain and stover.

The maximum storage interval of samples from harvest to analysis was 307 days (10.1 months) for popcorn grain and stover. Adequate storage stability data for field corn commodities (refer to DER for MRID 46695601) are available to support the storage conditions and intervals of samples from the popcorn field trials.

In trials reflecting Treatment A (two foliar applications totaling 0.161-0.170 lb ai/A), the maximum combined residues of parent and its metabolites (M5 + M6 + M2), as parent equivalents, were <0.050 ppm in/on popcorn grain and <0.281 ppm in/on popcorn stover. In the treated stover sample which bore the highest combined residues of <0.281 ppm, Metabolites M5 and M6 comprised 67% and 24% of the respective total residues; individual residues of the parent and Metabolite M2 were either below or slightly above the LOQ in the same stover sample.

Following Treatment B (one foliar application and one directed-spray application totaling 0.165-0.172 lb ai/A), the maximum combined residues of parent and its metabolites (M5 + M6 + M2), as parent equivalents, were <0.048 ppm in/on popcorn grain and <0.302 ppm in/on popcorn stover.

When only residues of the parent and Metabolite M5 are summed, as reflected in the proposed tolerance expression, the maximum combined residues from Treatment A trials were <0.02 ppm (combined LOQs) in/on popcorn grain and <0.199 ppm in/on popcorn stover. Following Treatment B, the maximum combined residues were <0.02 ppm in/on popcorn grain and <0.202 ppm in/on popcorn stover.

Based on the results of the side-by-side field trials, residues were similar in/on popcorn matrices treated with two foliar applications or treated with one foliar + one directed-spray application. Residues of the parent were nondetectable in all popcorn grain and stover samples from both treatment schemes.

In the popcorn decline trial, no total tembotrione residues were found in grain samples above the LOQ of 0.04 ppm at any sampling interval for both Treatments A and B. Total tembotrione residues in popcorn stover in both treatments showed a general tendency to decline with increasing PHIs.

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the field trial residue data are classified as scientifically acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document [DP# 325349].

COMPLIANCE:

Signed and dated Good Laboratory Practice (GLP), Quality Assurance and Data Confidentiality statements were provided. No deviations from regulatory requirements were reported which would have an impact on the validity of the study.

A. BACKGROUND INFORMATION

Tembotrione, a new herbicide with broad use against mono- and dicotyledons in selected crops such as corn, is a 4-hydroxyphenylpyruvate deoxygenase (HPPD) inhibitor (bleacher). Details of the test compounds nomenclature (tembotrione and its three metabolites) and physiochemical properties of tembotrione are given in Tables A.1 and A.2.

TABLE A.1. Test Compound Nomenclature for Tembotrione and its Metabolites AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2).

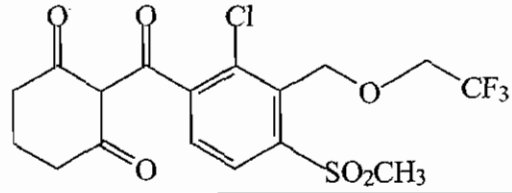
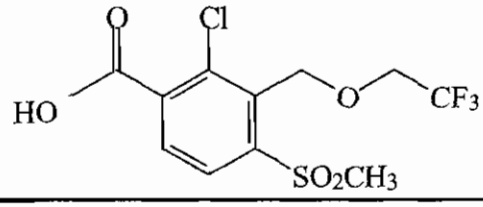
Compound: Tembotrione	Chemieal Structure 
Common name	Tembotrione (Parent)
Company experimental name	AE 0172747
IUPAC name	2-{2-Chloro-4-mesyl-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl}cyclohexane-1,3-dione
CAS name	2-[2-Chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione
CAS #	335104-84-2
End-use product/EP	AE 0172747 Herbicide, EPA Reg No. 264-xxx
Compound: AE 0456148	Chemical Structure 
Common name	Metabolite M6
Company experimental name	AE 0456148
IUPAC name	None provided

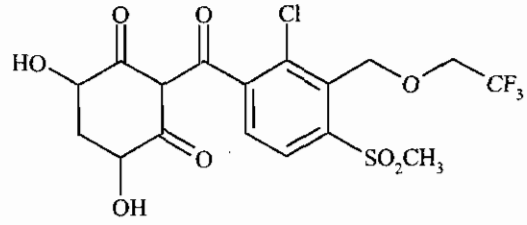
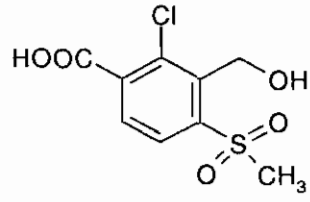
TABLE A.1. Test Compound Nomenclature for Tembotrione and its Metabolites AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2).	
CAS name	2-chloro-4-mesyl-3-[(2,2,2-trifluroethoxy)methyl]benzoic acid
CAS #	None provided
Compound: AE 1417268	Chemical Structure 
Common name	Metabolite M5
Company experimental name	AE 1417268
IUPAC name	None provided
CAS name	2-[2-chloro-4-(*methylsulfonyl*)-3-[2,2,2-*trifluoroethoxy*)methyl]benzoyl]-4,6-dihydroxycyclohexan-1,3-dione
CAS #	None provided
Compound: AE 1392936	*Chemical Structure* 
Common name	Metabolite M2
Company experimental name	AE 1392936
IUPAC name	None provided
CAS name	2-chloro-3-hydroxymethyl-4-mesylbenzoic acid
CAS #	None provided

TABLE A.2. Physicochemical Properties of Technical Grade Tembotrione.		
Parameter	Value	Reference (MRID#)
Melting point	117 °C	46695402
pH @ 24 °C	3.63	
Density (g/mL @ 20 °C)	1.56	
Water solubility (mg/L @ 20 °C)	0.22 at pH4 28.3 at pH 7 29.7 at pH 9	
Solvent solubility (g/L at 20 °C) DMSO Methylene Chloride Acetone Ethyl Acetate Toluene Hexane Ethanol	 >600 >600 300-600 180.2 75.7 47.6 8.2	
Vapor pressure (Torr, 20 °C)	8.25×10^{-11}	

TABLE A.2. Physicochemical Properties of Technical Grade Tembotrione.		
Parameter	Value	Reference (MRID#)
Dissociation constant (pK_a)	3.2	
Octanol/water partition coefficient (P_{ow} @ 23 °C) (P_{ow} @ 24 °C) (P_{ow} @ 23 °C)	 0.0430 at pH 9.0 0.0807 at pH 7.0 144.9 at pH 2.0	
UV/visible absorption spectrum (nm)	Primary: 205 Secondary: 284 Tertiary: 240	

B. EXPERIMENTAL DESIGN

B.1. Study Site Information

Four field trials were conducted in the United States encompassing Zones 5 (IL, KS, and NE; 3 trials) and 8 (TX; 1 trial) during the 2003 growing season.

AE 0172747 Herbicide is a SC formulation nominally containing 3.50 lb tembotrione ai/gallon (420 g ai/L). Each trial site consisted of one control plot and two treated plots. Two foliar spray applications of tembotrione were made to popcorn at 24-inch and 36-inch height in treated plot A at a target rate of 0.082 lb ai/A/application (0.092 kg ai/ha/application). Popcorn in treated plot B received one foliar spray application at the 36-inch height and one drop-nozzle (directed) spray one week later using the same target application rates. The target total application rate for both treatment plots was 0.164 lb ai/A (0.184 kg ai/ha). Applications were made using ground equipment in ~14-17 gal/A (132-154 L/ha). Both treated plots had the spray adjuvants methylated seed oil (MSO) at 1.5 pt/A and 28% or 32% urea ammonium nitrate (UAN) at 1.5 to 2 qt/A added to the tank mixture. Actual trial parameters are reported in Table B.1.2.

Agronomic practices typical of the trial locations were used for growing popcorn. The actual temperature recordings and rainfall averages were within average historical values for the residue study period; see Table B.1.1. All field trials supplemented normal rainfall amounts with irrigation as needed. Irrigation amounts from first application to final harvest ranged from 2 to 20 inches.

TABLE B.1.1 Trial Site Conditions.								
Study Location City, State	Trial Number (RAAEX0-)	Year	Soil Characteristics				Meteorological Data[1]	
			Type	% OM[2]	pH	CEC[2]	Total Precip (inch)	Temp Range (°F)
Springfield, NE	15-01H	2003	Silt loam	2.0	6.5	10.9	5.22	47-105
Seymour, IL	15-02H	2003	Silt loam	3.1	6.5	21	11.30	39-97
Stilwell, KS	15-03D	2003	Silt loam	2.6	6.6	15.9	15.39	39-105
Groom, TX	15-04H	2003	Clay loam	2.4	6.6	22.6	8.58	42-106

[1] Meteorologieal data from date of first application through date of final harvest.
[2] OM = Organic matter, CEC = Cation-exehange capacity (unit of measurement was not provided).

TABLE B.1.2. Study Use Pattern.

Location: City, State NAFTA Zone Trial Number (RAAEX015-) Year	End-Use Product[1]	Application							Tank Mix Adjuvant[6]
		Method	Timing[2]	Trtmt Pattern[3]	Rate lb ai/A (kg ai/ha)	RTI[4] (days)	Spray Volume[5] GPA (L/ha)	Total Rate lb ai/A (kg ai/ha)	
Springfield, NE Zone 5 01H 2003	420 SC	Foliar	24	A	0.082 (0.092)	--	14.7 (137)	0.164 (0.184)	MSO & UAN
		Foliar	36		0.082 (0.092)	3	14.9 (139)		
	420 SC	Foliar	36	B	0.083 (0.093)	--	15.0 (140)	0.165 (0.185)	MSO & UAN
		Directed	1 wk later		0.082 (0.092)	6	14.5 (136)		
Seymour, IL Zone 5 02H 2003	420 SC	Foliar	24	A	0.081 (0.091)	--	16.0 (150)	0.164 (0.184)	MSO & UAN
		Foliar	36		0.083 (0.093)	6	16.5 (154)		
	420 SC	Foliar	36	B	0.083 (0.093)	--	16.5 (154)	0.165 (0.185)	MSO & UAN
		Directed	1 wk later		0.082 (0.092)	9	14.9 (139)		
Stilwell, KS Zone 5 03D 2003	420 SC	Foliar	24	A	0.083 (0.093)	--	15.3 (143)	0.170 (0.191)	MSO & UAN
		Foliar	36		0.087 (0.098)	4	15.4 (144)		
	420 SC	Foliar	36	B	0.087 (0.098)	--	15.3 (143)	0.172 (0.193)	MSO & UAN
		Directed	1 wk later		0.085 (0.095)	6	16.4 (153)		
Groom, TX Zone 8 04H 2003	420 SC	Foliar	24	A	0.083 (0.093)	--	14.1 (132)	0.165 (0.185)	MSO & UAN
		Foliar	36		0.082 (0.092)	14	14.7 (137)		
	420 SC	Foliar	36	B	0.082 (0.092)	--	14.6 (136)	0.166 (0.186)	MSO & UAN
		Directed	1 wk later		0.084 (0.094)	7	16.2 (151)		

[1] The end-use product is a SC formulation of tembotrione and isoxadifen safener.
[2] Timing = Corn height in inches or 1 week later.
[3] Treatment Pattern A: Two foliar spray applications at 24-inch and 36-inch corn height.
Treatment Pattern B: One foliar spray application at 36-inch corn height and one directed-spray application one week later.
[4] RTI = Retreatment Interval.
[5] GPA = gallons per acre and L/ha = liters per hectare.
[6] Spray adjuvants methylated seed oil (MSO) and urea ammonium nitrate (UAN).

TABLE B.1.3. Trial Numbers and Geographical Locations.

NAFTA Growing Zones	Popcorn		
	Submitted	Requested	
		Canada	U.S.
5	3		
8	1		
Total	4		3[1]

[1] *According to* OPPTS 860.1500, Table 1, a minimum of three field trials is required for popcorn; specific zones for popcorn trials are not specified. According to OPPTS 860.1500, Table 6, the regional distribution of popcorn production (acreage basis) occurs in Zones 5 (91%) and 8 (4%).

B.2. Sample Handling and Preparation

In all of the trials, duplicate treated samples and a single control sample of popcorn grain and stover were collected at normal commercial harvest (72- to 93-day PHI). One trial collected additional samples at various PHIs to monitor residue decline.

All popcorn samples were harvested by hand and put into labeled plastic-coated cloth bags in the field and transported to a freezer within 2.25 hours of harvest. Following collection of the popcorn samples, reasonable attempts were made to maintain the samples under cool conditions in the field prior to being transferred to frozen storage. Samples remained in frozen storage at the field facilities until shipment via freezer truck to Bayer Research Park (BRP; Stilwell, KS) for analysis. In preparation for analysis, the popcorn RAC samples were homogenized in dry ice using a chopper. All samples remained frozen at all times except during homogenization and sub-sampling for analysis.

B.3. Analytical Methodology

The harvested popcorn RAC samples were analyzed for residues of the parent compound, tembotrione, and the metabolites AE 1392936 (M2), AE 1417268 (M5), and AE 0456148 (M6). The analytical method used was an liquid chromatography/mass spectroscopy (LC/MS)/MS method entitled "AE 0172747: An Analytical Method for the Determination of Residues of AE 0172747, and its major metabolites AE 0456148, AE 1417268, and AE 1392936 in Plant Matrices Using LC/MS/MS." This method quantifies all analytes from a single sample using isotopically labeled internal standards.

Briefly, residues of tembotrione and its metabolites M2, M5, and M6 were extracted from crop matrices with acetonitrile:water (1:1, v:v) using accelerated solvent extraction. Internal standards of the deuterated analytes were added to the extract. For parent, M5, and M6 analysis, an aliquot of the extract was concentrated via Turbo-Vap. For M2 analysis, an aliquot of the extract was loaded onto a strong anion exchange solid-phase extraction (SPE) cartridge and eluted with oxalic acid. The SPE eluate was concentrated. The concentrates were reconstituted in 0.1% formic acid and filtered for LC/MS/MS analysis. For the subject field trial study, reference standards were prepared in tembotrione molar equivalents, therefore, quantitating residues as parent equivalents.

Method validation was performed prior to sample analysis with field corn forage, grain, and stover (refer to 860.1340 DER for MRID 46695537), and concurrent recoveries were performed during sample analysis to demonstrate acceptable method performance.

The LOQs for tembotrione, M2, M5, and M6 were 0.010 ppm for each analyte based on field corn validation data. The LOQ is defined as the lowest fortification level of an analyte at which acceptable recovery data was achieved.

The calculated LODs were 0.0011 ppm for tembotrione, 0.0029 ppm for M6, 0.0025 ppm for M5, and 0.0017 ppm for M2 in corn grain. The calculated LODs were 0.0009 ppm for tembotrione, 0.0040 ppm for M6, 0.0013 ppm for M5, and 0.0024 ppm for M2 in corn stover. The LOD was calculated by multiplying the standard deviation of recovery measurements at the LOQ by $t_{0.99}$ (where $t_{0.99}$ is the one-tailed statistic at the 99% confidence level for n-1 replicates) and adding the average residue found in the untreated control samples.

C. RESULTS AND DISCUSSION

Sample storage conditions and intervals are summarized in Table C.2. The maximum storage interval of samples from harvest to analysis was 307 days (10.1 months) for popcorn grain and stover. The submitted storage stability data on field corn commodities (refer to DER for MRID 46695601) indicate that tembotrione, M2, M5, and M6 residues are stable (<30% decomposition) during frozen storage for at least 13 months prior to analysis with one exception. Residues of M5 in grain showed some apparent degradation with time; however, based on the results of the corn metabolism studies with tembotrione, M5 is not found in significant amounts in grain (<0.010 ppm). The field corn storage stability data may be translated to fulfill the requirements for storage stability data on popcorn commodities.

The analytical method (LC/MS/MS) was successfully validated for the analysis of tembotrione residues and its metabolites M2, M5, and M6 in/on various plant matrices (see DER for MRID 46695537). Recoveries of tembotrione, M6, M5, and M2 from popcorn matrices were measured concurrently with each set of samples to verify method performance. The concurrent recovery data are summarized in Table C.1. The data demonstrate acceptable method performance during sample analysis. Concurrent method recoveries from popcorn grain and stover controls fortified with tembotrione, M6, M5 or M2 at 0.02-1.0 ppm ranged from 78% to 120%. Apparent residues of all analytes were nondetectable in/on all untreated popcorn grain and stover samples, except one popcorn grain sample which bore residues of M2 (0.002 ppm) below the method LOQ.

Individual and total tembotrione residues found in treated popcorn grain and stover samples are presented in Tables C.3.1 and C.3.2, respectively. Total residues in popcorn matrices are summarized in Table C.4. Following Treatment A [two foliar applications of the SC formulation totaling 0.164-0.170 lb ai/A (0.184-0.191 kg ai/ha)], the sum of residues (parent + M5 + M6 + M2, as parent equivalents) as determined by the data-collection method were below the combined LOQ (<0.04 ppm) to <0.050 ppm in/on 8 samples of popcorn grain and <0.04-<0.281 ppm in/on 8 samples of popcorn stover. Following Treatment B [one foliar application and one directed-spray application of the SC formulation totaling 0.165-0.172 lb ai/A (0.185-0.193 kg

ai/ha)], the sum of parent + M5 + M6 + M2 residues were <0.04-<0.048 ppm in/on 8 samples of popcorn grain and <0.04-<0.302 ppm in/on 8 samples of popcorn stover.

Following Treatment A, the sum of parent + M5 residues were <0.02 ppm (combined LOQs) in/on 8 samples of popcorn grain and <0.02-<0.199 ppm in/on 8 samples of popcorn stover. Following Treatment B, the sum of parent + M5 residues were <0.02 ppm in/on 8 samples of popcorn grain and <0.02-<0.202 ppm in/on 8 samples of popcorn stover.

Based on the results of the side-by-side field trials, residues were similar in/on popcorn matrices treated with two foliar applications or treated with one foliar + one directed-spray application. Residues of the parent were nondetectable in all popcorn grain and stover samples from both treatment schemes.

In the popcorn decline trial, no total tembotrione residues were found in grain samples above the LOQ of 0.04 ppm at any sampling interval for both Treatments A and B. Total tembotrione residues in popcorn stover in both treatments showed a general tendency to decline with increasing PHIs.

TABLE C.1. Summary of Concurrent Recoveries of Tembotrione, M5, M6, and M2 from Popcorn Matrices.

Matrix	Analyte	Spike Level (mg/kg)	Sample Size (n)	Recoveries (%)	Mean Recovery (%) ± std dev[1]
Grain	Tembotrione	0.02	1	92	92
		0.05	1	101	101
		0.20	1	98	98
		0.50	1	88	88
	AE 0456148 (M6)	0.02	1	120	120
		0.05	1	116	116
		0.20	1	110	110
		0.50	1	99	99
	AE 1417268 (M5)	0.02	1	99	99
		0.05	1	100	100
		0.20	1	98	98
		0.50	1	92	92
	AE 1392936 (M2)	0.02	1	78	78
		0.05	1	90	90
		0.20	1	102	102
		0.50	1	94	94

TABLE C.1. Summary of Concurrent Recoveries of Tembotrione, M5, M6, and M2 from Popcorn Matrices.

Matrix	Analyte	Spike Level (mg/kg)	Sample Size (n)	Recoveries (%)	Mean Recovery (%) ± std dev[1]
Stover	Tembotrione	0.05	1	97	97
		0.10	1	95	95
		0.25	1	90	90
		1.00	1	78	78
	AE 0456148 (M6)	0.05	1	108	108
		0.10	1	107	107
		0.25	1	101	101
		1.00	1	79	79
	AE 1417268 (M5)	0.05	1	101	101
		0.10	1	92	92
		0.25	1	94	94
		1.00	1	99	99
	AE 1392936 (M2)	0.05	1	98	98
		0.10	1	113	113
		0.25	1	84	84
		1.00	1	79	79

[1] The standard deviation is not applicable for a sample size (n) of less than three.

TABLE C.2. Summary of Storage Conditions for Popcorn.

Residue Components	Matrix (RAC or Extract)	Storage Temp. (°C)[1]	Actual Storage Duration[2]	Interval of Demonstrated Storage Stability[3]
Tembotrione AE 0456148 (M6) AE 1417268 (M5) AE 1392936 (M2)	Grain Stover	< -15	279-307 days (9.2-10.1 months)	Tembotrione, M6, and M2 are stable for up to 12-13 months in frozen field corn grain, forage, and fodder. M5 is stable in frozen field corn forage and fodder for up to 12 months. M5 is stable in frozen field corn grain for up to 188 days but declined by 17% after 371 days (61% average corrected recovery).

[1] Storage temperature = storage temperature from receipt at Bayer CropScience through the last sample extraction.
[2] Actual study duration = time from field sampling through the last sample analyses. Samples were analyzed within 2-4 days of extraction.
[3] Field corn storage stability data; refer to the DER for MRID 46695601.

TABLE C.3.1. Residue Data from Popcorn Grain Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX015-) Year	Treatment Pattern[1]	Crop; Variety	Commodity	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Springfield, NE Zone 5 01H 2003	A	Popcorn; United	Grain	0.164 (0.184)	89	<LOD + <LOD + <LOD + <LOD = 0.0082 (**<0.04**) <LOD + <LOD + <LOD + <LOD = 0.0082 (**<0.04**)	<LOD + <LOD = 0.0036 (**<0.02**) <LOD + <LOD = 0.0036 (**<0.02**)
	B	Popcorn; United	Grain	0.165 (0.185)	83	<LOD + <LOD + <LOD + <LOD = 0.0082 (**<0.04**) <LOD + <LOD + <LOD + <LOD = 0.0082 (**<0.04**)	<LOD + <LOD = 0.0036 (**<0.02**) <LOD + <LOD = 0.0036 (**<0.02**)
Seymour, IL Zone 5 02H 2003	A	Popcorn; Robust White	Grain	0.164 (0.184)	81	<LOD + <LOD + 0.020 + <LOD = 0.0253 (**<0.050**) <LOD + <LOD + 0.017 + <LOD = 0.0223 (**<0.047**)	<LOD + <LOD = 0.0036 (**<0.02**) <LOD + <LOD = 0.0036 (**<0.02**)
	B	Popcorn; Robust White	Grain	0.165 (0.185)	72	<LOD + <LOD + 0.0163 + <LOD = 0.0216 (**<0.046**) <LOD + <LOD + 0.018 + <LOD = 0.0233 (**<0.048**)	<LOD + <LOD = 0.0036 (**<0.02**) <LOD + <LOD = 0.0036 (**<0.02**)
Groom, TX Zone 8 04H 2003	A	Popcorn; M2101 F1	Grain	0.165 (0.185)	93	<LOD + <LOD + <LOD + <LOD = 0.0082 (**<0.04**) <LOD + <LOD + <LOD + <LOD = 0.0082 (**<0.04**)	<LOD + <LOD = 0.0036 (**<0.02**) <LOD + <LOD = 0.0036 (**<0.02**)
	B	Popcorn; M2101 F1	Grain	0.166 (0.186)	86	<LOD + <LOD + <LOD + <LOD = 0.0082 (**<0.04**) <LOD + <LOD + <LOD + <LOD = 0.0082 (**<0.04**)	<LOD + <LOD = 0.0036 (**<0.02**) <LOD + <LOD = 0.0036 (**<0.02**)

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TABLE C.3.1. Residue Data from Popcorn Grain Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX015-) Year	Treatment Pattern[1]	Crop; Variety	Commodity	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Stilwell, KS Zone 5 03D 2003	A	Popcorn; Yellow	Grain	0.170 (0.191)	69	<LOD + <LOD + <LOD + <LOD = 0.0082 **(<0.04)** <LOD + <LOD + <LOD + <LOD = 0.0082 **(<0.04)**	<LOD + <LOD = 0.0036 **(<0.02)** <LOD + <LOD = 0.0036 **(<0.02)**
			Grain		77	<LOD + <LOD + <LOD + <LOD = 0.0082 **(<0.04)** <LOD + <LOD + <LOD + <LOD = 0.0082 **(<0.04)**	<LOD + <LOD = 0.0036 **(<0.02)** <LOD + <LOD = 0.0036 **(<0.02)**
			Grain		83	<LOD + <LOD + <LOD + <LOD = 0.0082 **(<0.04)** <LOD + <LOD + <LOD + <LOD = 0.0082 **(<0.04)**	<LOD + <LOD = 0.0036 **(<0.02)** <LOD + <LOD = 0.0036 **(<0.02)**
			Grain		90	<LOD + <LOD + <LOD + <LOD = 0.0082 **(<0.04)** <LOD + <LOD + 0.074 + <LOD = 0.0793 **(<0.104)**	<LOD + <LOD = 0.0036 **(<0.02)** <LOD + <LOD = 0.0036 **(<0.02)**
			Grain		97	<LOD + <LOD + <LOD + <LOD = 0.0082 **(<0.04)** <LOD + <LOD + <LOD + <LOD = 0.0082 **(<0.04)**	<LOD + <LOD = 0.0036 **(<0.02)** <LOD + <LOD = 0.0036 **(<0.02)**

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TABLE C.3.1. Residue Data from Popcorn Grain Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX015-) Year	Treatment Pattern[1]	Crop; Variety	Commodity	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Stilwell, KS (continued)	B	Popcorn; Yellow	Grain	0.172 (0.193)	63	<LOD + <LOD + *0.004* + <LOD = 0.0093 (**<0.04**) <LOD + <LOD + <LOD + <LOD = 0.0082 (**<0.04**)	<LOD + <LOD = 0.0036 (**<0.02**) <LOD + <LOD = 0.0036 (**<0.02**)
			Grain		71	<LOD + <LOD + <LOD + <LOD = 0.0082 (**<0.04**) <LOD + <LOD + <LOD + <LOD = 0.0082 (**<0.04**)	<LOD + <LOD = 0.0036 (**<0.02**) <LOD + <LOD = 0.0036 (**<0.02**)
			Grain		77	<LOD + <LOD + <LOD + <LOD = 0.0082 (**<0.04**) <LOD + <LOD + <LOD + <LOD = 0.0082 (**<0.04**)	<LOD + <LOD = 0.0036 (**<0.02**) <LOD + <LOD = 0.0036 (**<0.02**)
			Grain		84	<LOD + <LOD + <LOD + <LOD = 0.0082 (**<0.04**) <LOD + <LOD + <LOD + <LOD = 0.0082 (**<0.04**)	<LOD + <LOD = 0.0036 (**<0.02**) <LOD + <LOD = 0.0036 (**<0.02**)
			Grain		91	<LOD + <LOD + <LOD + *0.002* = 0.0085 (**<0.04**) <LOD + <LOD + <LOD + <LOD = 0.0082 (**<0.04**)	<LOD + <LOD = 0.0036 (**<0.02**) <LOD + <LOD = 0.0036 (**<0.02**)

[1] Treatment Pattern A: Two foliar spray applications at 24-inch and 36-inch corn height.
Treatment Pattern B: One foliar spray application at 36-inch corn height and one directed-spray application one week later.

[2] The LOD values for tembotrione (parent), M5, M6, and M2 in popcorn grain were 0.0011 ppm, 0.0025 ppm, 0.0029 ppm, and 0.0017 ppm, respectively. Residues below the LOQ (<0.01 ppm each analyte) but above the respective LOD are *italicized*. Total residues based on the LOQ of each analyte are **bolded** in parentheses.

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TABLE C.3.2. Residue Data from Popcorn Stover Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX026-) Year	Treatment Pattern[1]	Crop; Variety	Commodity	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Springfield, NE Zone 5 01H 2003	A	Popcorn; United	Stover	0.164 (0.184)	89	<LOD + 0.0290 + 0.0203 + *0.0020* = 0.0522 **(<0.069)** <LOD + 0.0204 + 0.0149 + *0.0026* = 0.0388 **(<0.055)**	<LOD + 0.0290 = 0.0299 **(<0.039)** <LOD + 0.0204 = 0.0213 **(<0.030)**
	B	Popcorn; United	Stover	0.165 (0.185)	83	<LOD + 0.0157 + 0.0161 + <LOD = 0.0351 **(<0.052)** <LOD + 0.0256 + 0.0202 + <LOD = 0.0491 **(<0.066)**	<LOD + 0.0157 = 0.0166 **(<0.026)** <LOD + 0.0256 = 0.0265 **(<0.036)**
Seymour, IL Zone 5 02H 2003	A	Popcorn; Robust White	Stover	0.164 (0.184)	81	<LOD + 0.1894 + 0.0678 + 0.0142 = 0.2723 **(<0.281)** <LOD + 0.1088 + 0.0617 + 0.0148 = 0.1862 **(<0.195)**	<LOD + 0.1894 = 0.1903 **(<0.199)** <LOD + 0.1088 = 0.1097 **(<0.119)**
	B	Popcorn; Robust White	Stover	0.165 (0.185)	72	<LOD + 0.1707 + 0.0674 + 0.0161 = 0.2551 **(<0.264)** <LOD + 0.1924 + 0.0821 + 0.0175 = 0.2929 **(<0.302)**	<LOD + 0.1707 = 0.1716 **(<0.181)** <LOD + 0.1924 = 0.1933 **(<0.202)**
Groom, TX Zone 8 04H 2003	A	Popcorn; M2101 F1	Stover	0.165 (0.185)	93	<LOD + <LOD + <LOD + *0.0057* = 0.0119 **(<0.04)** <LOD + <LOD + <LOD + *0.0073* = 0.0135 **(<0.04)**	<LOD + <LOD = 0.0022 **(<0.02)** <LOD + <LOD = 0.0022 **(<0.02)**
	B	Popcorn; M2101 F1	Stover	0.166 (0.186)	86	<LOD + <LOD + <LOD + *0.0075* = 0.0137 **(<0.04)** <LOD + <LOD + <LOD + *0.0073* = 0.0135 **(<0.04)**	<LOD + <LOD = 0.0022 **(<0.02)** <LOD + <LOD = 0.0022 **(<0.02)**

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TABLE C.3.2. Residue Data from Popcorn Stover Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX026-) Year	Treatment Pattern[1]	Crop; Variety	Commodity	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Stilwell, KS Zone 5 03D 2003	A	Popcorn; Yellow	Stover	0.170 (0.191)	69	<LOD + *0.0085* + <LOD + <LOD = 0.0158 **(<0.04)** <LOD + 0.0208 + 0.0236 + *0.0026* = 0.0479 **(<0.064)**	<LOD + *0.0085* = 0.0094 **(<0.02)** <LOD + 0.0208 = 0.0217 **(<0.031)**
			Stover		77	<LOD + *0.0080* + <LOD + <LOD = 0.0153 **(<0.04)** <LOD + *0.0078* + *0.0052* + <LOD = 0.0163 **(<0.04)**	<LOD + *0.0080* = 0.0089 **(<0.02)** <LOD + *0.0078* = 0.0087 **(<0.02)**
			Stover		83	<LOD + *0.0080* + <LOD + <LOD = 0.0153 **(<0.04)** <LOD + *0.0087* + *0.0080* + *0.0022* = 0.0198 **(<0.04)**	<LOD + *0.0080* = 0.0089 **(<0.02)** <LOD + *0.0087* = 0.0096 **(<0.02)**
			Stover		90	<LOD + *0.0091* + <LOD + <LOD = 0.0164 **(<0.04)** <LOD + *0.0087* + <LOD + <LOD = 0.0160 **(<0.04)**	<LOD + *0.0091* = 0.0100 **(<0.02)** <LOD + *0.0087* = 0.0096 **(<0.02)**
			Stover		97	<LOD + *0.0072* + <LOD + <LOD = 0.0145 **(<0.04)** <LOD + *0.0036* + <LOD + <LOD = 0.0109 **(<0.04)**	<LOD + *0.0072* = 0.0081 **(<0.02)** <LOD + *0.0036* = 0.0045 **(<0.02)**

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TABLE C.3.2. Residue Data from Popcorn Stover Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX026-) Year	Treatment Pattern[1]	Crop; Variety	Commodity	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Stilwell, KS (continued)	B	Popcorn; Yellow	Stover	0.172 (0.193)	63	<LOD + 0.0551 + 0.0365 + *0.0042* = 0.0967 **(<0.112)** <LOD + 0.0452 + 0.0262 + *0.0021* = 0.0744 **(<0.091)**	<LOD + 0.0551 = 0.0560 **(<0.065)** <LOD + 0.0452 = 0.0461 **(<0.055)**
			Stover		71	<LOD + 0.0305 + 0.0158 + <LOD = 0.0496 **(<0.066)** <LOD + 0.0414 + 0.0439 + *0.0039* = 0.0901 **(<0.105)**	<LOD + 0.0305 = 0.0314 **(<0.041)** <LOD + 0.0414 = 0.0423 **(<0.051)**
			Stover		77	<LOD + *0.0099* + <LOD + *0.0036* = 0.0184 **(<0.04)** <LOD + 0.0686 + 0.0254 + <LOD = 0.0973 **(<0.114)**	<LOD + *0.0099* = 0.0108 **(<0.02)** <LOD + 0.0686 = 0.0695 **(<0.079)**
			Stover		84	<LOD + 0.0236 + *0.0046* + *0.0032* = 0.0323 **(<0.054)** <LOD + 0.0518 + 0.0174 + *0.0029* = 0.0730 **(<0.089)**	<LOD + 0.0236 = 0.0245 **(<0.034)** <LOD + 0.0518 = 0.0527 **(<0.062)**
			Stover		91	<LOD + 0.0134 + <LOD + <LOD = 0.0207 **(<0.043)** <LOD + 0.0110 + <LOD + <LOD = 0.0183 **(<0.041)**	<LOD + 0.0134 = 0.0143 **(<0.023)** <LOD + 0.0110 = 0.0119 **(<0.021)**

[1] Treatment Pattern A: Two foliar spray applications at 24-inch and 36-inch corn height.
Treatment Pattern B: One foliar spray application at 36-inch corn height and one directed-spray application one week later.

[2] The LOD values for tembotrione (parent), M5, M6, and M2 in popcorn stover were 0.0009 ppm, 0.0013 ppm, 0.0040 ppm, and 0.0024 ppm, respectively. Residues below the LOQ (<0.01 ppm each analyte) but above the respective LOD are *italicized*. Total residues based on the LOQ of each analyte are **bolded** in parentheses.

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TABLE C.4. Summary of Residue Data from Popcorn Field Trials with Tembotrione.

Commodity	Treated[1]	PHI (days)	Sum of Residues: Parent + M5 + M6 + M2 (ppm in parent equivalents) [2]						
			n	Min	Max	HAFT	Median	Mean	Std. Dev.
Grain	A	81-93	8	<0.04	<0.050	<0.049	0.020	0.023	0.006
	B	72-86	8	<0.04	<0.048	<0.047	0.020	0.023	0.006
Stover	A	81-93	8	<0.04	<0.281	<0.238	0.033	0.081	0.098
	B	72-86	8	<0.04	<0.302	<0.283	0.049	0.102	0.112
Commodity	Treatment Pattern[1]	PHI (days)	Sum of Residues: Parent + M5 (ppm in parent equivalents)[2]						
			n	Min	Max	HAFT	Median	Mean	Std. Dev.
Grain	A	81-93	8	<0.02	<0.02	<0.02	0.01	0.01	N/A
	B	72-86	8	<0.02	<0.02	<0.02	0.01	0.01	N/A
Stover	A	81-93	8	<0.02	<0.199	<0.159	0.018	0.051	0.068
	B	72-86	8	<0.02	<0.202	<0.192	0.026	0.066	0.077

[1] Treatment Pattern A: two foliar spray applications at 24-inch and 36-inch corn height, for a total rate of 0.164-0.170 lb ai/A. Treatment Pattern B: One foliar spray application at 36-inch corn height and one directed-spray application one week later, for a total rate of 0.165-0.172 lb ai/A.

[2] The LOQ (0.01 ppm for each analyte) was used to determine the minimum, maximum, and highest-average field trial (HAFT). For the calculation of the median, mean and standard deviation ½ the LOQ (0.005 ppm for each analyte) was used for residues reported below the LOQ (or <LOD) in Tables C.3.1 and C.3.2.

D. CONCLUSION

The submitted popcorn field trial data are adequate and reflect the use of the SC formulation nominally containing 3.50 lb tembotrione ai/gallon (420 g ai/L) as two foliar applications made to popcorn at 24-inch and 36-inch height (Treatment A), or one foliar spray application to popcorn at 36-inch height plus one drop-nozzle (directed) spray one week later (Treatment B) at a target rate of 0.082 lb ai/A/application (0.092 kg ai/ha/application). Popcorn grain and stover samples were harvested 72-93 days following total applications at 0.164-0.172 lb ai/A (0.184-0.193 kg ai/ha). One trial collected additional samples at various PHIs to monitor residue decline. An acceptable method was used for quantitation of residues in/on popcorn grain and stover. Adequate data are available to support sample storage intervals and conditions.

In trials reflecting Treatment A (two foliar applications totaling 0.161-0.170 lb ai/A), the maximum combined residues of parent and its metabolites (M5 + M6 + M2), as parent equivalents, were <0.050 ppm in/on popcorn grain and <0.281 ppm in/on popcorn stover. In the treated stover sample which bore the highest combined residues of <0.281 ppm, Metabolites M5 and M6 comprised 67% and 24% of the respective total residues; individual residues of the parent and Metabolite M2 were either below or slightly above the LOQ in the same stover sample.

Following Treatment B (one foliar application and one directed-spray application totaling 0.165-0.172 lb ai/A), the maximum combined residues of parent and its metabolites (M5 + M6 + M2), as parent equivalents, were <0.048 ppm in/on popcorn grain and <0.302 ppm in/on popcorn stover.

E. REFERENCES

46695537.der.doc
46695601.der.doc

F. DOCUMENT TRACKING

RDI: RAB1 Chemists (1/10/07)
Petition Number: PP#5F7009
DP#s: 325349, 325663, and 331222
PC Code: 012801

Template Version June 2005

Tembotrione/AE 0172747/PC Code 012801/Bayer CropScience/264
DACO 7.4.1/7.4.2/OPPTS 860.1500/OECD IIA 6.3.1, 6.3.2, 6.3.3 and IIIA 8.3.1, 8.3.2, 8.3.3
Crop Field Trial/Residue Decline – Sweet Corn

Primary Evaluator	George F. Kramer, Ph.D., Senior Chemist Registration Action Branch (RAB1) Health Effects Division (HED) (7509P)	Date: 18-JUL-2007
Approved by	P.V. Shah, Ph.D., Branch Senior Scientist RAB1/HED (7509P)	Date: 18-JUL-2007

This DER was originally prepared under contract by Dynamac Corporation (2275 Research Boulevard, Suite 300; Rockville, MD 20850; submitted 11/30/2006). The DER has been reviewed by HED and revised to reflect current Office of Pesticide Programs (OPP) policies.

STUDY REPORT:

46695608 Harbin, A.; Mackie, S. (2005) AE 0172747: Magnitude of Residues in Sweet Corn Resulting from Foliar Applications of AE 0172747 02 SC52 A1 under Maximum Proposed Label Specifications (2003). Project Number: 03RAAEX026, RAAEX026, RAAEX026-01H. Unpublished study prepared by Bayer Corp., Crop Management Strategies, Inc. and Agricultural Chemistry Development Services, Inc. (ACDS). 484 p.

The petitioner has submitted an evaluation template for the study (Bayer CropScience DER for Study RAAEX026), which was used to generate this DER; selected sections were copied without alteration or were copied and modified to more specifically reflect the Agency's data evaluation requirements.

EXECUTIVE SUMMARY:

Bayer CropScience has submitted field trial data for tembotrione on sweet corn. Twelve sweet corn trials were conducted in the United States encompassing Zones 1 (NY and PA; 2 trials), 2 (GA; 1 trial), 3 (FL; 1 trial), 5 (IA, IL, IN, NE, and WI; 5 trials), 10 (CA; 1 trial), 11 (ID; 1 trial), and 12 (OR; 1 trial) during the 2003 and 2004 growing seasons.

Each trial site consisted of one control plot and two treated plots. Two foliar spray applications of a suspension-concentrate (SC) formulation (AE 0172747 Herbicide) nominally containing 3.50 lb tembotrione ai/gallon (420 g ai/L), were made to sweet corn at 24-inch and 36-inch height in treated plot A at a target rate of 0.082 lb ai/A/application (0.092 kg ai/ha/application). Sweet corn in treated plot B received one foliar spray application at the 36-inch height and one drop-nozzle (directed) spray one week later at the same target application rates. Applications were made using ground equipment in ~13-17 gal/A (122-163 L/ha). An adjuvant was added to the spray mixture for all applications. The achieved total seasonal rates ranged from 0.162 to 0.170 lb ai/A (0.182 to 0.190 kg ai/ha) for all treated plots at all trial sites.

Sweet corn forage and kernels plus cob with husk removed (K+CWHR) samples were harvested at a preharvest interval (PHI) of 44 to 46 days after the last application. Stover was harvested at commercial maturity (BBCH 87 to 89) at PHIs ranging from 46 to 95 days. At one trial location, sweet corn matrices were collected at additional sampling intervals to evaluate residue decline: sweet corn forage and K+CWHR were collected 35/36, 39, 44/45, 49/50, and 56 days and sweet

corn stover was collected 42/49, 50/57, 56/63, 64/71, and 70/77 days following the last application of Treatments A and B.

The harvested sweet corn raw agricultural commodity (RAC) samples were analyzed for residues of the parent compound, tembotrione, and the metabolites AE 1392936 (M2), AE 1417268 (M5), and AE 0456148 (M6) using a method entitled "AE 0172747: An Analytical Method for the Determination of Residues of AE 0172747, and its major metabolites AE 0456148, AE 1417268, and AE 1392936 in Plant Matrices Using LC/MS/MS." This method is acceptable for data collection based on adequate method validation and concurrent method recovery data. The limits of quantitation (LOQs) for tembotrione, M2, M5, and M6 were each 0.010 ppm in corn grain, forage and stover based on field corn validation data; the estimated method limits of detection (LODs) were ≤0.004 ppm for each analyte in corn grain, forage, and stover.

The maximum storage intervals of samples from harvest to analysis were 372 days (12.2 months) for sweet corn forage, 334 days (11.0 months) for sweet corn K+CWHR, and 313 days (10.3 months) for sweet corn stover. In addition, several forage and stover samples were reanalyzed 321-334 days after the initial analysis; the maximum storage intervals of these samples was 641 days (21.1 months) for forage and 635 days (20.9 months) for stover. Results of the reanalyses were not significantly different from the original analyses; therefore, stability may be inferred for the additional storage interval. Adequate storage stability data for field corn commodities (refer to 860.1380 DER for MRID 46695601) are available to support the storage conditions and intervals of samples from the sweet corn field trials.

In trials reflecting Treatment A (two foliar applications totaling 0.162-0.170 lb ai/A), the maximum combined residues of parent and its metabolites (M5 + M6 + M2), as parent equivalents, were <0.864 ppm in/on sweet corn forage, <0.082 ppm in/on sweet corn K+CWHR, and <0.973 ppm in/on sweet corn stover. In the treated stover sample which bore the highest combined residues of <0.973 ppm, Metabolites M5, M6, and M2 comprised 76%, 12%, and 10% of the total residues, respectively; residues of the parent were below the LOQ in the same stover sample.

Following Treatment B (one foliar application and one directed-spray application totaling 0.164-0.170 lb ai/A), the maximum combined residues of parent and its metabolites (M5 + M6 + M2), as parent equivalents, were <1.384 ppm in/on sweet corn forage, <0.082 ppm in/on sweet corn K+CWHR, and <0.720 ppm in/on sweet corn stover.

When only residues of the parent and Metabolite M5 are summed, the maximum combined residues following Treatment A were <0.738 ppm in/on sweet corn forage, <0.035 ppm in/on sweet corn K+CWHR, and <0.754 ppm in/on sweet corn stover. Following Treatment B, the maximum combined residues were <0.911 ppm in/on sweet corn forage, <0.02 ppm (combined LOQs) in/on sweet corn K+CWHR, and <0.465 ppm in/on sweet corn stover.

Based on the results of the side-by-side field trials, residues were similar in/on sweet corn K+CWHR treated with two foliar applications or treated with one foliar + one directed-spray application; however, residues were higher in forage treated with the two foliar applications but

higher in stover treated with the one foliar + one directed-spray applications. Residues of the parent were below the LOQ in all sweet corn matrices from both treatment regimes.

For sweet corn forage and stover, the total tembotrione residue declined with time by the later sampling intervals; residues initially increased in forage and then declined. The minimal total tembotrione residue in grain was not observed to decline with time; however, overall residues were nondetectable or very low.

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the field trial residue data are classified as scientifically acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document [DP# 325349].

COMPLIANCE:

Signed and dated Good Laboratory Practice (GLP), Quality Assurance and Data Confidentiality statements were provided. No deviations from regulatory requirements were reported which would have an impact on the validity of the study.

A. BACKGROUND INFORMATION

Tembotrione, a new herbicide with broad use against mono- and dicotyledons in selected crops such as corn, is a 4-hydroxyphenylpyruvate deoxygenase (HPPD) inhibitor (bleacher). Details of the test compounds nomenclature (tembotrione and its three metabolites) and physiochemical properties of tembotrione are given in Tables A.1 and A.2.

TABLE A.1. Test Compound Nomenclature for Tembotrione and its Metabolites AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2).

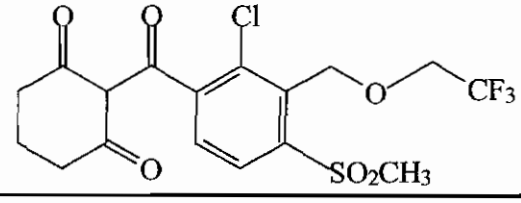
Compound: Tembotrione	Chemical Structure 
Common name	Tembotrione (Parent)
Company experimental name	*AE 0172747*
IUPAC name	2-{2-Chloro-4-mesyl-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl}cyclohexane-1,3-dione
CAS name	2-[2-Chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione
CAS #	335104-84-2
End-use product/EP	AE 0172747 Herbicide, EPA Reg No. 264-xxx

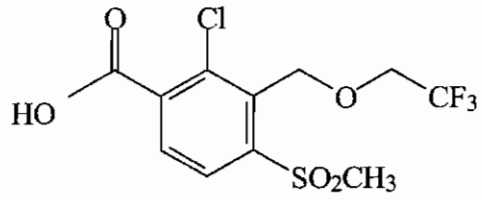
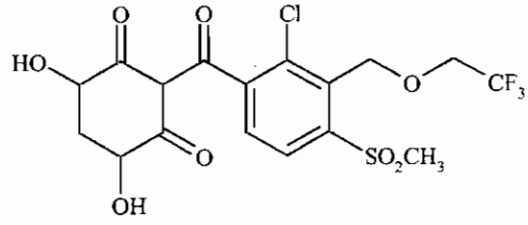
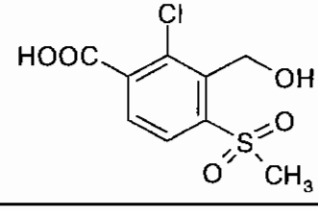
TABLE A.1. Test Compound Nomenclature for Tembotrione and its Metabolites AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2).	
Compound: AE 0456148	Chemical Structure 
Common name	Metabolite M6
Company experimental name	AE 0456148
IUPAC name	None provided
CAS name	2-chloro-4-mesyl-3-[(2,2,2-trifluroethoxy)methyl]benzoic acid
CAS #	None provided
Compound: AE 1417268	Chemical Structure 
Common name	Metabolite M5
Company experimental name	AE 1417268
IUPAC name	None provided
CAS name	2-[2-chloro-4-(methylsulfonyl)-3-[2,2,2-trifluoroethoxy)methyl]benzoyl]-4,6-dihydroxycyclohexan-1,3-dione
CAS #	None provided
Compound: AE 1392936	Chemical Structure 
Common name	Metabolite M2
Company experimental name	AE 1392936
IUPAC name	None provided
CAS name	2-chloro-3-hydroxymethyl-4-mesylbenzoic acid
CAS #	None provided

TABLE A.2. Physicochemical Properties of Technical Grade Tembotrione.		
Parameter	Value	Reference (MRID#)
Melting point	117 °C	46695402
pH @ 24 °C	3.63	
Density (g/mL @ 20 °C)	1.56	

TABLE A.2. Physicochemical Properties of Technical Grade Tembotrione.		
Parameter	Value	Reference (MRID#)
Water solubility (mg/L @ 20 °C)	0.22 at pH4 28.3 at pH 7 29.7 at pH 9	
Solvent solubility (g/L at 20 °C) DMSO Methylene Chloride Acetone Ethyl Acetate Toluene Hexane Ethanol	 >600 >600 300-600 180.2 75.7 47.6 8.2	
Vapor pressure (Torr, 20 °C)	8.25×10^{-11}	
Dissociation constant (pK_a)	3.2	
Octanol/water partition coeffieient (P_{ow} @ 23 °C) (P_{ow} @ 24 °C) (P_{ow} @ 23 °C)	 0.0430 at pH 9.0 0.0807 at pH 7.0 144.9 at pH 2.0	
UV/visible absorption spectrum (nm)	Primary: 205 Secondary: 284 Tertiary: 240	

B. EXPERIMENTAL DESIGN

B.1. Study Site Information

Twelve field trials were conducted in the United States encompassing Zones 1 (NY and PA; 2 trials), 2 (GA; 1 trial), 3 (FL; 1 trial), 5 (IA, IL, IN, NE, and WI; 5 trials), 10 (CA; 1 trial), 11 (ID; 1 trial), and 12 (OR; 1 trial) during the 2003 and 2004 growing seasons.

AE 0172747 Herbicide is a suspension concentrate (SC) formulation nominally containing 3.50 lb tembotrione ai/gallon (420 g ai/L). Each trial site consisted of one control plot and two treated plots. Two foliar spray applications of AE 0172747 Herbicide were made to sweet corn at 24-inch and 36-inch height in treated plot A at a target rate of 0.082 lb ai/A/application (0.092 kg ai/ha/application). Sweet corn in treated plot B received one foliar spray application at the 36-inch height and one drop-nozzle (directed) spray one week later at the same target application rates. The target total application rate for both treatment plots was 0.164 lb ai/A (0.184 kg ai/ha). Applications were made using ground equipment in ~13-17 gal/A (122-163 L/ha). Both treated plots had the spray adjuvants methylated seed oil (MSO) at 1.5 pt/A and 28% or 32% urea ammonium nitrate (UAN) at 1.5 to 2 qt/A added to each tank mixture. Actual trial parameters are reported in Table B.1.2.

Agronomic practices typical of the trial locations were used for growing sweet corn. Trial site conditions are presented in Table B.1.1. The crop varieties grown are identified in Table C.3. The actual temperature recordings and rainfall averages were within average historical values for the residue study period. Some field trials supplemented normal rainfall amounts with irrigation as needed. Irrigation amounts ranged from 0.5 to 20 inches.

TABLE B.1.1 Trial Site Conditions.

Study Location City, State	Trial Number (RAAEX0-)	Year	Soil Characteristics				Meteorological Data[1]	
			Type	% OM[2]	pH	CEC[2]	Total Precip (inch)	Temp Range (°F)
Germansville, PA	26-01H	2003	Loam	3.0	7.1	9.9	23.83	30-96
North Rose, NY	26-02H	2003	Silt Loam	3.9	5.4	8.3	10.21	34-85
Molino, FL	26-04H	2003	Sandy Loam	2.2	6.3	7.6	33.22	58-92
Arkansaw, WI	26-05H	2003	Sandy Loam	1.8	6.5	6.0	2.9	40-98
Springfield, NE	26-06H	2003	Silt Loam	2.7	6.3	10.9	3.81	52-101
Bagley, IA	26-07H	2003	Loam	4.0	6.0	20.8	10.32	27-101
Seymour, IL	26-08D	2003	Silt Loam	3.1	6.5	21	11.02	39-97
Oxford, IN	26-09H	2003	Clay Loam	4.7	5.9	17	10.82	46-94
Fresno, CA	26-11H	2003	Sandy Loam	0.4	6.1	1.4	0.00	53-103
Rupert, ID	26-12H	2003	Loam	1.6	7.8	28.8	1.08	25-107
Corvallis, OR	26-13H	2003	Silty Clay Loam	2.9	6.3	14.9	1.12	40-101
Tifton, GA	26-14H	2004	Sand	0.8	5.8	3.6	12.18	65-97

[1] Meteorological data from date of first application through date of final harvest.
[2] OM = Organic matter, CEC = Cation-exehange capacity (unit of measurement was not provided).

TABLE B.1.2. Study Use Pattern.

Location: City, State, NAFTA Zone Trial Number (RAAEX015-) Year	End-Use Product[1]	Application							Tank Mix Adjuvant[6]
		Method	Timing[2]	Trtmt Pattern[3]	Rate lb ai/A (kg ai/ha)	RTI[4] (days)	Spray Volume[5] GPA (L/ha)	Total Rate lb ai/A (kg ai/ha)	
Germansville, PA Zone 1 01H 2003	420 SC	Foliar	24	A	0.085 (0.095)	--	16.6 (155)	0.170 (0.190)	MSO & UAN
		Foliar	36		0.085 (0.095)	5	16.6 (155)		
	420 SC	Foliar	36	B	0.083 (0.094)	--	16.2 (151)	0.166 (0.188)	MSO & UAN
		Directed	1 wk later		0.083 (0.094)	6	16.3 (152)		
North Rose, NY Zone 1 02H 2003	420 SC	Foliar	24	A	0.082 (0.092)	--	15.0 (140)	0.164 (0.184)	MSO & -UAN
		Foliar	36		0.082 (0.092)	6	15.1 (141)		
	420 SC	Foliar	36	B	0.084 (0.094)	--	15.4 (144)	0.166 (0.186)	MSO & UAN
		Directed	1 wk later		0.082 (0.092)	7	14.9 (139)		
Molino, FL Zone 3 04H 2003	420 SC	Foliar	24	A	0.080 (0.090)	--	14.4 (135)	0.162 (0.182)	MSO & UAN
		Foliar	36		0.082 (0.092)	4	14.4 (135)		
	420 SC	Foliar	36	B	0.082 (0.092)	--	14.2 (133)	0.166 (0.186)	MSO & UAN
		Directed	1 wk later		0.084 (0.094)	9	15.2 (142)		

TABLE B.1.2. Study Use Pattern.

Location: City, State, NAFTA Zone Trial Number (RAAEX015-) Year	End-Use Product[1]	Application							Tank Mix Adjuvant[6]
		Method	Timing[2]	Trtmt Pattern[3]	Rate lb ai/A (kg ai/ha)	RTI[4] (days)	Spray Volume[5] GPA (L/ha)	Total Rate lb ai/A (kg ai/ha)	
Arkansaw, WI Zone 5 05H 2003	420 SC	Foliar	24	A	0.083 (0.094)	--	15.3 (143)	0.167 (0.188)	MSO & UAN
		Foliar	36		0.084 (0.094)	6	15.3 (143)		
	420 SC	Foliar	36	B	0.084 (0.094)	--	15.3 (143)	0.169 (0.189)	MSO & UAN
		Directed	1 wk later		0.085 (0.095)	8	15.4 (144)		
Springfield, NE Zone 5 06H 2003	420 SC	Foliar	24	A	0.082 (0.092)	--	14.8 (138)	0.164 (0.184)	MSO & UAN
		Foliar	36		0.082 (0.092)	6	15.0 (140)		
	420 SC	Foliar	36	B	0.082 (0.092)	--	14.9 (139)	0.164 (0.184)	MSO & UAN
		Directed	1 wk later		0.082 (0.092)	7	14.5 (136)		
Bagley, IA Zone 5 07H 2003	420 SC	Foliar	24	A	0.082 (0.092)	--	13.3 (124)	0.164 (0.184)	MSO & UAN
		Foliar	36		0.082 (0.092)	6	14.0 (131)		
	420 SC	Foliar	36	B	0.083 (0.094)	--	14.4 (135)	0.167 (0.188)	MSO & UAN
		Directed	1 wk later		0.084 (0.094)	7	15.0 (140)		
Seymour. IL Zone 5 08D 2003	420 SC	Foliar	24	A	0.082 (0.092)	--	16.2 (151)	0.165 (0.186)	MSO & UAN
		Foliar	36		0.083 (0.094)	7	16.1 (151)		
	420 SC	Foliar	36	B	0.084 (0.094)	--	16.3 (152)	0.167 (0.188)	MSO & UAN
		Directed	1 wk later		0.083 (0.094)	7	14.9 (139)		
Oxford, IN Zone 5 09H 2003	420 SC	Foliar	24	A	0.084 (0.094)	--	15.5 (145)	0.169 (0.189)	MSO & UAN
		Foliar	36		0.085 (0.095)	4	16.5 (154)		
	420 SC	Foliar	36	B	0.084 (0.094)	--	16.4 (153)	0.168 (0.188)	MSO & UAN
		Directed	1 wk later		0.084 (0.094)	7	14.6 (136)		
Fresno, CA Zone 10 11H 2003	420 SC	Foliar	24	A	0.083 (0.094)	--	16.1 (151)	0.166 (0.188)	MSO & UAN
		Foliar	36		0.083 (0.094)	11	16.2 (151)		
	420 SC	Foliar	36	B	0.086 (0.096)	--	16.7 (156)	0.170 (0.190)	MSO & UAN

TABLE B.1.2. Study Use Pattern.

Location: City, State, NAFTA Zone Trial Number (RAAEX015-) Year	End-Use Product[1]	Application							Tank Mix Adjuvant[6]
		Method	Timing[2]	Trtmt Pattern[3]	Rate lb ai/A (kg ai/ha)	RTI[4] (days)	Spray Volume[5] GPA (L/ha)	Total Rate lb ai/A (kg ai/ha)	
		Directed	1 wk later		0.084 (0.094)	7	13.9 (130)		
Rupert, ID Zone 11 12H 2003	420 SC	Foliar	24	A	0.082 (0.092)	--	13.8 (129)	0.164 (0.184)	MSO & UAN
		Foliar	36		0.082 (0.092)	8	13.4 (125)		
	420 SC	Foliar	36	B	0.082 (0.092)	--	13.1 (122)	0.166 (0.186)	MSO & UAN
		Directed	1 wk later		0.084 (0.094)	7	15.4 (144)		
Corvallis, OR Zone 12 13H 2003	420 SC	Foliar	24	A	0.083 (0.094)	--	14.9 (139)	0.166 (0.188)	MSO & UAN
		Foliar	36		0.083 (0.094)	5	14.9 (139)		
	420 SC	Foliar	36	B	0.084 (0.094)	--	14.9 (139)	0.169 (0.189)	MSO & UAN
		Directed	1 wk later		0.085 (0.095)	6	15.1 (141)		
Tifton, GA Zone 2 14H 2003	420 SC	Foliar	24	A	0.082 (0.092)	--	17.4 (163)	0.164 (0.184)	MSO & UAN
		Foliar	36		0.082 (0.092)	11	13.8 (129)		
	420 SC	Foliar	36	B	0.082 (0.092)	--	13.8 (129)	0.164 (0.184)	MSO & UAN
		Directed	1 wk later		0.082 (0.092)	7	13.4 (125)		

[1] The end-use product is a SC formulation of tembotrione and isoxadifen safener.
[2] Timing = Corn height in inches or 1 week later.
[3] Treatment Pattern A: Two foliar spray applications at 24-inch and 36-inch corn height.
Treatment Pattern B: One foliar spray application at 36-inch corn height and one directed-spray application one week later.
[4] RTI = Retreatment Interval.
[5] GPA = gallons per acre and L/ha = liters per hectare.
[6] Spray adjuvants methylated seed oil (MSO) and urea ammonium nitrate (UAN).

TABLE B.1.3. Trial Numbers and Geographical Locations.

NAFTA Growing Zones	Sweet Corn		
	Submitted	Requested	
		Canada	U.S.
1	2		2
2	1		1
3	1		1
5	5		5
10	1		1
11	1		1

TABLE B.1.3. Trial Numbers and Geographical Locations.			
NAFTA Growing Zones	Sweet Corn		
	Submitted	Requested	
		Canada	U.S.
12	1		1
Total	12		12

B.2. Sample Handling and Preparation

In all of the trials, duplicate treated samples and a single control sample of sweet corn forage, K+CWHR, and stover were collected at normal harvest times. Sweet corn forage and K+CWHR samples were harvested at a PHI of 44 to 46 days after the last application. Stover was harvested at commercial maturity (BBCH 87 to 89) at PHIs ranging from 46 to 95 days. One trial collected additional samples at various PHIs to monitor residue decline.

All corn samples were harvested by hand and put into labeled plastic-coated cloth bags in the field and transported to a freezer within 2 hours of harvest. Following collection of the sweet corn samples, reasonable attempts were made to maintain the samples under cool conditions in the field prior to being transferred to frozen storage. Samples remained in frozen storage at the field facilities until shipment via freezer truck to Bayer Research Park (BRP; Stilwell, KS) for analysis. In preparation for analysis, the sweet corn RAC samples were homogenized in dry ice using a chopper. All samples remained frozen at all times except during sub-sampling for analysis.

B.3. Analytical Methodology

The harvested sweet corn RAC samples were analyzed for residues of the parent compound, tembotrione, and the metabolites AE 1392936 (M2), AE 1417268 (M5), and AE 0456148 (M6). The analytical method used was a liquid chromatography/mass spectroscopy (LC/MS)/MS method entitled "AE 0172747: An Analytical Method for the Determination of Residues of AE 0172747, and its major metabolites AE 0456148, AE 1417268, and AE 1392936 in Plant Matrices Using LC/MS/MS." This method quantifies all analytes from a single sample using isotopically labeled internal standards.

Briefly, residues of tembotrione and its metabolites M2, M5, and M6 were extracted from crop matrices with acetonitrile:water (1:1, v:v) using accelerated solvent extraction. Internal standards of the deuterated analytes were added to the extract. For parent, M5, and M6 analysis, an aliquot of the extract was concentrated via Turbo-Vap. For M2 analysis, an aliquot of the extract was loaded onto a strong-anion exchange solid-phase extraction (SPE) cartridge and eluted with oxalic acid. The SPE eluate was concentrated. The concentrates were reconstituted in 0.1% formic acid and filtered for LC/MS/MS analysis. For the subject field trial study, reference standards were prepared in tembotrione molar equivalents, therefore, quantitating residues as parent equivalents.

Method validation was performed prior to sample analysis with field corn forage, grain, and stover (refer to 860.1340 DER for MRID 46695537), and concurrent recoveries were performed during sample analysis to demonstrate acceptable method performance.

The LOQs for tembotrione, M2, M5, and M6 were 0.010 ppm for each analyte based on field corn validation data. The LOQ is defined as the lowest fortification level of an analyte at which acceptable recovery data was achieved.

The calculated LODs were 0.0014 ppm for tembotrione, 0.0021 ppm for M6, 0.0023 ppm for M5, and 0.0021 ppm for M2 in corn forage. The calculated LODs were 0.0011 ppm for tembotrione, 0.0029 ppm for M6, 0.0025 ppm for M5, and 0.0017 ppm for M2 in corn grain. The calculated LODs were 0.0009 ppm for tembotrione, 0.0040 ppm for M6, 0.0013 ppm for M5, and 0.0024 ppm for M2 in corn stover. The LOD was calculated by multiplying the standard deviation of recovery measurements at the LOQ by $t_{0.99}$ (where $t_{0.99}$ is the one-tailed statistic at the 99% confidence level for n-1 replicates) and adding the average residue found in the untreated control samples. For purposes of residue evaluation, HED used the aggregate LOQs of each analyte in totaling combined residues of tembotrione.

C. RESULTS AND DISCUSSION

Sample storage conditions and intervals are summarized in Table C.2. The maximum storage intervals of samples from harvest to analysis were 372 days (12.2 months) for sweet corn forage, 334 days (11.0 months) for sweet corn K+CWHR, and 313 days (10.3 months) for sweet corn stover. In addition, seven forage and three stover samples from the decline trial (RAAEX026-08D) and two forage samples from the IA trial (RAAEX026-07H) were reanalyzed 321 to 334 days after the initial analysis; the maximum storage intervals of these samples were 641 days (21.1 months) for forage and 635 days (20.9 months) for stover. Results of the reanalyses were not significantly different from the original analyses; therefore, stability may be inferred for the additional storage interval. The submitted storage stability data on field corn RAC commodities (refer to 860.1380 DER for MRID 46695601) indicate that tembotrione, M2, M5, and M6 residues are stable (<30% decomposition) during frozen storage for at least 13 months prior to analysis with one exception. Residues of M5 in grain showed some apparent degradation with time; however, based on the results of the corn metabolism studies with tembotrione, M5 is not found in significant amounts in grain (<0.010 ppm). The field corn storage stability data may be translated to fulfill the requirements for storage stability data on sweet corn commodities.

The analytical method (LC/MS/MS) was successfully validated for the analysis of tembotrione residues and its metabolites M2, M5, and M6 in/on various plant matrices (see 860.1340 DER for MRID 46695537). Recoveries of tembotrione, M6, M5, and M2 from sweet corn matrices were measured concurrently with each set of samples to verify method performance. The concurrent recovery data are summarized in Tables C.1.1 (forage), C.1.2 (K+CWHR), and C.1.3 (stover). The data demonstrate acceptable method performance during sample analysis. Concurrent method recoveries from sweet corn K+CWHR and stover controls fortified with tembotrione, M6, M5 or M2 at 0.02-2.0 ppm, and forage fortified with each analyte at 0.01-1.5

ppm ranged from 70% to 123%. Apparent residues of all analytes were nondetectable in/on all untreated sweet corn forage, K+CWHR, and stover samples, except several control forage and K+CWHR samples bore residues of the metabolites below the method LOQ (0.01 ppm each analyte). One untreated sample of forage bore residues greater than the LOQ of M5, M6, and M2 at 0.376, 0.064, and 0.012 ppm, respectively; two untreated samples of K+CWHR bore residues greater than the LOQ of M5 and/or M6 at 0.014 and 0.012-0.016 ppm, respectively; and one untreated sample of stover bore residues greater than the LOQ of M5 and M6 at 0.044 and 0.041 ppm, respectively. The duplicate sample or re-analysis of these samples resulted in nonquantifiable residues, and the average residue was reported. However, one untreated K+CWHR sample had total residues of 0.029 ppm; no explanation was provided by the petitioner.

Individual and total tembotrione residues found in treated sweet corn forage, K+CWHR, and stover samples are presented in Tables C.3.1 through C.3.3, respectively. Total residues in sweet corn matrices are summarized in Table C.4. Following Treatment A [two foliar applications of the SC formulation totaling 0.162-0.170 lb ai/A (0.182-0.190 kg ai/ha)], the sum of residues (parent + M5 + M6 + M2, as parent equivalents) as determined by the data collection method were <0.110-<0.864 ppm in/on 24 samples of sweet corn forage, below the combined LOQ (<0.04 ppm) to <0.082 ppm in/on 24 samples of sweet corn K+CWHR, and <0.04-<0.973 ppm in/on 24 samples of sweet corn stover. Following Treatment B [one foliar application and one directed-spray application of the SC formulation totaling 0.164-0.170 lb ai/A (0.184-0.190 kg ai/ha)], the sum of parent + M5 + M6 + M2 residues were <0.04-<1.384 ppm in/on 24 samples of sweet corn forage, <0.04-<0.082 ppm in/on 24 samples of sweet corn K+CWHR, and <0.04-<0.720 ppm in/on 24 samples of sweet corn stover.

Following Treatment A, the sum of residues (parent + M5, as parent equivalents) included in the proposed tolerance expression were <0.085-<0.738 ppm in/on 24 samples of sweet corn forage, below the combined LOQ (<0.02 ppm) to <0.035 ppm in/on 24 samples of sweet corn K+CWHR, and <0.02-<0.754 ppm in/on 24 samples of sweet corn stover. Following Treatment B, the sum of parent + M5 residues were <0.02-<0.911 ppm in/on 24 samples of sweet corn forage, <0.02 ppm in/on 24 samples of sweet corn K+CWHR, and <0.02-<0.465 ppm in/on 24 samples of sweet corn stover.

Based on the results of the side-by-side field trials, residues were similar in/on sweet corn K+CWHR treated with two foliar applications or treated with one foliar + one directed-spray application; however residues were higher in forage treated with the two foliar applications but higher in stover treated with one foliar + one directed-spray applications. Residues of the parent were below the LOQ in all sweet corn matrices from both treatment regimes.

For sweet corn forage and stover, the total tembotrione residue declined with time by the later sampling intervals; residues initially increased in forage and then declined. The minimal total tembotrione residue in grain was not observed to decline with time; however, overall residues were nondetectable or very low.

TABLE C.1.1. Summary of Concurrent Recoveries of Tembotrione, M5, M6, and M2 from Sweet Corn Forage.

Matrix	Analyte	Spike Level (mg/kg)	Sample Size (n)	Recoveries (%)	Mean Recovery (%)± std dev[1]
Sweet Corn Forage	Tembotrione	0.01	1	74	74
		0.02	2	77, 84	81
		0.05	1	98	98
		0.1	2	87, 104	96
		0.2	5	97, 105, 108, 111, 113	107 ± 6
		0.25	2	89, 93	91
		0.5	1	83	83
		1	1	86	86
	AE 0456148 (M6)	0.01	1	106	106
		0.02	2	84, 95	90
		0.05	1	112	112
		0.1	2	108, 112	110
		0.2	4	114, 115, 116, 117	116 ± 1
		0.25	2	80, 111	96
		0.5	1	88	88
		1	1	75	75
		1.5	1	101	101
	AE 1417268 (M5)	0.01	1	73	73
		0.02	2	70, 93	82
		0.05	1	84	84
		0.1	2	103, 108	106
		0.2	5	82, 91, 99, 105, 107	97 ± 10
		0.25	2	106, 108	107
		0.5	1	104	104
		1	2	86, 94	90
		1.5	1	76	76
	AE 1392936 (M2)	0.01	1	95	95
		0.02	2	84, 100	92
		0.05	1	113	113
		0.1	2	103, 107	105
		0.2	4	99, 107, 109, 119.	109 ± 8
		0.25	2	94, 101	98
		0.5	1	94	94
		1	1	90	90

[1] The standard deviation is not applicable for a sample size (n) of less than three.

TABLE C.1.2. Summary of Concurrent Recoveries of Tembotrione, M5, M6, and M2 from Sweet Corn K+CWHR.

Matrix	Analyte	Spike Level (mg/kg)	Sample Size (n)	Recoveries (%)	Mean Recovery (%)± std dev[1]
Sweet Corn K+CWHR	Tembotrione	0.02	2	86, 87	87
		0.05	2	86, 87	87
		0.1	3	88, 93, 96	92 ± 4
		0.2	3	95, 96, 115	102 ± 11
		0.25	3	89, 90, 95	91 ± 3
		0.5	1	86	86
	AE 0456148 (M6)	0.02	2	80, 88	84
		0.05	3	101, 113, 114	109 ± 7
		0.1	2	104, 110	107
		0.2	3	110, 110, 113	111 ± 2
		0.25	3	98, 104, 108	103 ± 5
		0.5	1	87	87
	AE 1417268 (M5)	0.02	2	94, 98	96
		0.05	2	83, 107	95
		0.1	3	93, 105, 115	104 ± 11
		0.2	3	100, 100, 109	103 ± 5
		0.25	3	102, 107, 108	106 ± 3
		0.5	1	116	116
	AE 1392936 (M2)	0.02	1	85	85
		0.05	2	101, 119	110
		0.1	3	102, 106, 115	108 ± 7
		0.2	2	100, 102	101
		0.25	3	90, 96, 97	94 ± 4
		0.5	1	97	97

[1] The standard deviation is not applicable for a sample size (n) of less than three.

TABLE C.1.3. Summary of Concurrent Recoveries of Tembotrione, M5, M6, and M2 from Sweet Corn Stover.

Matrix	Analyte	Spike Level (mg/kg)	Sample Size (n)	Recoveries (%)	Mean Recovery (%)± std dev[1]
Sweet Corn Stover	Tembotrione	0.02	1	77	77
		0.05	2	82, 103	93
		0.1	3	89, 101, 103	98 ± 8
		0.2	3	90, 102, 115	102 ± 13
		0.25	2	90, 94	92
		0.5	1	85	85
		1	2	73, 77	75
	AE 0456148 (M6)	0.02	1	84	84
		0.05	2	106, 115	111
		0.1	3	100, 108, 118	109 ± 9
		0.2	3	108, 108, 114	110 ± 4
		0.25	2	98, 106	102
		0.5	1	97	97
		1	3	73, 82, 120	92 ± 25
		2	1	94	94
	AE 1417268 (M5)	0.02	1	99	99
		0.05	2	106, 119	113
		0.1	3	77, 91, 103	90 ± 13
		0.2	3	82, 92, 109	94 ± 14
		0.25	2	97, 99	98
		0.5	1	100	100
		1	3	81, 81, 123	95 ± 24
		2	1	87	87
	AE 1392936 (M2)	0.02	1	82	82
		0.05	3	98, 100, 107	102 ± 5
		0.1	3	98, 111, 113	107 ± 8
		0.2	2	105, 111	108
		0.25	2	87, 105	96
		0.5	1	99	99
		1	2	78, 88	83

[1] The standard deviation is not applicable for a sample size (n) of less than three.

TABLE C.2. Summary of Storage Conditions for Sweet Corn.

Residue Components	Matrix	Storage Temp. (°C)[1]	Actual Storage Duration[2]	Interval of Demonstrated Storage Stability[3]
Tembotrione AE 0456148 (M6) AE 1417268 (M5) AE 1392936 (M2)	Forage	< -15	68-372 days/ 641 days [4] (2.2-12.2 months/ 21.1 months)	Tembotrione, M6, and M2 are stable for up to 12-13 months in frozen field corn grain, forage, and fodder. M5 is stable in frozen field corn forage and fodder for up to 12 months. M5 is stable in frozen field corn grain for up to 188 days but declined by 17% after 371 days (61% average corrected recovery).
Tembotrione AE 0456148 (M6) AE 1417268 (M5) AE 1392936 (M2)	K+CWHR	< -15	68-334 days (2.2-11.0 months)	
Tembotrione AE 0456148 (M6) AE 1417268 (M5) AE 1392936 (M2)	Stover	< -15	46-313 days/ 635 days [4] (1.5-10.3 months/ 20.9 months)	

[1] Storage temperature = storage temperature from receipt at Bayer CropScience through the last sample extraction.

[2] Actual study duration = time from sweet sampling through the last sample analyses. Samples were analyzed within 1-9 days of extraction.

[3] Field corn storage stability data; refer to the 860.1380 DER for MRID 46695601.

[4] The analytical portion of the study was originally completed in October, 2004; however, a few forage and stover samples were reanalyzed in May 2005. The first number comprises study duration for initial analyses of all samples; the second number for those few samples reanalyzed in May, 2005.

TABLE C.3.1. Residue Data from Sweet Corn Forage Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX026-) Year	Treatment Pattern[1]	Crop; Variety	Commodity (% Dry Matter)	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total [2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Germansville, PA Zone 1 01H 2003	A	Sweet Corn; Argent	Forage (20)	0.170 (0.190)	45	<LOD + 0.293 + 0.023 + 0.029 = 0.346 (**<0.355**) <LOD + 0.314 + 0.022 + 0.026 = 0.363 (**<0.372**)	<LOD + 0.293 = 0.294 (**<0.303**) <LOD + 0.314 = 0.315 (**<0.324**)
	B	Sweet Corn; Argent	Forage (18)	0.166 (0.188)	44	<LOD + 0.192 + 0.023 + 0.025 = 0.241 (**<0.250**) <LOD + 0.245 + 0.028 + 0.028 = 0.302 (**<0.311**)	<LOD + 0.192 = 0.193 (**<0.202**) <LOD + 0.245 = 0.246 (**<0.255**)
North Rose, NY Zone 1 02H 2003	A	Sweet Corn; Golden Queen	Forage (17)	0.164 (0.184)	45	<LOD + 0.108 + *0.004* + 0.010 = 0.123 (**<0.138**) <LOD + 0.100 + *0.004* + 0.011 = 0.116 (**<0.131**)	<LOD + 0.108 = 0.109 (**<0.118**) <LOD + 0.100 = 0.101 (**<0.110**)
	B	Sweet Corn; Golden Queen	Forage (20)	0.166 (0.186)	45	<LOD + *0.210* + *0.011* + *0.020* = 0.242 (**<0.251**) <LOD + 0.160 + *0.009* + 0.014 = 0.184 (**<0.194**)	<LOD + *0.210* = *0.211* (**<0.220**) <LOD + 0.160 = 0.161 (**<0.170**)
Molino, FL Zone 3 04H 2003	A	Sweet Corn; Silver Queen	Forage (20)	0.162 (0.182)	44	<LOD + 0.210 + 0.013 + 0.020 = 0.244 (**<0.253**) <LOD + 0.200 + 0.016 + 0.016 = 0.233 (**<0.242**)	<LOD + 0.210 = 0.211 (**<0.220**) <LOD + 0.200 = 0.201 (**<0.210**)
	B	Sweet Corn; Silver Queen	Forage (21)	0.166 (0.186)	45	<LOD + 0.052 + 0.026 + 0.011 = 0.090 (**<0.099**) <LOD + 0.060 + 0.026 + 0.014 = 0.101 (**<0.110**)	LOD + 0.052 = 0.053 (**<0.062**) <LOD + 0.060 = 0.061 (**<0.070**)

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TABLE C.3.1. Residue Data from Sweet Corn Forage Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX026-) Year	Treatment Pattern[1]	Crop; Variety	Commodity (% Dry Matter)	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total [2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Arkansaw, WI Zone 5 05H 2003	A	Sweet Corn; Ambrosia	Forage (18)	0.167 (0.188)	46	<LOD + 0.354 + 0.028 + 0.014 = 0.397 **(<0.406)** <LOD + 0.204 + 0.020 + 0.014 = 0.239 **(<0.248)**	LOD + 0.354 = 0.355 **(<0.364)** <LOD + 0.204 = 0.205 **(<0.214)**
	B	Sweet Corn; Ambrosia	Forage (21)	0.169 (0.189)	45	<LOD + 0.270 + 0.042 + 0.014 = 0.327 **(<0.336)** <LOD + 0.217 + 0.032 + 0.012 = 0.262 **(<0.271)**	<LOD + 0.270 = 0.271 **(<0.280)** <LOD + 0.217 = 0.218 **(<0.227)**
Springfield, NE Zone 5 06H 2003	A	*Sweet Corn;* Serindipity	Forage (26)	0.164 (0.184)	45	<LOD + 0.220 + 0.051 + 0.036 = 0.308 **(<0.317)** <LOD + 0.288 + 0.062 + 0.040 = 0.391 **(<0.400)**	<LOD + 0.220 = 0.221 **(<0.230)** <LOD + 0.288 = 0.289 **(<0.298)**
	B	Sweet Corn; Serindipity	Forage (35)	0.164 (0.184)	45	<LOD + 0.403 + 0.283 + 0.074 = 0.761 **(<0.770)** <LOD + 0.288 + 0.512 + 0.041 = 0.842 **(<0.851)**	<LOD + 0.403 = 0.404 **(<0.413)** <LOD + 0.288 = 0.289 **(<0.298)**
Bagley, IA Zone 5 07H 2003	A	Sweet Corn; Bodacious	Forage (24)	0.164 (0.184)	44	<LOD + 0.728 + 0.081 + 0.029 = 0.839 **(<0.848)** <LOD + 0.728 + 0.094 + 0.032 = 0.855 **(<0.864)**	<LOD + 0.728 = 0.729 **(<0.738)** <LOD + 0.728 = 0.729 **(<0.738)**
	B	Sweet Corn; Bodacious	Forage (26)	0.167 (0.188)	44	<LOD + 0.393 + 0.076 + 0.020 = 0.490 **(<0.499)** <LOD + 0.483 + 0.076 + 0.020 = 0.580 **(<0.589)**	<LOD + 0.393 = 0.394 **(<0.403)** <LOD + 0.483 = 0.484 **(<0.493)**

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TABLE C.3.1. Residue Data from Sweet Corn Forage Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX026-) Year	Treatment Pattern[1]	Crop; Variety	Commodity (% Dry Matter)	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total [2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Oxford, IN 09H Zone 5 2003	A	Sweet Corn; IoChief	Forage (27)	0.169 (0.189)	46	<LOD + 0.103 + 0.026 + *0.003* = 0.133 (**<0.149**) <LOD + 0.075 + 0.015 + <LOD = 0.094 (**<0.110**)	<LOD + 0.103 = 0.104 (**<0.113**) <LOD + 0.075 = 0.076 (**<0.085**)
	B	Sweet Corn; IoChief	Forage (29)	0.168 (0.188)	44	<LOD + 0.038 + 0.018 + <LOD = 0.060 (**<0.076**) <LOD + 0.096 + 0.032 + *0.005* = 0.134 (**<0.148**)	<LOD + 0.038 = 0.039 (**<0.048**) <LOD + 0.096 = 0.097 (**<0.106**)
Fresno, CA Zone 10 11H 2003	A	Sweet Corn; Golden Queen	Forage (22)	0.166 (0.188)	45	<LOD + 0.199 + 0.123 + 0.056 = 0.379 (**<0.388**) <LOD + 0.225 + 0.173 + 0.087 = 0.486 (**<0.495**)	<LOD + 0.199 = 0.200 (**<0.209**) <LOD + 0.225 = 0.226 (**<0.235**)
	B	Sweet Corn; Golden Queen	Forage (26)	0.170 (0.190)	45	<LOD + 0.144 + 0.250 + 0.036 = 0.431 (**<0.440**) <LOD + 0.118 + 0.206 + 0.030 = 0.355 (**<0.364**)	<LOD + 0.144 = 0.145 (**<0.154**) <LOD + 0.118 = 0.119 (**<0.128**)
Rupert, ID Zone 11 12H 2003	A	Sweet Corn; Northern Xtra Swect	Forage (36)	0.164 (0.184)	45	<LOD + 0.350 + 0.041 + 0.013 = 0.405 (**<0.414**) <LOD + 0.293 + 0.032 + 0.014 = 0.340 (**<0.349**)	<LOD + 0.350 = 0.351 (**<0.360**) <LOD + 0.293 = 0.294 (**<0.303**)
	B	Sweet Corn; Northern Xtra Sweet	Forage (25)	0.166 (0.186)	45	<LOD + 0.135 + 0.024 + *0.008* = 0.168 (**<0.179**) <LOD + 0.193 + 0.039 + *0.009* = 0.242 (**<0.252**)	<LOD + 0.135 = 0.136 (**<0.145**) <LOD + 0.193 = 0.194 (**<0.203**)

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TABLE C.3.1. Residue Data from Sweet Corn Forage Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX026-) Year	Treatment Pattern[1]	Crop; Variety	Commodity (% Dry Matter)	Total Rate lb ai/A (kg ai/ha)	PHI (days)	*Sum of Residues as determined* by the data-collection method: Parent + M5 + M6 + M2 = Total [2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Corvallis, OR Zone 12 13H 2003	A	Sweet Corn; Seneca Pronto	Forage (20)	0.166 (0.188)	45	<LOD + 0.260 + *0.006* + <LOD = 0.270 **(<0.290)** <LOD + 0.317 + 0.010 + <LOD = 0.331 **(<0.347)**	<LOD + 0.260 = 0.261 **(<0.270)** <LOD + 0.317 = 0.318 **(<0.327)**
	B	Sweet Corn; Seneca Pronto	Forage (36)	0.169 (0.189)	46	<LOD + <LOD + <LOD + <LOD = 0.008 **(<0.04)** <LOD + <LOD + <LOD + <LOD = 0.008 **(<0.04)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**
Tifton, GA Zone 2 14H 2004	A	Sweet Corn; G-90	Forage (24)	0.164 (0.184)	45	<LOD + 0.086 + 0.020 + 0.013 = 0.120 **(<0.309)** <LOD + 0.092 + 0.023 + *0.008* = 0.124 **(<0.135)**	<LOD + 0.086 = 0.087 **(<0.096)** <LOD + 0.092 = 0.093 **(<0.102)**
	B	Sweet Corn; G-90	Forage (45)	0.164 (0.184)	45	<LOD + 0.070 + 0.037 + *0.006* = 0.114 **(<0.460)** <LOD + 0.061 + 0.041 + 0.011 = 0.114 **(<0.123)**	<LOD + 0.070 = 0.071 **(<0.080)** <LOD + 0.061 = 0.062 **(<0.071)**

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TABLE C.3.1. Residue Data from Sweet Corn Forage Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX026-) Year	Treatment Pattern[1]	Crop; Variety	Commodity (% Dry Matter)	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total [2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Seymour, IL Zone 5 08D 2003	A	Sweet Corn; Parfait	Forage (19)	0.165 (0.186)	36	<LOD + 0.376 + 0.064 + 0.012 = 0.453 (**<0.462**) <LOD + 0.379 + 0.057 + 0.013 = 0.450 (**<0.459**)	<LOD + 0.376 = 0.377 (**<0.386**) <LOD + 0.379 = 0.380 (**<0.389**)
			Forage (21)		39	<LOD + 0.563 + 0.154 + 0.029 = 0.747 (**<0.756**) <LOD + 0.572 + 0.164 + 0.029 = 0.766 (**<0.775**)	<LOD + 0.563 = 0.564 (**<0.573**) <LOD + 0.572 = 0.573 (**<0.582**)
			Forage (29)		45	<LOD + 0.467 + 0.195 + 0.027 = 0.690 (**<0.699**) <LOD + 0.352 + 0.178 + 0.023 = 0.554 (**<0.563**)	<LOD + 0.467 = 0.468 (**<0.477**) <LOD + 0.352 = 0.353 (**<0.362**)
			Forage (44)		49	<LOD + 0.395 + 0.216 + 0.025 = 0.638 (**<0.646**) <LOD + 0.481 + 0.281 + 0.029 = 0.792 (**<0.801**)	<LOD + 0.395 = 0.396 (**<0.405**) <LOD + 0.481 = 0.482 (**<0.491**)
			Forage (36)		56	<LOD + 0.011 + 0.019 + <LOD = 0.034 (**<0.050**) <LOD + 0.014 + 0.024 + <LOD = 0.042 (**<0.058**)	<LOD + 0.011 = 0.012 (**<0.021**) <LOD + 0.014 = 0.015 (**<0.024**)

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TABLE C.3.1. Residue Data from Sweet Corn Forage Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX026-) Year	Treatment Pattern[1]	Crop; Variety	Commodity (% Dry Matter)	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total [2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Seymour, IL (continued)	B	Sweet Corn; Parfait	Forage (30)	0.167 (0.188)	35	*0.0014* + 0.379 + 0.073 + 0.022 = 0.475 **(<0.484)** <LOD + 0.690 + 0.138 + 0.033 = 0.862 **(<0.871)**	<LOD + 0.379 = 0.380 **(<0.389)** <LOD + 0.690 = 0.691 **(<0.700)**
			Forage (40)		39	<LOD + 1.087 + 0.330 + 0.054 = 1.472 **(<1.481)** <LOD + 0.997 + 0.444 + 0.067 = 1.509 **(<1.518)**	<LOD + 1.087 = 1.088 **(<1.097)** <LOD + 0.997 = 0.998 **(<1.007)**
			Forage (45)		44	<LOD + 0.801 + 0.509 + 0.064 = 1.375 **(<1.384)** <LOD + 0.580 + 0.451 + 0.059 = 1.091 **(<1.100)**	<LOD + 0.801 = 0.802 **(<0.911)** <LOD + 0.580 = 0.581 **(<0.590)**
			Forage (39)		50	<LOD + 0.033 + 0.044 + *0.003* = 0.081 **(<0.097)** <LOD + 0.041 + 0.045 + *0.004* = 0.091 **(<0.106)**	<LOD + 0.033 = 0.034 **(<0.043)** <LOD + 0.041 = 0.042 **(<0.051)**
			Forage (78)		56	<LOD + 0.038 + 0.086 + *0.006* = 0.131 **(<0.144)** <LOD + 0.062 + 0.107 + 0.011 = 0.181 **(<0.190)**	<LOD + 0.038 = 0.039 **(<0.048)** <LOD + 0.062 = 0.063 **(<0.072)**

[1] Treatment Pattern A: Two foliar spray applications at 24-inch and 36-inch corn height.
Treatment Pattern B: One foliar spray application at 36-inch corn height and one directed-spray application one week later.

[2] The LOD values for tembotrione (parent), M5, M6, and M2 in corn forage were 0.0014 ppm, 0.0023 ppm, 0.0021 ppm, and 0.0021 ppm, respectively. Residues below the LOQ (<0.01 ppm each analyte) but above the respective LOD are *italicized*. Total residues based on the LOQ of each analyte are **bolded** in parentheses.

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TABLE C.3.2. Residue Data from Sweet Corn K+CWHR Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX026-) Year	Treatment Pattern[1]	Crop; Variety	Commodity	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Germansville, PA Zone 1 01H 2003	A	Sweet Corn; Argent	K+CWHR [3]	0.170 (0.190)	45	<LOD + <LOD + *0.004* + <LOD = 0.009 **(<0.04)** <LOD + <LOD + *0.005* + <LOD = 0.010 **(<0.04)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**
	B	Sweet Corn; Argent	K+CWHR	0.166 (0.188)	44	<LOD + <LOD + *0.007* + <LOD = 0.012 **(<0.04)** <LOD + <LOD + *0.008* + <LOD = 0.013 **(<0.04)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**
North Rose, NY Zone 1 02H 2003	A	Sweet Corn; Golden Queen	K+CWHR	0.164 (0.184)	45	<LOD + <LOD + *0.001* + <LOD = 0.006 **(<0.04)** <LOD + <LOD + *0.001* + <LOD = 0.006 **(<0.04)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**
	B	Sweet Corn; Golden Queen	K+CWHR	0.166 (0.186)	45	<LOD + *0.003* + *0.003* + <LOD = 0.009 **(<0.04)** <LOD + *0.003* + *0.003* + <LOD = 0.009 **(<0.04)**	<LOD + *0.003* = 0.004 **(<0.02)** <LOD + *0.003* = 0.004 **(<0.02)**
Molino, FL Zone 3 04H 2003	A	Sweet Corn; Silver Queen	K+CWHR	0.162 (0.182)	44	<LOD + *0.006* + 0.013 + <LOD = 0.022 **(<0.043)** <LOD + *0.009* + 0.013 + <LOD = 0.025 **(<0.043)**	<LOD + *0.006* = 0.007 **(<0.02)** <LOD + *0.009* = 0.010 **(<0.02)**
	B	Sweet Corn; Silver Queen	K+CWHR	0.166 (0.186)	45	<LOD + *0.007* + 0.014 + <LOD = 0.024 **(<0.044)** <LOD + *0.005* + *0.008* + <LOD = 0.016 **(<0.04)**	<LOD + *0.007* = 0.008 **(<0.02)** <LOD + *0.005* = 0.006 **(<0.02)**

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TABLE C.3.2. Residue Data from Sweet Corn K+CWHR Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX026-) Year	Treatment Pattern[1]	Crop; Variety	Commodity	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Arkansaw, WI Zone 5 05H 2003	A	Sweet Corn; Ambrosia	K+CWHR	0.167 (0.188)	46	<LOD + <LOD + 0.014 <LOD = 0.019 (**<0.044**) <LOD + <LOD + 0.019 <LOD = 0.024 (**<0.049**)	<LOD + <LOD = 0.004 (**<0.02**) <LOD + <LOD = 0.004 (**<0.02**)
	B	Sweet Corn; Ambrosia	K+CWHR	0.169 (0.189)	45	<LOD + <LOD + 0.022 <LOD = 0.027 (**<0.052**) <LOD + <LOD + 0.022 <LOD = 0.027 (**<0.052**)	<LOD + <LOD = 0.004 (**<0.02**) <LOD + <LOD = 0.004 (**<0.02**)
Springfield, NE Zone 5 06H 2003	A	Sweet Corn; Serindipity	K+CWHR	0.164 (0.184)	45	<LOD + <LOD + *0.007* + <LOD = 0.012 (**<0.04**) <LOD + <LOD + *0.005* + <LOD = 0.010 (**<0.04**)	<LOD + <LOD = 0.004 (**<0.02**) <LOD + <LOD = 0.004 (**<0.02**)
	B	Sweet Corn; Serindipity	K+CWHR	0.164 (0.184)	45	<LOD + <LOD + 0.017 + <LOD = 0.022 (**<0.047**) <LOD + <LOD + 0.018 + <LOD = 0.023 (**<0.048**)	<LOD + <LOD = 0.004 (**<0.02**) <LOD + <LOD = 0.004 (**<0.02**)
Bagley, IA Zone 5 07H 2003	A	Sweet Corn; Bodacious	K+CWHR	0.164 (0.184)	44	<LOD + *0.004* + 0.052 + <LOD = 0.059 (**<0.082**) <LOD + *0.005* + 0.047 + <LOD = 0.055 (**<0.077**)	<LOD + *0.004* = 0.005 (**<0.02**) <LOD + *0.005* = 0.006 (**<0.02**)
	B	Sweet Corn; Bodacious	K+CWHR	0.167 (0.188)	44	<LOD + <LOD + 0.024 + <LOD = 0.029 (**<0.054**) <LOD + <LOD + 0.023 + <LOD = 0.028 (**<0.053**)	<LOD + <LOD = 0.004 (**<0.02**) <LOD + <LOD = 0.004 (**<0.02**)

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TABLE C.3.2. Residue Data from Sweet Corn K+CWHR Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX026-) Year	Treatment Pattern[1]	Crop; Variety	Commodity	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Oxford, IN 09H Zone 5 2003	A	Sweet Corn; IoChief	K+CWHR	0.169 (0.189)	46	<LOD + 0.010 + 0.016 + <LOD = 0.029 **(<0.046)** <LOD + *0.008* + 0.010 + <LOD = 0.021 **(<0.040)**	<LOD + 0.010 = 0.011 **(<0.02)** <LOD + *0.008* = 0.009 **(<0.02)**
	B	Sweet Corn; IoChief	K+CWHR	0.168 (0.188)	44	<LOD + *0.008* + *0.008* + <LOD = 0.019 **(<0.04)** <LOD + <LOD + <LOD + <LOD = 0.008 **(<0.04)**	<LOD + *0.008* = 0.009 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**
Fresno, CA Zone 10 11H 2003	A	Sweet Corn; Golden Queen	K+CWHR	0.166 (0.188)	45	<LOD + <LOD + 0.018 + <LOD = 0.023 **(<0.048)** <LOD + <LOD + 0.021 + <LOD = 0.010 **(<0.056)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**
	B	Sweet Corn; Golden Queen	K+CWHR	0.170 (0.190)	45	<LOD + <LOD + 0.018 + <LOD = 0.023 **(<0.048)** <LOD + <LOD + *0.019* + <LOD = 0.024 **(<0.049)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = *0.004* **(<0.02)**
Rupert, ID Zone 11 12H 2003	A	Sweet Corn; Northern Xtra Sweet	K+CWHR	0.164 (0.184)	45	<LOD + 0.025 + 0.018 + <LOD = 0.046 **(<0.063)** <LOD + *0.004* + 0.015 + *0.002* = 0.022 **(<0.045)**	<LOD + 0.025 = 0.026 **(<0.035)** <LOD + *0.004* = 0.005 **(<0.02)**
	B	Sweet Corn; Northern Xtra Sweet	K+CWHR	0.166 (0.186)	45	<LOD + <LOD + 0.015 + <LOD = 0.020 **(<0.045)** <LOD + <LOD + 0.015 + <LOD = 0.020 **(<0.045)**	<LOD + <LOD = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**

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TABLE C.3.2. Residue Data from Sweet Corn K+CWHR Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX026-) Year	Treatment Pattern[1]	Crop; Variety	Commodity	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Corvallis, OR Zone 12 13H 2003	A	Sweet Corn; Seneca Pronto	K+CWHR	0.166 (0.188)	45	<LOD + <LOD + <LOD + <LOD = 0.008 (**<0.04**) <LOD + <LOD + <LOD + <LOD = 0.008 (**<0.04**)	<LOD + <LOD = 0.004 (**<0.02**) <LOD + <LOD = 0.004 (**<0.02**)
	B	Sweet Corn; Seneca Pronto	K+CWHR	0.169 (0.189)	46	<LOD + <LOD + 0.031 + <LOD = 0.036 (**<0.061**) <LOD + <LOD + 0.033 + <LOD = 0.038 (**<0.063**)	<LOD + <LOD = 0.004 (**<0.02**) <LOD + <LOD = 0.004 (**<0.02**)
Tifton, GA Zone 2 14H 2004	A	Sweet Corn; G-90	K+CWHR	0.164 (0.184)	45	<LOD + <LOD + <LOD + <LOD = 0.008 (**<0.04**) <LOD + <LOD + *0.005* + <LOD = 0.010 (**<0.04**)	<LOD + <LOD = 0.004 (**<0.02**) <LOD + <LOD = 0.004 (**<0.02**)
	B	Sweet Corn; G-90	K+CWHR	0.164 (0.184)	45	<LOD + <LOD + *0.005* + <LOD = 0.010 (**<0.04**) <LOD + <LOD + *0.005* + <LOD = 0.010 (**<0.04**)	<LOD + <LOD = 0.004 (**<0.02**) <LOD + <LOD = 0.004 (**<0.02**)

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TABLE C.3.2. Residue Data from Sweet Corn K+CWHR Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX026-) Year	Treatment Pattern[1]	Crop; Variety	Commodity	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Seymour, IL Zone 5 08D 2003	A	Sweet Corn; Parfait	K+CWHR	0.165 (0.186)	36	<LOD + *0.003* + 0.016 + <LOD = 0.022 **(<0.046)** <LOD + *0.004* + 0.015 + <LOD = 0.022 **(<0.045)**	<LOD + *0.003* = 0.004 **(<0.02)** <LOD + *0.004* = 0.005 **(<0.02)**
			K+CWHR		39	<LOD + *0.003* + 0.010 + <LOD = 0.016 **(<0.040)** <LOD + <LOD + 0.022 + <LOD = 0.027 **(<0.052)**	<LOD + *0.003* = 0.004 **(<0.02)** <LOD + <LOD = 0.004 **(<0.02)**
			K+CWHR		45	<LOD + *0.003* + 0.020 + <LOD = 0.026 **(<0.050)** <LOD + *0.003* + 0.021 + <LOD = 0.027 **(<0.051)**	<LOD + *0.003* = 0.004 **(<0.02)** <LOD + *0.003* = 0.004 **(<0.02)**
			K+CWHR		49	<LOD + *0.005* + 0.025 + <LOD = 0.033 **(<0.055)** <LOD + *0.006* + 0.032 + <LOD = 0.041 **(<0.062)**	<LOD + *0.005* = 0.006 **(<0.02)** <LOD + *0.006* = 0.007 **(<0.02)**
			K+CWHR		56	<LOD + *0.006* + 0.031 + <LOD = 0.040 **(<0.061)** <LOD + *0.004* + 0.030 + <LOD = 0.037 **(<0.060)**	<LOD + *0.006* = 0.007 **(<0.02)** <LOD + *0.004* = 0.005 **(<0.02)**

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TABLE C.3.2. Residue Data from Sweet Corn K+CWHR Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX026-) Year	Treatment Pattern[1]	Crop; Variety	Commodity	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Seymour, IL (continued)	B	Sweet Corn; Parfait	K+CWHR	0.167 (0.188)	35	<LOD + *0.003* + 0.020 + <LOD = 0.026 **(<0.050)** <LOD + *0.004* + 0.026 + <LOD = 0.033 **(<0.056)**	<LOD + *0.003* = 0.004 **(<0.02)** <LOD + *0.004* = 0.005 **(<0.02)**
			K+CWHR		39	<LOD + *0.006* + 0.029 + <LOD = 0.038 **(<0.059)** <LOD + *0.008* + 0.045 + <LOD = 0.056 **(<0.075)**	<LOD + *0.006* = 0.007 **(<0.02)** <LOD + *0.008* = 0.009 **(<0.02)**
			K+CWHR		44	<LOD + *0.009* + 0.052 + <LOD = 0.064 **(<0.082)** <LOD + *0.007* + 0.043 + <LOD = 0.053 **(<0.073)**	<LOD + *0.009* = 0.010 **(<0.02)** <LOD + *0.007* = 0.008 **(<0.02)**
			K+CWHR		50	<LOD + *0.007* + 0.056 + <LOD = 0.066 **(<0.086)** <LOD + *0.006* + 0.050 + <LOD = 0.059 **(<0.080)**	<LOD + *0.007* = 0.008 **(<0.02)** <LOD + *0.006* = 0.007 **(<0.02)**
			K+CWHR		56	<LOD + *0.008* + 0.054 + <LOD = 0.065 **(<0.084)** <LOD + *0.008* + 0.067 + <LOD = 0.078 **(<0.097)**	<LOD + *0.008* = 0.009 **(<0.02)** <LOD + *0.008* = 0.009 **(<0.02)**

[1] Treatment Pattern A: Two foliar spray applications at 24-inch and 36-inch corn height.
Treatment Pattern B: One foliar spray application at 36-inch corn height and one directed-spray application one week later.
[2] The LOD values for tembotrione (parent), M5, M6, and M2 in field corn grain were 0.0011 ppm, 0.0025 ppm, 0.0029 ppm, and 0.0017 ppm, respectively. Residues below the LOQ (<0.01 ppm each analyte) but above the respective LOD are *italicized*. Total residues based on the LOQ of each analyte are **bolded** in parentheses.
[3] K+CWHR = kernels plus cob with husk removed.

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TABLE C.3.3. Residue Data from Sweet Corn Stover Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX026-) Year	Treatment Pattern[1]	Crop; Variety	Commodity (% Dry Matter)	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Germansville, PA Zone 1 01H 2003	A	Sweet Corn; Argent	Stover (34)	0.170 (0.190)	92	<LOD + 0.012 + 0.010 + *0.006* = 0.029 **(<0.042)** <LOD + *0.009* + *0.006* + *0.006* = 0.022 **(<0.04)**	<LOD + 0.012 = 0.013 **(<0.022)** <LOD + *0.009* = 0.010 **(<0.02)**
	B	Sweet Corn; Argent	Stover (30)	0.166 (0.188)	88	<LOD + 0.023 + 0.015 + <LOD = 0.041 **(<0.058)** <LOD + 0.024 + 0.023 + *0.007* = 0.055 **(<0.067)**	<LOD + 0.023 = 0.024 **(<0.033)** <LOD + 0.024 = 0.025 **(<0.034)**
North Rose, NY Zone 1 02H 2003	A	Sweet Corn; Golden Queen	Stover (22)	0.164 (0.184)	87	<LOD + 0.038 + 0.010 + *0.006* = 0.055 **(<0.068)** <LOD + 0.055 + 0.013 + *0.008* = 0.077 **(<0.088)**	<LOD + 0.038 = 0.039 **(<0.048)** <LOD + 0.055 = 0.056 **(<0.065)**
	B	Sweet Corn; Golden Queen	Stover (26)	0.166 (0.186)	80	<LOD + 0.079 + 0.026 + *0.007* = 0.113 **(<0.125)** <LOD + 0.046 + 0.017 + *0.006* = 0.070 **(<0.083)**	<LOD + 0.079 = 0.080 **(<0.089)** <LOD + 0.046 = 0.047 **(<0.056)**
Molino, FL Zone 3 04H 2003	A	Sweet Corn; Silver Queen	Stover (34)	0.162 (0.182)	69	<LOD + 0.011 + *0.008* + <LOD = 0.022 **(<0.041)** <LOD + *0.009* + *0.006* + <LOD = 0.018 **(<0.04)**	<LOD + 0.011 = 0.012 **(<0.021)** <LOD + *0.009* = 0.010 **(<0.02)**
	B	Sweet Corn; Silver Queen	Stover (33)	0.166 (0.186)	60	<LOD + *0.007* + *0.003* + <LOD = 0.013 **(<0.04)** <LOD + *0.008* + *0.005* + <LOD = 0.016 **(<0.04)**	<LOD + *0.007* = 0.008 **(<0.02)** <LOD + *0.008* = 0.009 **(<0.02)**

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TABLE C.3.3. Residue Data from Sweet Corn Stover Field Trials with Tembotrione.

Loeation (City, State) NAFTA Zone Trial Number (RAAEX026-) Year	Treatment Pattern[1]	Crop; Variety	Commodity (% Dry Matter)	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-colleetion method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Arkansaw, WI Zone 5 05H 2003	A	Sweet Corn; Ambrosia	Stover (27)	0.167 (0.188)	67	<LOD + 0.207 + 0.072 + *0.008* = 0.288 (**<0.299**) <LOD + 0.290 + 0.103 + 0.012 = 0.406 (**<0.415**)	<LOD + 0.207 = 0.208 (**<0.217**) <LOD + 0.290 = 0.291 (**<0.300**)
	B	Sweet Corn; Ambrosia	Stover (35)	0.169 (0.189)	59	<LOD + 0.290 + 0.127 + 0.018 = 0.436 (**<0.445**) <LOD + 0.258 + 0.113 + 0.015 = 0.387 (**<0.396**)	<LOD + 0.290 = 0.291 (**<0.300**) <LOD + 0.258 = 0.259 (**<0.268**)
Springfield, NE Zone 5 06H 2003	A	Sweet Corn; Serindipity	Stover (38)	0.164 (0.184)	47	<LOD + 0.744 + 0.118 + 0.101 = 0.964 (**<0.973**) <LOD + 0.564 + 0.139 + 0.122 = 0.826 (**<0.835**)	<LOD + 0.744 = 0.745 (**<0.754**) <LOD + 0.564 = 0.565 (**<0.574**)
	B	Sweet Corn; Serindipity	Stover (39)	0.164 (0.184)	46	<LOD + 0.455 + 0.161 + 0.094 = 0.711 (**<0.720**) <LOD + 0.377 + 0.171 + 0.101 = 0.650 (**<0.659**)	<LOD + 0.455 = 0.456 (**<0.465**) <LOD + 0.377 = 0.378 (**<0.387**)
Bagley, IA Zone 5 07H 2003	A	Sweet Corn; Bodacious	Stover (59)	0.164 (0.184)	95	<LOD + *0.004* + 0.027 + *0.008* = 0.040 (**<0.057**) <LOD + <LOD + <LOD + <LOD = 0.009 (**<0.04**)	<LOD + *0.004* = 0.005 (**<0.02**) <LOD +<LOD = 0.002 (**<0.02**)
	B	Sweet Corn; Bodacious	Stover (47)	0.167 (0.188)	88	<LOD + *0.008* + 0.024 + *0.006* = 0.039 (**<0.054**) <LOD + *0.008* + 0.031 + *0.005* = 0.045 (**<0.061**)	<LOD + *0.008* = 0.009 (**<0.02**) <LOD + *0.008* = 0.009 (**<0.02**)

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TABLE C.3.3. Residue Data from Sweet Corn Stover Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX026-) Year	Treatment Pattern[1]	Crop; Variety	Commodity (% Dry Matter)	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Oxford, IN 09H Zone 5 2003	A	Sweet Corn; IoChief	Stover (36)	0.169 (0.189)	65	<LOD + 0.031 + 0.028 + *0.004* = 0.064 (**<0.079**) <LOD + 0.026 + 0.022 + <LOD = 0.051 (**<0.068**)	<LOD + 0.031 = 0.032 (**<0.041**) <LOD + 0.026 = 0.027 (**<0.036**)
	B	Sweet Corn; IoChief	Stover (39)	0.168 (0.188)	58	<LOD + 0.048 + 0.035 + <LOD = 0.086 (**<0.103**) <LOD + 0.023 + 0.018 + *0.003* = 0.045 (**<0.061**)	<LOD + 0.048 = 0.049 (**<0.058**) <LOD + 0.023 = 0.024 (**<0.033**)
Fresno, CA Zone 10 11H 2003	A	Sweet Corn; Golden Queen	Stover (31)	0.166 (0.188)	84	<LOD + 0.012 + 0.042 + 0.016 = 0.071 (**<0.080**) <LOD + 0.022 + 0.088 + 0.044 = 0.155 (**<0.164**)	<LOD + 0.012 = 0.013 (**<0.022**) <LOD + 0.022 = 0.023 (**<0.032**)
	B	Swect Corn; Golden Queen	Stover (37)	0.170 (0.190)	77	<LOD + 0.022 + 0.106 + 0.022 = 0.151 (**<0.160**) <LOD + 0.039 + 0.174 + 0.040 = 0.254 (**<0.263**)	<LOD + 0.022 = 0.023 (**<0.032**) <LOD + 0.039 = 0.040 (**<0.049**)
Rupert, ID Zone 11 12H 2003	A	Sweet Corn; Northern Xtra Sweet	Stover (40)	0.164 (0.184)	90	<LOD + 0.037 + 0.033 + 0.011 = 0.082 (**<0.091**) <LOD + 0.113 + 0.044 + 0.015 = 0.173 (**<0.182**)	<LOD + 0.037 = 0.038 (**<0.047**) <LOD + 0.113 = 0.114 (**<0.123**)
	B	Sweet Corn; Northern Xtra Sweet	Stover (59)	0.166 (0.186)	83	<LOD + 0.057 + 0.046 + 0.013 = 0.117 (**<0.126**) <LOD + 0.073 + 0.077 + 0.027 = 0.178 (**<0.187**)	<LOD + 0.057 = 0.058 (**<0.067**) <LOD + 0.073 = 0.074 (**<0.083**)

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TABLE C.3.3. Residue Data from Sweet Corn Stover Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX026-) Year	Treatment Pattern[1]	Crop; Variety	Commodity (% Dry Matter)	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Corvallis, OR Zone 12 13H 2003	A	Sweet Corn; Seneca Pronto	Stover (38)	0.166 (0.188)	86	<LOD + 0.226 + 0.058 + *0.005* = 0.290 **(<0.304)** <LOD + 0.184 + 0.053 + *0.004* = 0.242 **(<0.257)**	<LOD + 0.226 = 0.227 **(<0.236)** <LOD + 0.184 = 0.185 **(<0.194)**
	B	Sweet Corn; Seneca Pronto	Stover (34)	0.169 (0.189)	80	<LOD + *0.006* + <LOD + <LOD = 0.013 **(<0.04)** <LOD + *0.004* + <LOD + <LOD = 0.011 **(<0.04)**	<LOD + *0.006* = 0.007 **(<0.02)** <LOD + *0.004* = 0.005 **(<0.02)**
Tifton, GA Zone 2 14H 2004	A	Sweet Corn; G-90	Stover (39)	*0.164* (0.184)	74	<LOD + *0.008* + 0.016 + <LOD = 0.027 **(<0.046)** <LOD + *0.009* + 0.020 + *0.003* = 0.033 **(<0.050)**	<LOD + *0.008* = 0.009 **(<0.02)** <LOD + *0.009* = 0.010 **(<0.02)**
	B	Sweet Corn; G-90	Stover (34)	0.164 (0.184)	67	<LOD + *0.005* + 0.010 + <LOD = 0.018 **(<0.040)** <LOD + *0.007* + 0.021 + <LOD = 0.031 **(<0.051)**	<LOD + *0.005* = 0.006 **(<0.02)** <LOD + *0.007* = 0.008 **(<0.02)**

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TABLE C.3.3. Residue Data from Sweet Corn Stover Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX026-) Year	Treatment Pattern[1]	Crop; Variety	Commodity (% Dry Matter)	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Seymour, IL Zone 5 08D 2003	A	Sweet Corn; Parfait	Stover (45)	0.165 (0.186)	49	<LOD + 0.576 + 0.137 + 0.018 = 0.732 **(<0.741)** <LOD + 0.521 + 0.274 + 0.039 = 0.835 **(<0.844)**	<LOD + 0.576 = 0.577 **(<0.586)** <LOD + 0.521 = 0.522 **(<0.531)**
			Stover (28)		57	<LOD + 0.021 + 0.027 + <LOD = 0.051 **(<0.068)** <LOD + 0.030 + 0.037 + <LOD = 0.070 **(<0.087)**	<LOD + 0.021 = 0.022 **(<0.031)** <LOD + 0.030 = 0.031 **(<0.040)**
			Stover (39)		63	<LOD + 0.035 + 0.076 + <LOD = 0.114 **(<0.131)** <LOD + 0.026 + 0.050 + <LOD = 0.079 **(<0.096)**	<LOD + 0.035 = 0.036 **(<0.045)** <LOD + 0.026 = 0.027 **(<0.036)**
			Stover (52)		71	<LOD + 0.039 + 0.096 + *0.003* = 0.139 **(<0.155)** <LOD + 0.040 + 0.118 + *0.003* = 0.162 **(<0.178)**	<LOD + 0.039 = 0.040 **(<0.049)** <LOD + 0.040 = 0.041 **(<0.050)**
			Stover (32)		77	<LOD + 0.017 + 0.039 + <LOD = 0.059 **(<0.076)** <LOD + 0.030 + 0.071 + <LOD = 0.104 **(<0.121)**	<LOD + 0.017 = 0.018 **(<0.027)** <LOD + 0.030 = 0.031 **(<0.040)**

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TABLE C.3.3. Residue Data from Sweet Corn Stover Field Trials with Tembotrione.

Location (City, State) NAFTA Zone Trial Number (RAAEX026-) Year	Treatment Pattern[1]	Crop; Variety	Commodity (% Dry Matter)	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Residues as determined by the data-collection method: Parent + M5 + M6 + M2 = Total[2] (ppm in parent equivalents)	Sum of Parent + M5 = Total[2] (ppm in parent equivalents)
Seymour, IL (continued	B	Sweet Corn; Parfait	Stover (56)	0.167 (0.188)	42	<LOD + 0.901 + 0.527 + 0.071 = 1.500 **(<1.509)** <LOD + 1.720 + 0.722 + 0.114 = 2.557 **(<2.566)**	<LOD + 0.901 = 0.902 **(<0.911)** <LOD + 1.720 = 1.721 **(<1.730)**
			Stover (38)		50	<LOD + 0.042 + 0.048 + <LOD = 0.093 **(<0.110)** <LOD + 0.034 + 0.043 + <LOD = 0.080 **(<0.097)**	<LOD + 0.042 = 0.043 **(<0.052)** <LOD + 0.034 = 0.035 **(<0.044)**
			Stover (62)		56	<LOD + 0.059 + 0.114 + *0.003* = 0.177 **(<0.193)** <LOD + 0.062 + 0.097 + *0.004* = 0.164 **(<0.179)**	<LOD + 0.059 = 0.060 **(<0.069)** <LOD + 0.062 = 0.063 **(<0.072)**
			Stover (79)		64	<LOD + 0.066 + 0.161 + *0.004* = 0.232 **(<0.247)** <LOD + 0.081 + 0.170 + *0.004* = 0.256 **(<0.271)**	<LOD + 0.066 = 0.067 **(<0.076)** <LOD + 0.081 = 0.082 **(<0.091)**
			Stover (81)		70	<LOD + 0.053 + 0.104 + <LOD = 0.160 **(<0.177)** <LOD + 0.039 + 0.091 + <LOD = 0.133 **(<0.150)**	<LOD + 0.053 = 0.054 **(<0.063)** <LOD + 0.039 = 0.040 **(<0.049)**

[1] Treatment Pattern A: Two foliar spray applications at 24-inch and 36-inch corn height.
Treatment Pattern B: One foliar spray application at 36-inch corn height and one directed-spray application one week later.

[2] The LOD values for tembotrione (parent), M5, M6, and M2 in corn stover were 0.0009 ppm, 0.0013 ppm, 0.0040 ppm, and 0.0024 ppm, respectively. Residues below the LOQ (<0.01 ppm each analyte) but above the respective LOD are *italicized*. Total residues based on the LOQ of each analyte are **bolded** in parentheses.

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TABLE C.4. Summary of Residue Data from Sweet Corn Field Trials with Tembotrione.

Commodity	Treated[1]	PHI (days)	Sum of Residues: Parent + M5 + M6 + M2 (ppm in parent equivalents)[2]						
			n	Min	Max	HAFT	Median	Mean	Std. Dev.
Forage	A	44-46	24	<0.110	<0.864	<0.856	0.341	0.361	0.208
	B	44-46	24	<0.04	<1.384	<1.242	0.256	0.373	0.345
K+CWHR	A	44-46	24	<0.04	<0.082	<0.080	0.029	0.031	0.013
	B	44-46	24	<0.04	<0.082	<0.078	0.031	0.032	0.013
Stover (fodder)	A	47-95	24	<0.04	<0.973	<0.904	0.077	0.176	0.246
	B	46-88	24	<0.04	<0.720	<0.690	0.083	0.164	0.196
Commodity	Treated[1]	PHI (days)	Sum of Residues: Parent + M5 (ppm in parent equivalents)[2]						
			n	Min	Max	HAFT	Median	Mean	Std. Dev.
Forage	A	44-46	24	<0.085	<0.738	<0.738	0.248	0.279	0.174
	B	44-46	24	<0.02	<0.911	<0.751	0.181	0.222	0.195
K+CWHR	A	44-46	24	<0.02	<0.035	<0.028	0.010	0.011	0.004
	B	44-46	24	<0.02	<0.02	<0.02	0.010	0.010	NA
Stover (fodder)	A	47-95	24	<0.02	<0.754	<0.664	0.034	0.116	0.188
	B	46-88	24	<0.02	<0.465	<0.426	0.037	0.087	0.126

[1] Treatment Pattern A: two foliar spray applications at 24-inch and 36-inch corn height, for a total rate of 0.162-0.170 lb ai/A. Treatment Pattern B: One foliar spray applieation at 36-inch corn height and one directed-spray application one week later, for a total rate of 0.164-0.170 lb ai/A.

[2] The LOQ (0.01 ppm for each analyte) was used to determine the minimum, maximum, and highest-average field trial (HAFT). For the ealculation of the median, mean and standard deviation ½ the LOQ (0.005 ppm for each analyte) was used for residues reported below the LOQ (or <LOD) in Tables C.3.1-C.3.3.

D. CONCLUSION

The submitted sweet corn field trial data are adequate and reflect the use of the SC formulation nominally containing 3.50 lb tembotrione ai/gallon (420 g ai/L) as two foliar applications made to sweet corn at 24-inch and 36-inch height (Treatment A), or one foliar spray application to sweet corn at 36-inch height plus one drop-nozzle (directed) spray one week later (Treatment B) at a target rate of 0.082 lb ai/A/application (0.092 kg ai/ha/application). Sweet corn forage and K+CWHR samples were harvested 44-46 days following total applications at 0.162-0.170 lb ai/A (0.182-0.190 kg ai/ha), and stover was harvested at commercial maturity (BBCH 87 to 89) at PHIs ranging from 46 to 95 days. One trial collected additional samples at various PHIs to monitor residue decline. An acceptable method was used for quantitation of residues in/on sweet corn forage, K+CWHR, and stover. Adequate data are available to support sample storage intervals and conditions.

In trials reflecting Treatment A (two foliar applications totaling 0.162-0.170 lb ai/A), the maximum combined residues of parent and its metabolites (M5 + M6 + M2), as parent equivalents, were <0.864 ppm in/on sweet corn forage, <0.082 ppm in/on sweet corn K+CWHR, and <0.973 ppm in/on sweet corn stover. In treated stover sample which bore the highest combined residues of <0.973 ppm, Metabolites M5, M6, and M2 comprised 76%, 12%, and 10%

of the total residues, respectively; residues of the parent were below the LOQ in the same stover sample.

Following Treatment B (one foliar application and one directed-spray application totaling 0.164-0.170 lb ai/A), the maximum combined residues of parent and its metabolites (M5 + M6 + M2), as parent equivalents, were <1.384 ppm in/on sweet corn forage, <0.082 ppm in/on sweet corn K+CWHR, and <0.720 ppm in/on sweet corn stover.

E. REFERENCES

46695537.der.doc
46695601.der.doc

F. DOCUMENT TRACKING

RDI: RAB1 Chemists (1/17/07)
Petition Number: PP#5F7009
DP#s: 325349, 325663, and 331222
PC Code: 012801

Template Version June 2005

Tembotrione/AE 0172747/PC Code 012801/Bayer CropScience/264
DACO 7.4.5/OPPTS 860.1520/OECD IIA 6.5.4 and IIIA 8.5
Processed Food and Feed – Field Corn

Primary Evaluator	George F. Kramer, Ph.D., Senior Chemist Registration Action Branch (RAB1) Health Effects Division (HED) (7509P)	Date: 18-JUL-2007
Approved by	P.V. Shah, Ph.D., Branch Senior Scientist RAB1/HED (7509P)	Date: 18-JUL-2007

This DER was originally prepared under contract by Dynamac Corporation (2275 Research Boulevard, Suite 300; Rockville, MD 20850; submitted 11/30/2006). The DER has been reviewed by HED and revised to reflect current Office of Pesticide Programs (OPP) policies.

STUDY REPORT:

46695610 Pither, K.; and Mackie, S. (2005) AE 0172747: Magnitude of Residues in Processed Corn Fractions Following Exaggerated Rate Applications of AE 0172747 02 SC52 A1 (2003) [Including Residue Reduction Information]. Project Number: 03RAAEX011, RAAEX011, RAAEX011/01P. Unpublished study prepared by Bayer Corp. and Texas A & M Food Protein Research & and Bayer CropScience Midwest Field Technology Station. 233 p.

The petitioner has submitted an evaluation template for the study (Bayer CropScience DER for Study RAAEX011), which was used to generate this DER; selected sections were copied without alteration or were copied and modified to more specifically reflect the Agency's data evaluation requirements.

EXECUTIVE SUMMARY:

Bayer CropScience has submitted a processing study with tembotrione on field corn. In one trial conducted in IL during the 2003 growing season, field corn grain was harvested 71 days following the last of two foliar broadcast applications of the suspension-concentrate (SC) formulation for a total rate of 0.82 lb ai/A (0.914 kg ai/ha). Corn grain samples were processed into dry milled commodities (grits, meal, flour, and refined oil) and wet milled commodities (starch and refined oil).

Samples of corn grain and its processed commodities were analyzed for residues of the parent compound, tembotrione, and the metabolites AE 1392936 (M2), AE 1417268 (M5), and AE 0456148 (M6). The analytical method was entitled "AE 0172747: An Analytical Method for the Determination of Residues of AE 0172747, and its major metabolites AE 0456148, AE 1417268, and AE 1392936 in Plant Matrices Using LC/MS/MS." This method is acceptable for data collection based on adequate method validation and concurrent method recovery data. The limits of quantitation (LOQ) for tembotrione, M2, M5, and M6 were 0.010 ppm for each analyte in corn grain and all processed corn commodities. The calculated method limits of detection (LODs) were $\leq$0.003 ppm for each analyte in corn grain and its processed commodities.

The maximum storage intervals of crop samples from harvest/processing to analysis were 460 days (15.1 months) for corn grain and 19-38 days (0.6-1.3 months) for corn processed commodities. Adequate storage stability data for field corn commodities (refer to 860.1380 DER

for MRID 46695601) are available to support the storage conditions and intervals of raw agricultural commodity (RAC) samples from the processing study. No storage stability data are required for processed commodities because samples were stored less than approximately 30 days prior to analysis.

The average total residues of tembotrione and its metabolites (as parent equivalents) were 0.370 ppm in/on field corn grain (RAC) treated at a total rate of 0.82 lb ai/A (0.914 kg ai/ha). Following processing of the treated RAC, total residues concentrated slightly in meal (0.415 ppm; 1.12x processing factor) but reduced in oil (0.003 ppm; 0.01x), flour (0.323 ppm; 0.87x), grits (0.363 ppm; 0.98x), and starch (0.018 ppm; 0.05x). Residues were significantly reduced by 95% in starch and 99% in corn oil. The average total residues of tembotrione plus M5 (as parent equivalents) were 0.046 ppm in/on field corn grain. Following processing of the treated RAC, total residues concentrated slightly in meal (0.053 ppm; 1.2x processing factor) but did not concentrate in oil (0.001 ppm; 0.02x), flour (0.037 ppm; 0.80x), grits (0.046 ppm; 1.0x), and starch (0.001 ppm; 0.02x). Residues were significantly reduced in starch and in corn oil. The observed processing factors are less than the theoretical concentration factors of 25x for corn oil (based on separation into components; OPPTS 860.1520, Table 3).

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the processed commodity residue data are classified as scientifically acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document [DP# 325349].

COMPLIANCE:

Signed and dated Good Laboratory Practice (GLP), Quality Assurance and Data Confidentiality statements were provided. No deviations from regulatory requirements were reported which would have an impact on the validity of the study.

A. BACKGROUND INFORMATION

Tembotrione, a new herbicide with broad use against mono- and dicotyledons in selected crops such as corn, is a 4-hydroxyphenylpyruvate deoxygenase (HPPD) inhibitor (bleacher). Details of the test compounds nomenclature (tembotrione and its three metabolites) and physiochemical properties of tembotrione are given in Tables A.1 and A.2.

TABLE A.1. Test Compound Nomenclature for Tembotrione and its Metabolites AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2).

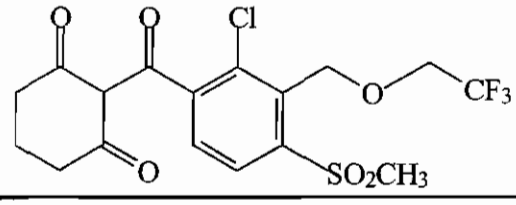
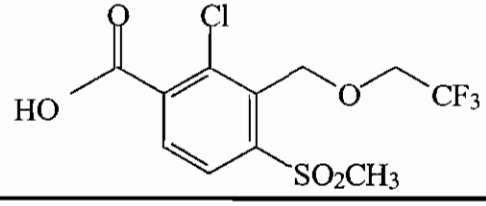
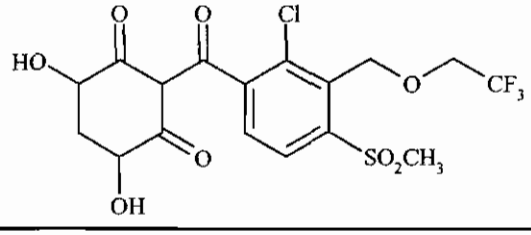
Compound: Tembotrione	Chemical Structure 
Common name	Tembotrione (Parent)
Company experimental name	AE 0172747
IUPAC name	2-{2-Chloro-4-mesyl-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl}cyclohexane-1,3-dione
CAS name	2-[2-Chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione
CAS #	335104-84-2
End-use product/EP	AE 0172747 Herbicide, EPA Reg No. 264-xxx
Compound: AE 0456148	Chemical Structure 
Common name	Metabolite M6
Company experimental name	AE 0456148
IUPAC name	None provided
CAS name	2-chloro-4-mesyl-3-[(2,2,2-trifluroethoxy)methyl]benzoic acid
CAS #	None provided
Compound: AE 1417268	Chemical Structure 
Common name	Metabolite M5
Company experimental name	AE 1417268
IUPAC name	None provided
CAS name	2-[2-chloro-4-(methylsulfonyl)-3-[2,2,2-trifluoroethoxy)methyl]benzoyl]-4,6-dihydroxycyclohexan-1,3-dione
CAS #	None provided

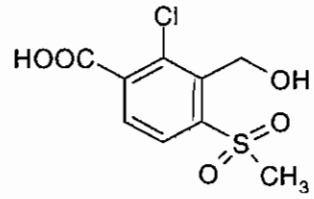
TABLE A.1. Test Compound Nomenclature for Tembotrione and its Metabolites AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2).	
Compound: AE 1392936	Chemical Structure 
Common name	Metabolite M2
Company experimental name	AE 1392936
IUPAC name	None provided
CAS name	2-chloro-3-hydroxymethyl-4-mesylbenzoic acid
CAS #	None provided

TABLE A.2. Physicochemical Properties of Technical Grade Tembotrione.		
Parameter	Value	Reference (MRID#)
Melting point	117 °C	46695402
pH @ 24 °C	3.63	
Density (g/mL @ 20 °C)	1.56	
Water solubility (mg/L @ 20 °C)	0.22 at pH4 28.3 at pH 7 29.7 at pH 9	
Solvent solubility (g/L at 20 °C) DMSO Methylene Chloride Acetone Ethyl Acetate Toluene Hexane Ethanol	 >600 >600 300-600 180.2 75.7 47.6 8.2	
Vapor pressure (Torr, 20 °C)	8.25×10^{-11}	
Dissociation constant (pK_a)	3.2	
Octanol/water partition coefficient (P_{ow} @ 23 °C) (P_{ow} @ 24 °C) (P_{ow} @ 23 °C)	 0.0430 at pH 9.0 0.0807 at pH 7.0 144.9 at pH 2.0	
UV/visible absorption spectrum (nm)	Primary: 205 Secondary: 284 Tertiary: 240	

B. EXPERIMENTAL DESIGN

In one trial conducted in IL during the 2003 growing season, field corn grain was harvested 71 days following the last of two foliar broadcast applications of the SC formulation at 0.41 lb ai/A/application (0.460 kg ai/ha/application), for a total rate of 0.82 lb ai/A (0.914 kg ai/ha). Applications were made using ground equipment with spray adjuvants methylated seed oil (MSO) at 1.5 pt/A and urea ammonium nitrate (UAN) at 1.5 to 2 qt/A added to each tank mixture. The trial use pattern is reported in Table B.1.1. Corn grain samples were processed into dry milled commodities (grits, meal, flour, and refined oil) and wet milled commodities (starch and refined oil).

B.1. Application and Crop Information

TABLE B.1.1. Study Use Pattern.

Location: City, State NAFTA Zone Trial Number (RAAEX011-) Year	End-Use Product[1]	Application						
		Method	Timing[2]	Rate lb ai/A (kg ai/ha)	RTI[3] (days)	Spray Volume GPA[4] (L/ha)	Total Rate lb ai/A (kg ai/ha)	
Seymour, IL Zone 5 01P 2003	420 SC	Foliar	36	0.41 (0.457)	--	16.1 (151)	0.82 (0.914)	Tank Mix MSO & UAN
		Foliar	6 days later	0.41 (0.457)	6	15.8 (148)		

[1] The end-use product is a SC formulation of tembotrione and isoxadifen safener.
[2] Timing = Corn height in inches or days later.
[3] RTI = Retreatment Interval.
[4] GPA = gallons per acre and L/ha = liters per hectare.
[5] Spray adjuvants methylated seed oil (MSO) and urea ammonium nitrate (UAN).

B.2. Sample Handling and Processing Procedures

Two bulk corn grain samples (one untreated and one treated) were harvested by mechanical combine 71 days after the last application, frozen within 30 minutes of collection, and shipped frozen to Bayer CropScience (Stilwell, KS) by freezer truck. The frozen samples were subsequently shipped by freezer truck to Texas A&M University GLP Food Processing Center (Bryan, TX) for subsampling and processing.

Prior to processing, subsamples of corn grain were collected. The bulk corn grain samples were processed to dry milled commodities (grits, meal, flour, refined oil) and wet milled commodities (starch, refined oil) using methodology and equipment that simulated commercial practice. Processing of corn grain commenced 421-422 days after harvest. Subsamples were shipped back to Bayer CropScience via Federal Express on dry ice for analysis. In preparation for analysis, the corn grain (RAC) subsamples were homogenized in dry ice using a chopper. No further processing of the corn processed commodities was necessary. All samples remained frozen except during subsampling for analysis.

Field corn processing procedures are summarized below in Figures 1 (dry milled processing) and 2 (wet milled processing), which were copied without alteration from MRID 46695610.

FIGURE 1. Dry Mill Processing Flowchart for Corn Grain.

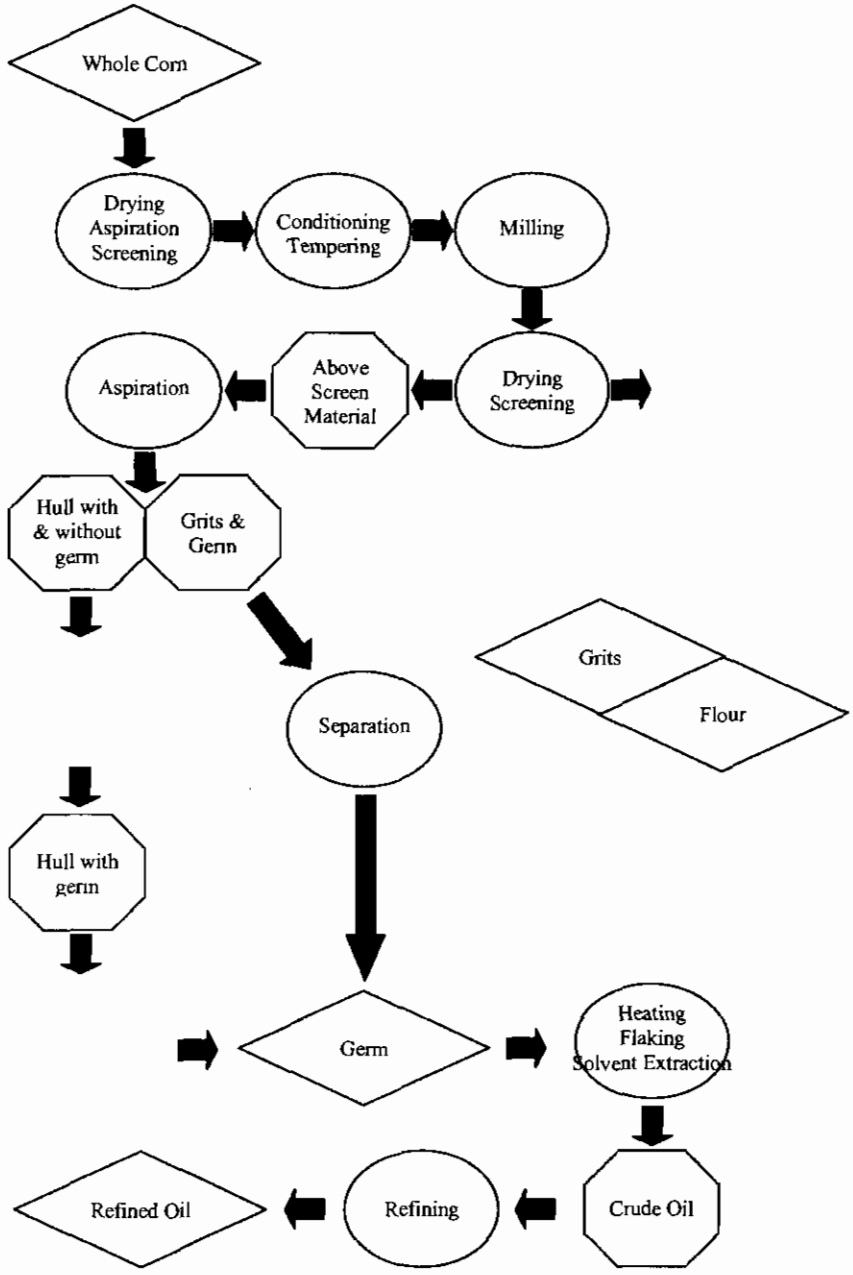
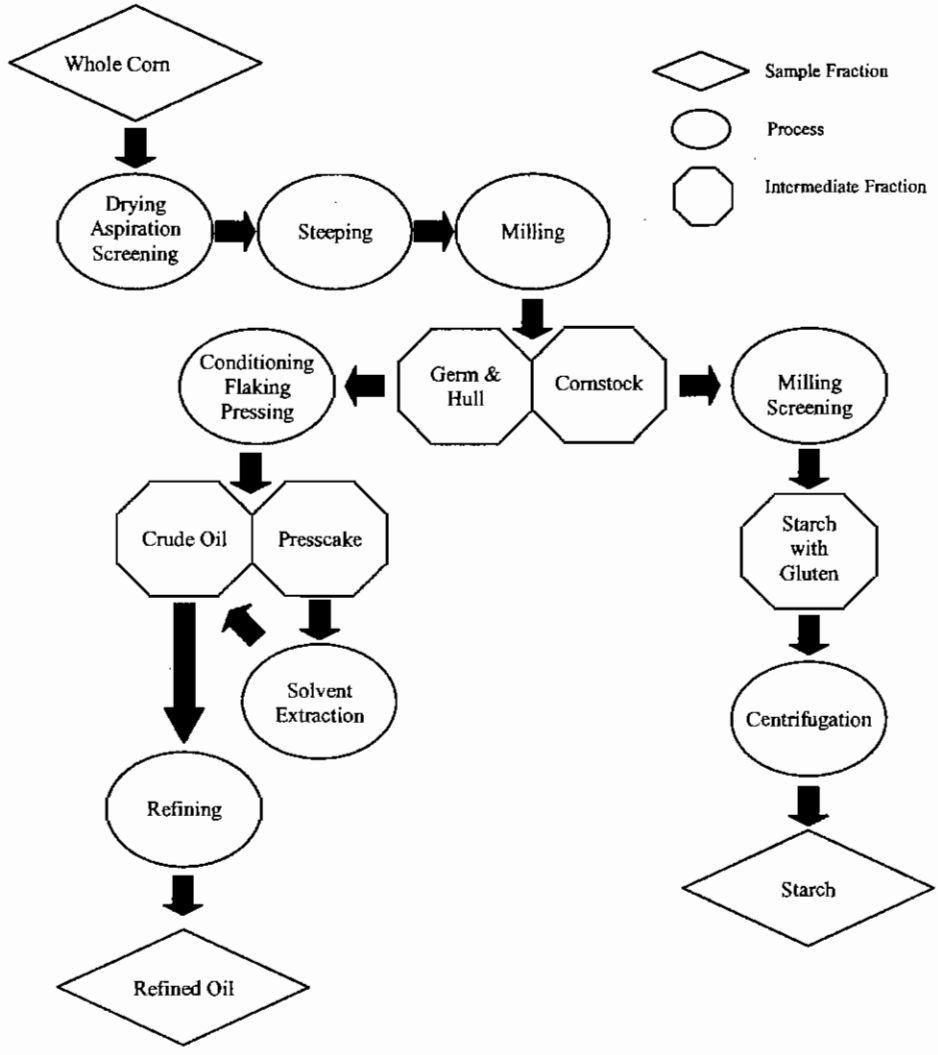


FIGURE 2. Wet Mill Processing Flowchart for Corn Grain.



B.3. Analytical Methodology

Samples of field corn grain and its processed commodities were analyzed for residues of the parent compound, tembotrione, and the metabolites M2, M5) and M6. The analytical method used was an liquid chromatography/mass spectroscopy (LC/MS)/MS method entitled "AE 0172747: An Analytical Method for the Determination of Residues of AE 0172747, and its major metabolites AE 0456148, AE 1417268, and AE 1392936 in Plant Matrices Using LC/MS/MS." This method quantifies all analytes from a single sample using isotopically labeled internal standards.

Briefly, residues of tembotrione and its metabolites M2, M5, and M6 were extracted from crop matrices with acetonitrile:water (1:1, v:v) using accelerated solvent extraction. Internal standards of the deuterated analytes were added to the extract. For parent, M5, and M6 analysis, an aliquot of the extract was concentrated via Turbo-Vap. For M2 analysis, an aliquot of the

extract was loaded onto a strong anion-exchange solid-phase extraction (SPE) cartridge and eluted with oxalic acid. The SPE eluate was concentrated. The concentrates were reconstituted in 0.1% formic acid and filtered for LC/MS/MS analysis. The method was modified for extraction of corn oil by substituting Dionex ASE Prep D.E. for Varian hydromatrix.

For the subject processing study, reference standards were prepared in tembotrione molar equivalents, therefore, quantitating residues as parent equivalents.

Method validation was performed prior to sample analysis with field corn grain as part of another study (refer to DER for MRID 46695537). In conjunction with the processing study, method verification was conducted on the processed commodities using flour, grits, meal, starch, and oil purchased at a local grocery store. Concurrent recoveries were also performed during sample analysis to demonstrate acceptable method performance.

The LOQ for tembotrione, M2, M5, and M6 was 0.010 ppm for each analyte in corn grain and the processed corn commodities. The LOQ is defined as the lowest fortification level of an analyte at which acceptable recovery data was achieved.

The LODs for grain (also used for flour, grits, meal, and starch) were 0.0011 ppm for tembotrione, 0.0029 ppm for M6, 0.0025 ppm for M5, and 0.0017 ppm for M2. The calculated LODs for oil were 0.0012 ppm for tembotrione, 0.0011 ppm for M6 and M5, and 0.0021 ppm for M2. The LOD was calculated by multiplying the standard deviation of recovery measurements at the LOQ by $t_{0.99}$ (where $t_{0.99}$ is the one-tailed statistic at the 99% confidence level for n-1 replicates) and adding the average residue found in the untreated control samples.

C. RESULTS AND DISCUSSION

Sample storage conditions and intervals are summarized in Table C.2. The maximum storage intervals of crop samples from harvest/processing to analysis were 460 days (15.1 months) for corn grain and 19-38 days (0.6-1.3 months) for corn processed commodities. The submitted storage stability data on field corn RAC commodities (refer to DER for MRID 46695601) indicate that tembotrione, M2, M5, and M6 residues are stable (<30% decomposition) during frozen storage for at least 13 months prior to analysis with one exception. Residues of M5 in grain showed some apparent degradation with time; however, based on the results of the corn metabolism studies with tembotrione, M5 is not found in significant amounts in grain (<0.010 ppm). Although the grain (RAC) samples from the processing study were stored for a period of time longer than the available data support, these data will be considered adequate to support the storage conditions of RAC samples from the processing study. No storage stability data are required for processed commodities because samples were stored less than approximately 30 days prior to analysis.

The analytical method (LC/MS/MS) was successfully validated for the analysis of tembotrione residues and its metabolites M2, M5, and M6 in/on various plant matrices (see DER for MRID 46695537). Residues of tembotrione, M6, M5, and M2 from processed corn matrices were also adequately recovered in a method validation study conducted prior to analysis of the treated

samples. Recoveries of tembotrione, M6, M5, and M2 from grain (RAC) and the processed commodities were measured concurrently with each set of samples to verify method performance. The method validation and concurrent recovery data are summarized in Table C.1. The data demonstrate acceptable method performance during sample analysis. Concurrent method recoveries from field corn grain, flour, grits, meal, starch, and oil controls fortified with tembotrione, M6, M5 or M2 at 0.01-2.0 ppm ranged from 70% to 119%. No apparent residues were found in the untreated corn grain or any untreated processed corn commodity.

Residue data from the field corn processing study are reported in Table C.3. The average total residues of tembotrione and its metabolites (as parent equivalents) were 0.370 ppm in/on field corn grain (RAC) treated at a total rate of 0.82 lb ai/A (0.914 kg ai/ha). Following processing of the treated RAC, total residues concentrated slightly in meal (0.415 ppm; 1.12x processing factor) but reduced in oil (0.003 ppm; 0.01x), flour (0.323 ppm; 0.87x), grits (0.363 ppm; 0.98x), and starch (0.018 ppm; 0.05x). Residues were significantly reduced in starch and in corn oil. The average total residues of tembotrione plus M5 (as parent equivalents) were 0.046 ppm in/on field corn grain. Following processing of the treated RAC, total residues concentrated slightly in meal (0.053 ppm; 1.2x processing factor) but did not concentrate in oil (0.001 ppm; 0.02x), flour (0.037 ppm; 0.80x), grits (0.046 ppm; 1.0x), and starch (0.001 ppm; 0.02x). Residues were significantly reduced by 95% in starch and 99% in corn oil. The observed processing factors are less than the theoretical concentration factors of 25x for corn oil (based on separation into components; OPPTS 860.1520, Table 3).

TABLE C.1. Summary of Concurrent and Method Recoveries of Tembotrione, M5, M6, and M2 from Field Corn Grain and Processed Commodities.

Matrix	Analyte	Spike Level (mg/kg)	Sample Size (n)	Recoveries (%)	Mean Recovery (%)± std dev[1]
Concurrent					
Grain	Tembotrione	0.01	1	108	NA
		0.50	1	100	NA
	AE 0456148 (M6)	0.01	2	89, 105	97
		0.50	1	98	NA
	AE 1417268 (M5)	0.01	1	108, 97	103
		0.02	1	107	NA
		0.10	2	99, 101	100
	AE 1392936 (M2)	0.01	1	88	NA
Flour	Tembotrione	0.01	1	119	NA
	AE 0456148 (M6)	0.01	1	118	NA
		0.50	1	99	NA
	AE 1417268 (M5)	0.01	2	93, 84	89
		0.02	2	96	NA
		0.10	2	75, 107	91
	AE 1392936 (M2)	0.01	1	97	NA
Grits	Tembotrione	0.01	1	103	NA
	AE 0456148 (M6)	0.01	1	108	NA
		0.50	1	99	NA

TABLE C.1. Summary of Concurrent and Method Recoveries of Tembotrione, M5, M6, and M2 from Field Corn Grain and Processed Commodities.

Matrix	Analyte	Spike Level (mg/kg)	Sample Size (n)	Recoveries (%)	Mean Recovery (%)± std dev[1]
	AE 1417268 (M5)	0.01	1	86	NA
		0.05	1	89	NA
	AE 1392936 (M2)	0.01	1	89	NA
Meal	Tembotrione	0.01	1	104	NA
		0.50	1	100	NA
	AE 0456148 (M6)	0.01	1	119, 119	119
		0.50	1	94	NA
	AE 1417268 (M5)	0.01	1	112	NA
		0.50	1	99	NA
	AE 1392936 (M2)	0.01	1	76	NA
Starch	Tembotrione	0.01	1	104	NA
	AE 0456148 (M6)	0.01	1	107	NA
		0.05	1	83	NA
	AE 1417268 (M5)	0.01	1	87	NA
	AE 1392936 (M2)	0.01	1	82	NA
Oil [2]	Tembotrione	0.01	2	104, 109	107
	AE 0456148 (M6)	0.01	2	109, 102	106
	AE 1417268 (M5)	0.01	2	86, 96	91
	AE 1392936 (M2)	0.01	2	87, 85	86
Method Validation					
Refined oil	Tembotrione	0.010	9	80, 80, 83, 85, 85, 86, 87, 90, 90	85 ± 4
		0.050	5	74, 75, 81, 89, 89	82 ± 7
		0.200	2	83, 92	88
	AE 0456148 (M6)	0.010	9	70, 72, 75, 75, 76, 78, 80, 90, 93	79 ± 8
		0.050	5	86, 86, 87, 91, 92	89 ± 3
		0.200	2	86, 91	89
	AE 1417268 (M5)	0.010	9	72, 73, 74, 75, 76, 80, 81, 82, 100	79 ± 9
		0.050	5	88, 90, 93, 97, 99	93 ± 5
		0.200	2	87, 87	87
	AE 1392936 (M2)	0.010	9	72, 78, 80, 80, 81, 84, 86, 89, 91	82 ± 6
		0.050	5	78, 81, 82, 85, 86	82 ± 3
		0.200	2	82, 85	84
Flour	Tembotrione	0.010	3	91, 92, 92	92 ± 1
	AE 0456148 (M6)	0.010	3	88, 97, 99	95 ± 6
	AE 1417268	0.010	3	110, 117, 118	115 ± 4

TABLE C.1. Summary of Concurrent and Method Recoveries of Tembotrione, M5, M6, and M2 from Field Corn Grain and Processed Commodities.

Matrix	Analyte	Spike Level (mg/kg)	Sample Size (n)	Recoveries (%)	Mean Recovery (%)± std dev[1]
	(M5)				
	AE 1392936 (M2)	0.010	3	84, 92, 96	91 ± 6
Grits	Tembotrione	0.010	3	83, 84, 89	85 ± 3
	AE 0456148 (M6)	0.010	3	85, 85, 90	87 ± 3
	AE 1417268 (M5)	0.010	3	105,106, 111	107 ± 3
	AE 1392936 (M2)	0.010	3	77, 84, 85	82 ±4
Meal	Tembotrione	0.010	3	89, 89, 91	89 ± 1
	AE 0456148 (M6)	0.010	3	94, 95, 95	95 ± 1
	AE 1417268 (M5)	0.010	3	113, 116, 119	116 ± 3
	AE 1392936 (M2)	0.010	3	88, 100, 101	96 ± 7
Starch	Tembotrione	0.010	3	91, 93, 94	92 ± 2
	AE 0456148 (M6)	0.010	3	83, 83, 89	85 ± 4
	AE 1417268 (M5)	0.010	3	107, 113, 118	113 ± 6
	AE 1392936 (M2)	0.010	3	88, 90, 98	92 ± 5

[1] The standard deviation is not applicable (NA) for a sample size (n) of less than three.
[2] Represents values from both dry and wet milling.

TABLE C.2. Summary of Storage Conditions for Field Corn.

Residue Components	Matrix	Storage Temp. (°C)	Actual Storage Duration[1]	Interval of Demonstrated Storage Stability
Tembotrione AE 0456148 (M6) AE 1417268 (M5) AE 1392936 (M2)	Grain	< -15	460 days (15.1 months)	Tembotrione, M6, and M2 are stable for up to 13 months in frozen field corn grain.[2] M5 is stable in frozen field corn grain for up to 188 days but declined by 17% after 371 days (61% average corrected recovery).[2]
	Grits	< -15	22 days (0.7 months)	None available
	Meal		21 days (0.7 months)	
	Flour		38 days (1.3 months)	
	Oil		19 days (0.6 months)	
	Starch		22 days (0.7 months)	

[1] Actual study duration = number of days between harvest/processing and analysis; actual collection dates were not provided for processed commodities therefore the processing initiation date was used to calculate storage intervals. Corn grain processing started 421-422 days after harvest. All samples were analyzed within 3 days of extraction.
[2] Field corn RAC storage stability data; refer to the DER for MRID 46695601.

TABLE C.3.a. Residue Data from Field Corn Processing Study with Tembotrione.

RAC	Processed Commodity	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Total Tembotrione Residues: Parent + M5 + M6 + M2 = Total[1] (ppm in parent equivalents)	Processing Factor[2]
Grain	RAC	0.82 (0.914)	71	<LOD + 0.045 + 0.321 + <LOD = 0.368 <LOD + 0.044 + 0.325 + 0.003 = 0.372 (0.370)	--
	Refined oil (dry milled)			<LOD + <LOD + <LOD + <LOD = 0.003 <LOD + <LOD + <LOD + <LOD = 0.003 (0.003)	0.01x
	Refined oil (wet milled)			<LOD + <LOD + <LOD + <LOD = 0.003 <LOD + <LOD + <LOD + <LOD = 0.003 (0.003)	0.01x
	Flour			<LOD + 0.037 + 0.282 + 0.004 = 0.323 <LOD + 0.035 + 0.286 + <LOD = 0.323 (0.323)	0.87x
	Grits			<LOD + 0.047 + 0.314 + <LOD = 0.362 <LOD + 0.044 + 0.318 + <LOD = 0.364 (0.363)	0.98x
	Meal			0.003 + 0.051 + 0.358 + 0.002 = 0.414 <LOD + 0.051 + 0.362 + <LOD = 0.415 (0.415)	1.12x
	Starch			<LOD + <LOD + 0.012 + <LOD = 0.015 <LOD + <LOD + 0.017 + <LOD = 0.020 (0.017)	0.05x

[1] Total tembotrione residue is the sum of the individual analytes (quantitated as parent equivalents) as calculated by the petitioner; individual analyte residues reported as "<LOD" were assigned a finite value of ½ the respective analyte LOD. The LOD values for tembotrione (parent), M5, M6, and M2 in field corn grain (also used for flour, grits, meal, and starch) were 0.0011 ppm, 0.0025 ppm, 0.0029 ppm, and 0.0017 ppm, respectively; LODs for refined oil were 0.0012 ppm, 0.0011 ppm, 0.0011 ppm, and 0.0021 ppm, respectively. Average total residue is reported in parentheses.
[2] Processing factor = Average residue in processed sample/residue in unprocessed sample.

TABLE C.3.b. Residue Data from Field Corn Processing Study with Tembotrione.

RAC	Processed Commodity	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Total Tembotrione Residues: Parent + M5 = Total[1] (ppm in parent equivalents)	Processing Factor[2]
Grain	RAC	0.82 (0.914)	71	<LOD + 0.045 = 0.046 <LOD + 0.044 = 0.045 (0.046)	--
	Refined oil (dry milled)			<LOD + <LOD = 0.001 <LOD + <LOD = 0.001 (0.001)	0.02x
	Refined oil (wet milled)			<LOD + <LOD = 0.001 <LOD + <LOD = 0.001 (0.001)	0.02x
	Flour			<LOD + 0.037 = 0.038 <LOD + 0.035 = 0.036 (0.037)	0.80x
	Grits			<LOD + 0.047 = 0.048 <LOD + 0.044 = 0.045 (0.046)	1.0x
	Meal			0.003 + 0.051 = 0.054 <LOD + 0.051 = 0.052 (0.053)	1.2x

TABLE C.3.b. Residue Data from Field Corn Processing Study with Tembotrione.

RAC	Processed Commodity	Total Rate lb ai/A (kg ai/ha)	PHI (days)	Sum of Total Tembotrione Residues: Parent + M5 = Total[1] (ppm in parent equivalents)	Processing Factor[2]
	Starch			<LOD + <LOD = 0.001 <LOD + <LOD = 0.001 (0.001)	0.02x

[1] Total tembotrione residue is the sum of the individual analytes (quantitated as parent equivalents) as calculated by the petitioner; individual analyte residues reported as "<LOD" were assigned a finite value of ½ the respective analyte LOD. The LOD values for tembotrione (parent), and M5 in field corn grain (also used for flour, grits, meal, and starch) were 0.0011 ppm, and 0.0025 ppm, respectively; LODs for refined oil were 0.0012 ppm, 0.0011 ppm, respectively. Average total residue is reported in parentheses.

[2] Processing factor = Average residue in processed sample/residue in unprocessed sample.

D. CONCLUSION

The submitted field trial data reflect the use of two foliar broadcast applications of the SC formulation for a total rate of 0.82 lb ai/A (0.914 kg ai/ha) to field corn. Field corn grain was processed into commodities of flour, grits, meal, starch, and oil. Total tembotrione residues in oil, flour, grits and starch were less than those found in the unprocessed grain; therefore, no concentration (<1x) of tembotrione residues occurred during production of these commodities. Total tembotrione residues in meal were slightly higher than that found in unprocessed grain with a processing factor of 1.12x. An acceptable method was used for quantitation of residues in corn grain and its processed commodities, and adequate data are available to support sample storage intervals and conditions.

E. REFERENCES

46695537.der.doc
46695601.der.doc

F. DOCUMENT TRACKING

RDI: RAB1 Chemists (1/17/07)
Petition Number: PP#5F7009
DP#s: 325349, 325663, and 331222
PC Code: 012801

Template Version June 2005

Tembotrione/AE 0172747/PC Code 012801/Bayer CropScience/264
DACO 7.4.4/OPPTS 860.1900/OECD IIA 6.6.3, 6.8.7 and IIIA 8.6
Field Accumulation in Rotational Crops – Winter Wheat

Primary Evaluator	George F. Kramer, Ph.D., Senior Chemist Registration Action Branch (RAB1) Health Effects Division (HED) (7509P)	Date: 18-JUL-2007
Approved by	P.V. Shah, Ph.D., Branch Senior Scientist RAB1/HED (7509P)	Date: 18-JUL-2007

This DER was originally prepared under contract by Dynamac Corporation (2275 Research Boulevard, Suite 300; Rockville, MD 20850; submitted 10/31/2006). The DER has been reviewed by HED and revised to reflect current Office of Pesticide Programs (OPP) policies.

STUDY REPORT:

46695613 Lenz, C.; Mackie, S. (2005) AE 0172747: Magnitude of Residues in Winter Wheat When used as a Rotational Crop after Corn that has had Foliar Applications of AE 0172747 02 SC52 A1 at the Maximum Proposed Label Specifications (2003). Project Number: 03RAAEY002, RAAEY002, RAAEY002/01H. Unpublished study prepared by Bayer Corp., Bayer Research Farm and Bayer Research Farm. 447 p.

The petitioner has submitted an evaluation template for the study (Bayer CropScience DER for Study RAAEY002), which was used to generate this DER; several sections were copied without alteration or modified to more specifically reflect the Agency's data evaluation requirements.

EXECUTIVE SUMMARY:

Bayer CropScience has submitted the results of a limited field rotational crop study. A suspension-concentrate formulation (SC; AE 0172747 Herbicide) nominally containing 3.50 lb tembotrione ai/gallon, was applied to the primary crop in 10 corn field trials (field corn, sweet corn, or popcorn) at a seasonal rate ranging from 0.164 to 0.174 lb ai/A. Once the primary crops were harvested, the plots were prepared according to local commercial practice for planting of winter wheat. Using the same plots where corn was grown, winter wheat was planted approximately 90-120 days after the last application of the test formulation. The winter wheat crops were allowed to grow according to good agricultural practices, and appropriate winter wheat commodities were harvested at commercial maturity.

The harvested wheat raw agricultural commodities (RACs) were analyzed for residues of the parent compound, tembotrione, and the metabolites AE 1392936 (M2), AE 1417268 (M5), and AE 0456148 (M6) using a method entitled "AE 0172747: An Analytical Method for the Determination of Residues of tembotrione, and its major metabolites AE 0456148, AE 1417268, and AE 1392936 in Plant Matrices Using LC/MS/MS." This method is acceptable for data collection based on adequate method validation and concurrent method recovery data. The limits of quantitation (LOQs) for tembotrione, M2, M5, and M6 were each 0.010 ppm in all matrices; the estimated method limits of detection (LODs) were ≤0.004 ppm for each analyte.

Samples of winter wheat hay, grain, and straw were held in frozen storage for intervals of 109-147 days prior to extraction; wheat forage was stored for up to 381 days prior to extraction. All extracts were analyzed within 5 days of extraction. Adequate storage stability data for field corn commodities (refer to DER for MRID 46695601) are available to support the storage conditions and intervals of samples from the wheat rotational crop trials.

The results from this study indicate that the total residues of tembotrione, M2, M5, and M6 were <0.04 ppm in/on all samples of rotated wheat forage, hay, grain, and straw planted at the 83-158 day plantback interval (PBI).

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the data depicting residues in rotational crops are classified as scientifically acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document [DP# 325349].

COMPLIANCE:

Signed and dated Good Laboratory Practice (GLP), Quality Assurance and Data Confidentiality statements were provided. No deviations from regulatory requirements were reported which would have an impact on the validity of the study.

A. BACKGROUND INFORMATION

Tembotrione, a new herbicide with broad use against mono- and dicotyledons in selected crops such as corn, is a 4-hydroxyphenylpyruvate deoxygenase (HPPD) inhibitor (bleacher). Details of the test compounds nomenclature (tembotrione and its three metabolites) and physiochemical properties of tembotrione are given in Tables A.1 and A.2.

TABLE A.1. Test Compound Nomenclature for Tembotrione and its Metabolites AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2).

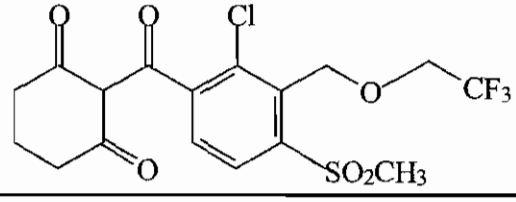
Compound: Tembotrione	Chemical Structure 
Common name	Tembotrione (Parent)
Company experimental name	AE 0172747
IUPAC name	2-{2-Chloro-4-mesyl-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl}cyclohexane-1,3-dione
CAS name	2-[2-Chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione
CAS #	335104-84-2

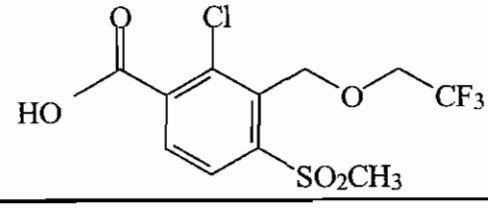
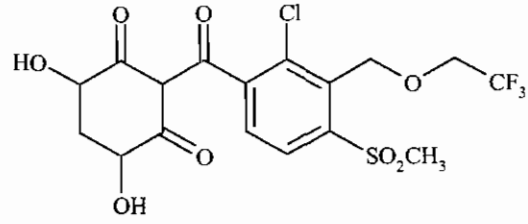
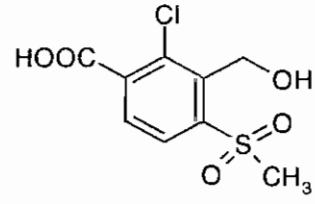
TABLE A.1.	***Test Compound Nomenclature for Tembotrione and its Metabolites AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2).***
End-use product/EP	AE 0172747 Herbicide, EPA Reg No. 264-xxx
Compound: AE 0456148	Chemieal Structure 
Common name	Metabolite M6
Company experimental name	AE 0456148
IUPAC name	None provided
CAS name	2-chloro-4-mesyl-3-[(2,2,2-trifluroethoxy)methyl]benzoic acid
CAS #	None provided
Compound: AE 1417268	Chemical Structure 
Common name	Metabolite M5
Company experimental name	AE 1417268
IUPAC name	None provided
CAS name	2-[2-chloro-4-(methylsulfonyl)-3-[2,2,2-trifluoroethoxy)methyl]benzoyl]-4,6-dihydroxycyclohexan-1,3-dione
CAS #	None provided
Compound: AE 1392936	Chemical Structure 
Common name	Metabolite M2
Company experimental name	AE 1392936
IUPAC name	None provided
CAS name	2-chloro-3-hydroxymethyl-4-mesylbenzoic acid
CAS #	None provided

TABLE A.2.	**Physicochemical Properties of Technical Grade Tembotrione.**	
Parameter	Value	Reference (MRID#)
Melting point	117 °C	46695402
pH @ 24 °C	3.63	

TABLE A.2. Physicochemical Properties of Technical Grade Tembotrione.		
Parameter	Value	Reference (MRID#)
Density (g/mL @ 20 °C)	1.56	
Water solubility (mg/L @ 20 °C)	0.22 at pH4 28.3 at pH 7 29.7 at pH 9	
Solvent solubility (g/L at 20 °C) DMSO Methylene Chloride Acetone Ethyl Acetate Toluene Hexane Ethanol	 >600 >600 300-600 180.2 75.7 47.6 8.2	
Vapor pressure (Torr, 20 °C)	8.25×10^{-11}	
Dissociation constant (pK_a)	3.2	
Octanol/water partition coefficient (P_{ow} @ 23 °C) (P_{ow} @ 24 °C) (P_{ow} @ 23 °C)	 0.0430 at pH 9.0 0.0807 at pH 7.0 144.9 at pH 2.0	
UV/visible absorption spectrum (nm)	Primary: 205 Secondary: 284 Tertiary: 240	

B. EXPERIMENTAL DESIGN

In ten corn field trials, AE 0172747 Herbicide, a SC formulation nominally containing 3.50 lb tembotrione ai/gallon (420 g ai/L), was applied as a single foliar spray application to the primary crop (corn at the 36-inch height) followed one week later with one drop-nozzle (directed) spray application at a target rate of 0.082 lb ai/A/application (0.092 kg ai/ha/application). Applications were made using ground equipment in ~13-17 gal/A with the spray adjuvants methylated seed oil (MSO) at 1.5 pt/A and 28% or 32% urea ammonium nitrate (UAN) at 1.5 to 2 qt/A added to the tank mixture. Actual test parameters are reported in Table B.1.2.

Once the primary crops were harvested, the plots were prepared according to local commercial practice for planting of the rotational crop, winter wheat. Using the same plots where corn was grown, winter wheat was planted approximately 90-120 days after the last application of the test formulation.

B.1. Study Site Information

TABLE B.1.1 Trial Site Conditions.								
Study Location City, State	Trial Number (RAAEY0-)	Year	Soil Characteristics				Meteorological Data[1]	
			Type	% OM[2]	pH	CEC[2]	Total Precip (in)	Temp Range (°F)
Tifton, GA	02-01H	2003	Sand	1.9	4.8	3.0	48.57	25 to 95
Ellendale, MN	02-02H	2003	Sandy Clay	4.2	7.8	34.2	37.82	-19 to 93
Springfield, NE	02-03H	2003	Silt Loam	2	6.5	10.9	31.34	-9 to 105
Seymour, IL	02-04H	2003	Silt	3.1	6.5	21	48.81	-12 to 98

New Holland, OH	02-05H	2003	Loam	1.9	7.0	11	49.60	-6 to 90
Stilwell, KS	02-06H	2003	Silt Loam	1.5	5.0	14.8	42.34	-1 to 106
Dexter, MO	02-07H	2003	Silt Loam	0.9	7.0	9.7	42.59	11 to 98
East Bernard, TX	02-08D	2003	Sandy Loam	0.7	6.4	8.2	45.34	25 to 102
Groom, TX	02-09H	2003	Clay Loam	2.4	6.6	22.6	20.53	-4 to 106
Rupert, ID	02-10H	2003	Silt Loam	1.6	7.8	28.8	7.71	-11 to 101

[1] Meteorological data from date of first application to primary crop through date last sampling of rotational wheat.
[2] OM = Organic matter, CEC = Cation-exchange capacity (unit of measurement was not provided).

It was reported that the actual temperature recordings and rainfall were comparable to average historical values for the residue study period. Some field trials supplemented normal rainfall amounts with irrigation as needed. Irrigation amounts ranged from 2.0 to 22 inches. Trial RAAEY002-04H had a rainfall event of 0.15 inches within 24 hours of the last application. No other rainfall events occurred within 24 hours of the last test substance application at any of the other trial sites.

TABLE B.1.2. Study Use Pattern.

City, State, NAFTA Zone Trial Number (RAAEY002-) Year		Application to Primary Crop						
		Method	Timing[2]	Rate lb ai/A (kg ai/ha)	RTI[3] (days)	Spray Volume[4] GPA (L/ha)	Total Rate lb ai/A (kg ai/ha)	Tank Mix Adjuvant[5]
Tifton, GA Zone 2 01H 2003	End-Use Product[1] 420 SC	Foliar	36	0.082 (0.092)	--	13.3 (124)	0.164 (0.184)	MSO & UAN
		Directed	1 wk later	0.082 (0.092)	7	13.9 (130)		
Ellendale, MN Zone 5 02H 2003	420 SC	Foliar	36	0.082 (0.092)	--	15.6 (146)	0.165 (0.185)	MSO & UAN
		Directed	1 wk later	0.083 (0.093)	7	15.5 (145)		
Springfield, NE Zone 5 03H 2003	420 SC	Foliar	36	0.082 (0.092)	--	14.7 (137)	0.164 (0.184)	MSO & UAN
		Direeted	1 wk later	0.082 (0.092)	8	14.4 (135)		
Seymour, IL Zone 5 04H 2003	420 SC	Foliar	36	0.083 (0.093)	--	16.3 (152)	0.165 (0.185)	MSO & UAN
		Directed	1 wk later	0.082 (0.092)	7	14.9 (139)		
New Holland, OH Zone 5 05H 2003	420 SC	Foliar	36	0.085 (0.096)	--	14.7 (137)	0.168 (0.189)	MSO & UAN
		Directed	1 wk later	0.083 (0.093)	6	16.3 (152)		
Stilwell, KS Zone 5 06H 2003	420 SC	Foliar	36	0.085 (0.096)	--	15.1 (141)	0.174 (0.195)	MSO & UAN
		Directed	1 wk later	0.089 (0.099)	6	17.2 (161)		
Dexter, MO Zone 5 07H 2003	420 SC	Foliar	36	0.082 (0.092)	--	16.6 (155)	0.165 (0.185)	MSO & UAN
		Directed	1 wk later	0.083 (0.093)	7	15.1 (151)		
East Bernard, TX Zone 6 08H 2003	420 SC	Foliar	36	0.084 (0.094)	--	15.9 (149)	0.166 (0.186)	MSO & UAN
		Directed	1 wk later	0.082 (0.092)	8	16.4 (153)		
Groom, TX Zone 8 09H 2003	420 SC	Foliar	36	0.083 (0.093)	--	14.1 (132)	0.165 (0.185)	MSO & UAN
		Directed	1 wk later	0.082 (0.092)	7	14.7 (137)		
Rupert, ID Zone 11 10H 2003	420 SC	Foliar	36	0.081 (0.091)	--	13.1 (122)	0.166 (0.186)	MSO & UAN
		Directed	1 wk later	0.085 (0.095)	7	15.4 (144)		

[1] The end-use product is a SC formulation of tembotrione and isoxadifen safener
[2] Timing = Corn height in inches or 1 week later
[3] RTI = Retreatment Interval.
[4] GPA = gallons per acre and L/ha = liters per hectare
[5] Spray adjuvants methylated seed oil (MSO) and urea ammonium nitrate (UAN).

B.2. Sample Handling and Preparation

A single untreated and duplicate treated samples of the rotated wheat RACs (forage, hay, grain, and straw) were collected from each field trial. Wheat forage was harvested at a target growth stage of 6 to 8 inches plant height to the beginning of stem elongation. In two trials (RAAEY002-03H and RAAEY002-10H), additional forage samples were collected at a slightly later growth stage because the original forage samples were compromised by freezer malfunctions. Wheat hay was cut at early flower (boot) to soft dough stage and allowed to dry in the field for 3-7 days prior to collection. Mature wheat grain was harvested at normal commercial harvest and wheat straw was sampled after grain was threshed.

All samples of winter wheat commodities were put into labeled plastic-coated cloth bags in the field and transported to a freezer within three hours of harvest. Following collection of the wheat samples, reasonable attempts were made to maintain the samples under cool conditions in the field prior to being transferred to frozen storage. Samples remained in frozen storage at the field facilities until shipment via freezer truck to Bayer Research Park (BRP; Stilwell, KS) for analysis. In preparation for analysis, the wheat RAC samples were homogenized in dry ice using a chopper. All samples remained frozen at all times except during sub-sampling for analysis.

B.3. Analytical Methodology

Rotated wheat RAC samples were analyzed for tembotrione, M6, M5, and M2. The liquid chromatography/mass spectroscopy (LC/MS)/MS method used was entitled "AE 0172747: An Analytical Method for the Determination of Residues of AE 0172747, and its major metabolites AE 0456148, AE 1417268, and AE 1392936 in Plant Matrices Using LC/MS/MS." This method quantifies all analytes from a single sample using isotopically labeled internal standards.

Briefly, residues of tembotrione and its metabolites M2, M5, and M6 were extracted from crop matrices with acetonitrile:water (1:1, v:v) using accelerated solvent extraction. Internal standards of the deuterated analytes were added to the extract. For parent, M5, and M6 analysis, an aliquot of the extract was concentrated via Turbo-Vap. For M2 analysis, an aliquot of the extract was loaded onto a strong anion-exchange solid-phase extraction (SPE) cartridge and eluted with oxalic acid. The SPE eluate was concentrated. The concentrates were reconstituted in 0.1% formic acid and filtered for LC/MS/MS analysis.

For the subject study, reference standards were prepared in tembotrione molar equivalents, therefore, quantitating residues as parent equivalents.

Method validation was performed prior to sample analysis with field corn forage, grain, and stover (refer DER for MRID 46695544), and concurrent recoveries were performed during sample analysis to demonstrate acceptable method performance.

The LOQ for tembotrione, M2, M5, and M6 was 0.010 ppm in the rotated matrices of wheat. The LOQ was the lowest fortification level of an analyte at which acceptable recovery data was achieved. Any total tembotrione residue measured to be less than the LOQ was reported as <0.010 ppm by the petitioner.

The calculated LODs from corn forage (herein used to support wheat forage) were 0.0014 ppm for tembotrione, 0.0021 ppm for M6, 0.0023 ppm for M5, and 0.0021 ppm for M2. The calculated LODs from corn grain (herein used to support wheat grain) were 0.0011 ppm for tembotrione, 0.0029 ppm for M6, 0.0025 ppm for M5, and 0.0017 ppm for M2. The calculated LODs from corn stover (herein used to support wheat hay and wheat straw) were 0.0009 ppm for tembotrione, 0.0040 ppm for M6, 0.0013 ppm for M5, and 0.0024 ppm for M2. The LOD was calculated by multiplying the standard deviation of recovery measurements at the LOQ by $t_{0.99}$ (where $t_{0.99}$ is the one-tailed statistic at the 99% confidence level for n-1 replicates) and adding the average residue found in the untreated control samples. The petitioner used the highest LOD of the individual analytes in a particular matrix as the LOD for total tembotrione residues (sum of tembotrione, M6, M5, and M2 residues).

C. RESULTS AND DISCUSSION

A summary of the storage intervals and conditions incurred by samples in this study is listed in Table C.2. Samples of wheat hay, grain, and straw were held in frozen storage for intervals of 109-147 days prior to extraction; wheat forage was stored for up to 381 days prior to extraction. All extracts were analyzed within 5 days of extraction. The submitted storage stability data on field corn commodities (refer to DER for MRID 46695601) indicate that tembotrione, M2, M5, and M6 residues are stable (<30% decomposition) during frozen storage for at least 13 months prior to analysis with one exception. Residues of M5 in grain showed some apparent degradation with time; however, based on the results of the confined rotational crop study with tembotrione, M5 is not found in significant amounts in grain (<0.010 ppm). The field corn storage stability data may be translated to fulfill the requirements for storage stability data on rotated wheat commodities.

The analytical method (LC/MS/MS) was successfully validated for the analysis of tembotrione residue and its metabolites M2, M5, and M6 in/on various plant matrices (refer to DER for MRID 46695537). Recoveries of tembotrione, M6, M5, and M2 from wheat matrices were measured concurrently with each set of samples to verify method performance. The concurrent recovery data are summarized in Table C.1. The data demonstrate acceptable method performance during sample analysis. Recoveries from wheat forage, hay, grain and straw controls fortified with tembotrione, M6, M5 or M2 at 0.01-0.10 ppm ranged from 71% to 117%. The chromatograms of control samples of various wheat matrices are free from interferences.

The total tembotrione residues found in the rotated wheat forage, wheat hay, wheat grain, and wheat straw samples are presented in Tables C.3.1 through C.3.4 and are summarized in Table C.4. The results show that total tembotrione residues were less than the LOQ of 0.010 ppm in rotated wheat forage, hay, grain, and straw at 83- to 158-day PBIs. Apparent residues in control samples of wheat commodities were less than the LOQ for total tembotrione residue in all trials.

TABLE C.1. Summary of Concurrent Recoveries of Tembotrione, M5, M6, and M2 from Wheat Matrices.

Matrix	Analyte	Spike Level (mg/kg)	Sample Size (n)	Recoveries (%)	Mean Recovery (%)± *std dev*[1]
Wheat Forage	Tembotrione	0.010	11	70, 73, 74, 82, 83, 83, 91, 92, 93, 95, 98	85 ± 9.6
		0.020	1	90	90
		0.100	1	89	89
	AE 0456148 (M6)	0.010	11	82, 83, 87, 88, 88, 89, 90, 91, 94, 97, 111	91 ± 7.9
		0.020	1	103	103
		0.100	1	105	105
	AE 1417268 (M5)	0.010	12	89, 89, 90, 96, 97, 98, 99, 100, 102, 102, 106, 116	99 ± 7.7
	AE 1392936 (M2)	0.010	10	72, 74, 76, 78, 78, 81, 84, 94, 98, 104	84 ± 11
		0.020	1	106	106
		0.100	1	113	113
Wheat Hay	Tembotrione	0.010	7	77, 80, 81, 82, 83, 90, 110	86 ± 11
		0.020	1	93	93
		0.050	1	83	83
		0.100	1	91	91
	AE 0456148 (M6)	0.010	8	73, 83, 89, 91, 92, 93, 94, 94,	89 ± 7.3
		0.020	1	106	106
		0.050	1	99	99
		0.100	1	111	111
	AE 1417268 (M5)	0.010	9	78, 82, 91, 91, 91, 93, 96, 97, 97	91 ± 6.6
		0.050	1	108	108
	AE 1392936 (M2)	0.010	7	72, 74, 76, 79, 82, 85, 96	81 ± 8.2
		0.020	1	103	103
		0.050	1	99	99
		0.100	1	111	111
Wheat Grain	Tembotrione	0.010	9	76, 82, 84, 86, 88, 89, 93, 96, 108	89 ± 9.2
		0.020	1	85	85
		0.100	1	93	93
	AE 0456148 (M6)	0.010	9	81, 81, 82, 89, 91, 93, 94, 99, 100	90 ± 7.4
		0.020	1	103	103
		0.100	1	109	109
	AE 1417268 (M5)	0.010	10	79, 91, 92, 97, 98, 99, 102, 106, 109, 117	99 ± 11
	AE 1392936 (M2)	0.010	8	71, 73, 73, 73, 74, 77, 76, 93	76 ± 7.0
		0.020	1	101	101
		0.100	1	105	105
Wheat Straw	Tembotrione	0.010	9	74, 75, 77, 79, 80, 84, 87, 88, 108	84 ± 10
		0.020	1	88	88
		0.050	1	80	80
	AE 0456148 (M6)	0.010	8	74, 75, 86, 87, 94, 99, 101, 108	91 ± 12
		0.020	1	105	105
		0.050	1	95	95
	AE 1417268 (M5)	0.010	10	85, 90, 90, 92, 92, 95, 96, 98, 104, 106	95 ± 6.5
		0.050	1	99	99

TABLE C.1. Summary of Concurrent Recoveries of Tembotrione, M5, M6, and M2 from Wheat Matrices.

Matrix	Analyte	Spike Level (mg/kg)	Sample Size (n)	Recoveries (%)	Mean Recovery (%)± std dev[1]
	AE 1392936 (M2)	0.010	8	71, 72, 75, 75, 81, 87, 98, 99	82 ± 11
		0.020	1	99	99
		0.050	1	96	96

[1] The standard deviation is not applicable for a sample size (n) of less than three.

TABLE C.2. Summary of Storage Conditions for Wheat Matrices.

Residue Components	Matrix (RAC)	Storage Temp. (°C)[1]	Actual Storage Duration [2]	Interval of Demonstrated Storage Stability[3]
Tembotrione AE 0456148 (M6) AE 1417268 (M5) AE 1392936 (M2)	Forage	< -15	114-381 days (3.8-12.5 months)	Tembotrione, M6, and M2 are stable for up to 12-13 months in frozen field corn grain, forage, and fodder. M5 is stable in frozen field corn forage and fodder for up to 12 months. M5 is stable in frozen field corn grain for up to 188 days but declined by 17% after 371 days (61% average corrected recovery).
Tembotrione AE 0456148 (M6) AE 1417268 (M5) AE 1392936 (M2)	Hay	< -15	80-147 days (2.6-4.8 months)	
Tembotrione AE 0456148 (M6) AE 1417268 (M5) AE 1392936 (M2)	Grain	< -15	55-109 days (1.8-3.6 months)	
Tembotrione AE 0456148 (M6) AE 1417268 (M5) AE 1392936 (M2)	Straw	< -15	55-109 days (1.8-3.6 months)	

[1] Storage temperature from receipt at BRP through the last sample extraction.
[2] Field sampling date through sample extraction. Samples were analyzed within 5 days of extraction.
[3] Field corn storage stability data; refer to the 860.1380 DER for MRID 46695601.

TABLE C.3.1. Residue Data in Forage from Rotational Wheat Field Trials with Tembotrione.

City, State NAFTA Zone Trial Number (RAAEY002-) Year	Wheat Variety	Commodity	% Dry Matter	Total Rate lb ai/A (kg ai/ha)	Harvest DAP[1] (days)	PBI[2] (days)	Total Residue (ppm; parent equivalents)[3]
Tifton, GA Zone 2 01H 2003	Georgia Gore	Forage	27	0.164 (0.184)	115	158	<0.04 <0.04
Ellendale, MN Zone 5 02H 2003	Crimson	Forage	21	0.165 (0.185)	228	92	<0.04 <0.04
Springfield, NE Zone 5 03H 2003	Wahoo	Forage	22	0.164 (0.184)	189, 208	91	<0.04 <0.04
Seymour, IL Zone 5 04H 2003	FS539	Forage	33	0.165 (0.185)	176	106	<0.04 <0.04

TABLE C.3.1. Residue Data in Forage from Rotational Wheat Field Trials with Tembotrione.

City, State NAFTA Zone Trial Number (RAAEY002-) Year	Wheat Variety	Commodity	% Dry Matter	Total Rate lb ai/A (kg ai/ha)	Harvest DAP[1] (days)	PBI[2] (days)	Total Residue (ppm; parent equivalents)[3]
New Holland, OH Zone 5 05H 2003	SC 1358	Forage	34	0.168 (0.189)	189	112	<0.04 <0.04
Stilwell, KS Zone 5 06H 2003	P2137	Forage	27	0.174 (0.195)	165	116	<0.04 <0.04
Dexter, MO Zone 5 07H 2003	TV8466	Forage	54	0.165 (0.185)	161	120	<0.04 <0.04
East Bernard , TX Zone 6 08H 2003	MIT	Forage	25	0.166 (0.186)	142	115	<0.04 <0.04
Groom , TX Zone 8 09H 2003	TAM110	Forage	40	0.165 (0.185)	164	108	<0.04 <0.04
Rupert, ID Zone 5 10H 2003	Garland	Forage	27	0.166 (0.186)	199, 222	83	<0.04 <0.04

[1] DAP = Days after planting.
[2] PBI = Plantback interval.
[3] The total tembotrione residue measured is the sum of the individual analytes total tembotrione, M5, M6, and M2. For the purpose of calculating the total residues (or any calculations), individual analyte residues that are reported as "<LOD" were assigned by the petitioner a finite value of ½ the value of the respective analyte LOD. Any total tembotrione residue measured to be less than the LOQ was reported as <0.010 ppm.

TABLE C.3.2. Residue Data in Hay from Rotational Wheat Field Trials with Tembotrione.

City, State NAFTA Zone Trial Number (RAAEY002-) Year	Crop Variety	Commodity	% Dry Matter	Total Rate lb ai/A (kg ai/ha)	Harvest DAP[1] (days)	PBI[2] (days)	Total Residue (ppm; parent equivalents)[3]
Tifton, GA Zone 2 01H 2003	Georgia Gore	Hay	88	0.164 (0.184)	193	158	<0.04 <0.04
Ellendale, MN Zone 5 02H 2003	Crimson	Hay	77	0.165 (0.185)	262	92	<0.04 <0.04
Springfield, NE Zone 5 03H 2003	Wahoo	Hay	55	0.164 (0.184)	236	91	<0.04 <0.04

TABLE C.3.2. Residue Data in Hay from Rotational Wheat Field Trials with Tembotrione.

City, State NAFTA Zone Trial Number (RAAEY002-) Year	Crop Variety	Commodity	% Dry Matter	Total Rate lb ai/A (kg ai/ha)	Harvest DAP[1] (days)	PBI[2] (days)	Total Residue (ppm; parent equivalents)[3]
Seymour, IL Zone 5 04H 2003	FS539	Hay	53	0.165 (0.185)	203	106	<0.04 <0.04
New Holland, OH Zone 5 05H 2003	SC 1358	Hay	63	0.168 (0.189)	210	112	<0.04 <0.04
Stilwell, KS Zone 5 06H 2003	P2137	Hay	77	0.174 (0.195)	212	116	<0.04 <0.04
Dexter, MO Zone 5 07H 2003	TV8466	Hay	55	0.165 (0.185)	213	120	<0.04 <0.04
East Bernard , TX Zone 6 08H 2003	MIT	Hay	79	0.166 (0.186)	224	115	<0.04 <0.04
Groom , TX Zone 8 09H 2003	TAM110	Hay	72	0.165 (0.185)	224	108	<0.04 <0.04
Rupert, ID Zone 5 10H 2003	Garland	Hay	88	0.166 (0.186)	263	83	<0.04 <0.04

[1] DAP = Days after planting.
[2] PBI = Plantback interval.
[3] The total tembotrione residue measured is the sum of the individual analytes total tembotrione, M5, M6, and M2. For the purpose of calculating the total residues (or any calculations), individual analyte residues that are reported as "<LOD" were assigned by the petitioner a finite value of ½ the value of the respective analyte LOD. Any total tembotrione residue measured to be less than the LOQ was reported as <0.010 ppm.

TABLE C.3.3. Residue Data in Grain from Rotational Wheat Field Trials with Tembotrione.

City, State NAFTA Zone Trial Number (RAAEY002-) Year	Crop Variety	Commodity	% Dry Matter	Total Rate lb ai/A (kg ai/ha)	Harvest DAP[1] (days)	PBI[2] (days)	Total Residue (ppm; parent equivalents)[3]
Tifton, GA Zone 2 01H 2003	Georgia Gore	Grain	87	0.164 (0.184)	222	158	<0.04 <0.04
Ellendale, MN Zone 5 02H 2003	Crimson	Grain	89	0.165 (0.185)	287	92	<0.04 <0.04

Tembotrione/AE 0172747/PC Code 012801/Bayer CropScience/264
DACO 7.4.4/OPPTS 860.1900/OECD IIA 6.6.3, 6.8.7 and IIIA 8.6
Field Accumulation in Rotational Crops – Winter Wheat

TABLE C.3.3. Residue Data in Grain from Rotational Wheat Field Trials with Tembotrione.

City, State NAFTA Zone Trial Number (RAAEY002-) Year	Crop Variety	Commodity	% Dry Matter	Total Rate lb ai/A (kg ai/ha)	Harvest DAP[1] (days)	PBI[2] (days)	Total Residue (ppm; parent equivalents)[3]
Springfield, NE Zone 5 03H 2003	Wahoo	Grain	87	0.164 (0.184)	236	91	<0.04 <0.04
Seymour, IL Zone 5 04H 2003	FS539	Grain	90	0.165 (0.185)	251	106	<0.04 <0.04
New Holland, OH Zone 5 05H 2003	SC 1358	Grain	88	0.168 (0.189)	236	112	<0.04 <0.04
Stilwell, KS Zone 5 06H 2003	P2137	Grain	89	0.174 (0.195)	243	116	<0.04 <0.04
Dexter, MO Zone 5 07H 2003	TV8466	Grain	87	0.165 (0.185)	235	120	<0.04 <0.04
East Bernard , TX Zone 6 08H 2003	MIT	Grain	88	0.166 (0.186)	262	115	<0.04 <0.04
Groom , TX Zone 8 09H 2003	TAM110	Grain	89	0.165 (0.185)	255	108	<0.04 <0.04
Rupert, ID Zone 5 10H 2003	Garland	Grain	96	0.166 (0.186)	292	83	<0.04 <0.04

[1] DAP = Days after planting.

[2] PBI = Plantback interval.

[3] The total tembotrione residue measured is the sum of the individual analytes total tembotrione, M5, M6, and M2. For the purpose of calculating the total residues (or any calculations), individual analyte residues that are reported as "<LOD" were assigned by the petitioner a finite value of ½ the value of the respective analyte LOD. Any total tembotrione residue measured to be less than the LOQ was reported as <0.010 ppm.

TABLE C.3.4. Residue Data in Straw from Rotational Wheat Field Trials with Tembotrione.

City, State NAFTA Zone Trial Number (RAAEY002-) Year	Crop Variety	Commodity	% Dry Matter	Total Rate lb ai/A (kg ai/ha)	Harvest DAP[1] (days)	PBI[2] (days)	Total Residue (ppm); parent equivalents)[3]
Tifton, GA Zone 2 01H 2003	Georgia Gore	Straw	86	0.164 (0.184)	222	158	<0.04 <0.04
Ellendale, MN Zone 5 02H 2003	Crimson	Straw	83	0.165 (0.185)	287	92	<0.04 <0.04
Springfield, NE Zone 5 03H 2003	Wahoo	Straw	87	0.164 (0.184)	290	91	<0.04 <0.04
Seymour, IL Zone 5 04H 2003	FS539	Straw	79	0.165 (0.185)	253	106	<0.04 <0.04
New Holland, OH Zone 5 05H 2003	SC 1358	Straw	43	0.168 (0.189)	236	112	<0.04 <0.04
Stilwell, KS Zone 5 06H 2003	P2137	Straw	41	0.174 (0.195)	246	116	<0.04 <0.04
Dexter, MO Zone 5 07H 2003	TV8466	Straw	87	0.165 (0.185)	235	120	<0.04 <0.04
East Bernard , TX Zone 6 08H 2003	MIT	Straw	86	0.166 (0.186)	262	115	<0.04 <0.04
Groom , TX Zone 8 09H 2003	TAM110	Straw	59	0.165 (0.185)	255	108	<0.04 <0.04
Rupert, ID Zone 5 10H 2003	Garland	Straw	91	0.166 (0.186)	292	83	<0.04 <0.04

[1] DAP = Days after planting.

[2] PBI = Plantback interval.

[3] The total tembotrione residue measured is the sum of the individual analytes total tembotrione, M5, M6, and M2. For the purpose of calculating the total residues (or any calculations), individual analyte residues that are reported as "<LOD" were assigned by the petitioner a finite value of ½ the value of the respective analyte LOD. Any total tembotrione residue measured to be less than the LOQ was reported as <0.010 ppm.

TABLE C.4. Summary of Residue Data from Wheat Rotational Crop Field Trials with Tembotrione.

Commodity	Total Application Rate lb ai/A (kg ai/ha)	PBI[1] (Days)	Total Residue Levels (ppm)[2]						
			n	Min	Max	HAFT[3]	Median	Mean	Std. Dev.
Forage	0.164 - 0.174 (0.184 – 0.195)	83 - 158	20	<0.04	<0.04	<0.04	<0.04	<0.04	N/A
Hay		83 - 158	20	<0.04	<0.04	<0.04	<0.04	<0.04	N/A
Grain		83 - 158	20	<0.04	<0.04	<0.04	<0.04	<0.04	N/A
Straw		83 - 158	20	<0.04	<0.04	<0.04	<0.04	<0.04	N/A

[1] PBI = Plantback interval.
[2] Total Residue levels is the sum of the individual analytes (tembotrione, M6, M5, and M2) in parent equivalents.
[3] HAFT = highest-average field trial residue.

D. CONCLUSION

The rotational crop field trial data reflect the use of a SC formulation as one foliar spray application to the primary crop (corn at 36-inch height) plus one directed spray one week later for a total rate of 0.164-0.174 lb ai/A (0.184-0.195 kg ai/ha). The rotational crop, winter wheat, was planted at 83- to 158-day plantback intervals.

Total tembotrione residues, the sum of the residues of tembotrione, M6, M5, and M2, was less than the limit of quantitation (0.04 ppm) in all commodities of rotated winter wheat (forage, hay, grain, and straw) planted at the 83- to 158-day PBI. An acceptable method was used for quantitation of residues in/on wheat matrices, and adequate data are available to support sample storage intervals and conditions.

E. REFERENCES

46695537.der.doc
46695544.der.doc
46695601.der.doc

F. DOCUMENT TRACKING

RDI: RAB1 Chemists (1/25/07)
Petition Number: PP#5F7009
DP#s: 325349, 325663, and 331222
PC Code: 012801

Template Version June 2005

Tembotrione/AE 0172747/PC Code 012801/Bayer CropScience/264
DACO 7.4.4/OPPTS 860.1900/OECD IIA 6.6.3, 6.8.7 and IIIA 8.6
Field Accumulation in Rotational Crops – Mustard Greens, Turnips, Squash, and Bell Peppers

Primary Evaluator	George F. Kramer, Ph.D., Senior Chemist Registration Action Branch (RAB1) Health Effects Division (HED) (7509P)	Date: 18-JUL-2007
Approved by	P.V. Shah, Ph.D., Branch Senior Scientist RAB1/HED (7509P)	Date: 18-JUL-2007

This DER was originally prepared under contract by Dynamac Corporation (2275 Research Boulevard, Suite 300; Rockville, MD 20850; submitted 11/30/2006). The DER has been reviewed by HED and revised to reflect current Office of Pesticide Programs (OPP) policies.

STUDY REPORT:

46695614 Lemke, V. (2005) AE 0172747: Magnitude of Residues in Mustard Greens, Turnips, Summer Squash, and Bell Peppers when used as Rotational Crops Behind Corn that was Treated with AE 0172747 02 SC52 A1 at the Maximum Proposed Label Specifications (2003). Project Number: 03RAAEX012, RAAEX012, RAAEX012-01H. Unpublished study prepared by Bayer Corp., Bayer Research Farm and Aventis CropScience. 263 p.

The petitioner has submitted an evaluation template for the study (Bayer CropScience DER for Study RAAEX012), which was used to generate this DER; several sections were copied without alteration or modified to more specifically reflect the Agency's data evaluation requirements.

EXECUTIVE SUMMARY:

Bayer CropScience has submitted the results of a limited field rotational crop study. A suspension-concentrate formulation (SC, AE 0172747 Herbicide) nominally containing 3.50 lb tembotrione ai/gallon, was applied in three trials as broadcast foliar sprays to a target primary crop of either field corn or sweet corn at a total rate ranging from 0.165 to 0.166 lb ai/A. Once the corn was harvested, the plots were prepared according to local commercial practice for each rotated crop. Using the same plots where corn was grown, rotational crops (mustard greens, turnips, and summer squash) were planted approximately 90-120 days after the last application for the "fall" plantback interval (PBI). The rotational crops were allowed to grow according to good agricultural practices and were harvested at commercial maturity. In addition, rotational crops (mustard greens, turnips, and bell peppers) were planted 273-349 days after the last application for the "spring" PBI.

The harvested rotational crop raw agricultural commodities (RACs) were analyzed for residues of the parent compound, tembotrione, and the metabolites AE 1392936 (M2), AE 1417268 (M5), and AE 0456148 (M6) using a method entitled "AE 0172747: An Analytical Method for the Determination of Residues of AE 0172747, and its major metabolites AE 0456148, AE 1417268, and AE 1392936 in Plant Matrices Using LC/MS/MS." This method is acceptable for data collection based on adequate method validation and concurrent method recovery data. The limits of quantitation (LOQs) for tembotrione, M2, M5, and M6 were each 0.010 ppm in all matrices; the estimated method limits of detection (LODs) were ≤0.004 ppm for each analyte.

The rotational crop commodities were held in frozen storage for a maximum of 10.7 months (326 days) prior to extraction. All extracts were analyzed within 5 days of extraction. Adequate storage stability data for mustard greens, turnip roots, and summer squash (refer to DER for MRID 46695602) are available to support the storage conditions and intervals of samples from the rotational crop trials.

The results from this study indicate that residues of the parent and its metabolites (M2, M5, and M6) were each <0.010 ppm in/on all rotated crop commodities (mustard greens, turnip top, turnip root, and summer squash) planted at the 91-117 day PBI. Additional rotational crops (mustard greens, turnips, and bell peppers) planted 273-349 days after the last application for the "spring" PBI were not analyzed since residues of tembotrione and its metabolites M2, M5, and M6 were nonquantifiable in crop samples from the earlier PBI.

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the data depicting residues in rotational crops are classified as scientifically acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document [DP# 325349].

COMPLIANCE:

Signed and dated Good Laboratory Practice (GLP), Quality Assurance and Data Confidentiality statements were provided. No deviations from regulatory requirements were reported which would have an impact on the validity of the study.

A. BACKGROUND INFORMATION

Tembotrione, a new herbicide with broad use against mono- and dicotyledons in selected crops such as corn, is a 4-hydroxyphenylpyruvate deoxygenase (HPPD) inhibitor (bleacher). Details of the test compounds nomenclature (tembotrione and its three metabolites) and physiochemical properties of tembotrione are given in Tables A.1 and A.2.

TABLE A.1. Test Compound Nomenclature for Tembotrione and its Metabolites AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2).

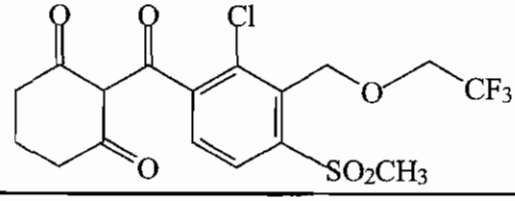
Compound: Tembotrione	Chemical Strueture 
Common name	Tembotrione (Parent)
Company experimental name	AE 0172747
IUPAC name	2-{2-Chloro-4-mesyl-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl}cyclohexane-1,3-dione

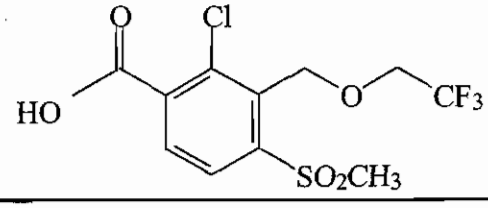
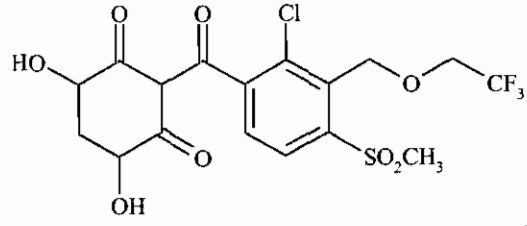
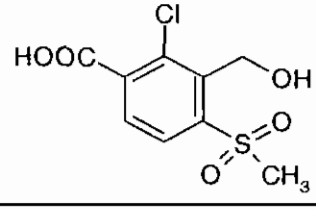
TABLE A.1. Test Compound Nomenclature for Tembotrione and its Metabolites AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2).	
CAS name	2-[2-Chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione
CAS #	335104-84-2
End-use product/EP	AE 0172747 Herbicide, EPA Reg No. 264-xxx
Compound: AE 0456148	Chemical Structure 
Common name	Metabolite M6
Company experimental name	AE 0456148
IUPAC name	None provided
CAS name	2-chloro-4-mesyl-3-[(2,2,2-trifluroethoxy)methyl]benzoic acid
CAS #	None provided
Compound: AE 1417268	Chemical Structure 
Common name	Metabolite M5
Company experimental name	AE 1417268
IUPAC name	None provided
CAS name	2-[2-chloro-4-(methylsulfonyl)-3-[2,2,2-trifluoroethoxy)methyl]benzoyl]-4,6-dihydroxycyclohexan-1,3-dione
CAS #	None provided
Compound: AE 1392936	Chemical Structure 
Common name	Metabolite M2
Company experimental name	AE 1392936
IUPAC name	None provided
CAS name	2-chloro-3-hydroxymethyl-4-mesylbenzoic acid
CAS #	None provided

TABLE A.2. Physicochemical Properties of Technical Grade Tembotrione.		
Parameter	Value	Reference (MRID#)
Melting point	117 °C	46695402
pH @ 24 °C	3.63	
Density (g/mL @ 20 °C)	1.56	
Water solubility (mg/L @ 20 °C)	0.22 at pH4 28.3 at pH 7 29.7 at pH 9	
Solvent solubility (g/L at 20 °C) DMSO Methylene Chloride Acetone Ethyl Acetate Toluene Hexane Ethanol	 >600 >600 300-600 180.2 75.7 47.6 8.2	
Vapor pressure (Torr, 20 °C)	8.25×10^{-11}	
Dissociation constant (pK_a)	3.2	
Octanol/water partition coefficient (P_{ow} @ 23 °C) (P_{ow} @ 24 °C) (P_{ow} @ 23 °C)	 0.0430 at pH 9.0 0.0807 at pH 7.0 144.9 at pH 2.0	
UV/visible absorption spectrum (nm)	Primary: 205 Secondary: 284 Tertiary: 240	

B. EXPERIMENTAL DESIGN

In three corn field trials, AE 0172747 Herbicide, a SC formulation nominally containing 3.50 lb tembotrione ai/gallon (420 g ai/L), was applied as a single foliar spray application to the primary crop (corn at the 36-inch height) followed one week later with one drop-nozzle (directed) spray application at a target rate of 0.082 lb ai/A/application (0.092 kg ai/ha/application). Applications were made using ground equipment in ~13-16 gal/A with the spray adjuvants methylated seed oil (MSO) at 1.5 pt/A and 28% or 32% urea ammonium nitrate (UAN) at 1.5 to 2 qt/A added to the tank mixture. Actual test parameters are reported in Table B.1.2.

Once the primary crops were harvested, the plots were prepared according to local commercial practice for planting of the rotational crops, mustard greens, turnips, summer squash, and/or bell peppers. Using the same plots where corn was grown, rotational crops (mustard greens, turnips, and summer squash) were planted approximately 90-120 days after the last application for the "fall" PBI. In addition, rotational crops (mustard greens, turnips, and bell peppers) were planted 273-349 days after the last application for the "spring" PBI.

B.1. Study Site Information

TABLE B.1.1. Trial Site Conditions.

Study Location City, State NAFTA Zone	Trial Number	Soil Characteristics				Meteorological Data[1]	
		Type	% OM[2]	pH	CEC[2]	Total Rainfall (in)	Temp. Range (°F)[3]
Tifton, GA Zone 2	RAAEX012-01H	Sand	1.86	4.8	3.0	3.57- 6.04	45 – 95
Molino, FL Zone 3	RAAEX012-02H	Sandy Loam	2.2	6.3	7.6	4.91 - 5.67	38 – 91
East Bernard, TX Zone 6	RAAEX012-03H	Sandy Loam	0.7	6.4	8.2	3.91 - 7.91	42 – 93

[1] The meteorological data are for the interval from planting to the last sampling.
[2] OM = Organic matter, CEC = Cation-exchange capacity (unit of measurement was not provided).
[3] Actual temperature data for the interval from first application to final harvest was not available. Averages are based on available monthly data.

It was reported that the actual temperature recordings and rainfall were comparable to average historical values for the residue study period. There were no meteorological abnormalities that may have impacted the study. In all three of the field trials, normal rainfall amounts were supplemented with irrigation as needed. Irrigation amounts ranged from 0.5 inches to 3.0 inches.

TABLE B.1.2. Study Use Pattern.

Trial Number NAFTA Zone *City, State;* Year	End Use Product[1]	Application to Primary Crop					Tank Mix Adjuvants[4]
		Method/Timing	Volume[2] GPA (L/ha)	Rate, lb ai/A (kg ai/ha)	RTI[3] (days)	Total Rate, (lb ai/A) (kg ai/ha)	
RAAEY012-01H Zone 2 Tifton GA; 2003	420 SC	1. Broadcast Foliar Application to Corn at Height of 36 in.	13.3 (124)	0.083 (0.092)	--	0.165 (0.184)	MSO and UAN
		2. Directed Application to Corn One Week After First Application.	13.9 (130)	0.082 (0.092)	7		MSO and UAN
RAAEY012-02H Zone 3 Molino, FL; 2003	420 SC	1. Broadcast Foliar Application to Corn at Height of 36 in.	14.2 (133)	0.082 (0.092)	--	0.166 (0.186)	MSO and UAN
		2. Directed Application to Corn One Week After First Application.	15.2 (142)	0.084 (0.094)	9		MSO and UAN
RAAEY012-01H Zone 6 East Bernard, TX; 2003	420 SC	1. Broadcast Foliar Application to Corn at Height of 36 in.	15.9 (149)	0.084 (0.093)	--	0.166 (0.186)	MSO and UAN
		2. Directed Application to Corn One Week After First Application.	16.4 (153)	0.082 (0.092)	8		MSO and UAN

[1] The end-use product is a SC formulation of tembotrione and isoxadifen safener.
[2] GPA = gallons per acre and L/ha = liters per hectare
[3] RTI = Retreatment interval.
[4] MSO = methylated seed oil. UAN = urea ammonium nitrate

B.2. Sample Handling and Preparation

Samples of rotated mustard green leaves, turnip tops (leaves) and roots, and the fruit of summer squash from the "fall" PBI were harvested at normal commercial harvest. The collected samples represent the appropriate raw agricultural commodities of each rotational crop tested. All samples were frozen within two hours after collection and were shipped via freezer truck to Bayer Research Park (Stillwell, KS) for analysis. In preparation for analysis, the samples were homogenized in dry ice and returned to frozen storage immediately. The samples remained in frozen storage at all times except during sub-sampling for analysis.

Samples of rotated crop matrices from the "spring" PBI were not analyzed because residues of tembotrione and its metabolites were nonquantifiable in crop samples from the earlier PBI.

B.3. Analytical Methodology

The harvested rotated RAC samples were analyzed for residues of the parent compound, tembotrione, and the metabolites M6, M5, and M2. The analytical method used was an liquid chromatography/mass spectroscopy (LC/MS)/MS method entitled "AE 0172747: An Analytical Method for the Determination of Residues of AE 0172747, and its major metabolites AE 0456148, AE 1417268, and AE 1392936 in Plant Matrices Using LC/MS/MS." This method quantifies all analytes from a single sample using isotopically labeled internal standards.

Briefly, residues of tembotrione and its metabolites M2, M5, and M6 were extracted from crop matrices with acetonitrile:water (1:1, v:v) using accelerated solvent extraction. Internal standards of the deuterated analytes were added to the extract. For parent, M5, and M6 analysis, an aliquot of the extract was concentrated via Turbo-Vap. For M2 analysis, an aliquot of the extract was loaded onto a strong anion-exchange solid-phase extraction (SPE) cartridge and eluted with oxalic acid. The SPE eluate was concentrated. The concentrates were reconstituted in 0.1% formic acid and filtered for LC/MS/MS analysis.

For the subject study, reference standards were prepared in tembotrione molar equivalents, therefore, quantitating residues as parent equivalents

Method validation was performed prior to sample analysis with various crops (refer to DER for MRID 46695537), and concurrent recoveries were performed during sample analysis to demonstrate acceptable method performance.

The LOQ for tembotrione, M2, M5, and M6 was 0.010 ppm in the rotated matrices of wheat. The LOQ was the lowest fortification level of an analyte at which acceptable recovery data was achieved. Any total tembotrione residue measured to be less than the LOQ was reported as <0.010 ppm by the petitioner.

The LOD values for tembotrione, AE 1417268 (M5), AE 0456148 (M6), and AE 1392936 (M2) in mustard greens and turnip tops were 0.0014 ppm, 0.0023 ppm, 0.0021 ppm, and 0.0021 ppm, respectively. The LOD values for tembotrione, AE 1417268 (M5), AE 0456148 (M6), and AE

1392936 (M2) in turnip roots and summer squash were 0.0027 ppm, 0.0031 ppm, 0.0025 ppm, and 0.0034 ppm, respectively.

C. RESULTS AND DISCUSSION

A summary of the storage intervals and conditions incurred by samples in this study is listed in Table C.2. The rotational crops were held in frozen storage for a maximum of 10.7 months (326 days) prior to extraction. All extracts were analyzed within 5 days of extraction. The results of a freezer storage stability study (see DER for MRID 46695602) show that tembotrione and its metabolites M2, M5, and M6 are reasonably stable in/on mustard greens, turnip roots, and summer squash for 11-12 months. These data adequately support the storage conditions and intervals of crop samples from the rotational crop study.

The analytical method (LC/MS/MS) was successfully validated for the analysis of tembotrione residue and its metabolites M2, M5, and M6 in/on various plant matrices (see DER for MRID 46695537). Recoveries of tembotrione and its metabolites M6, M5, and M2 from rotated crop matrices were measured concurrently with sets of their respective samples to verify method performance. The concurrent recovery data are summarized in Table C.1. The data demonstrate acceptable method performance during sample analysis. Recoveries from mustard greens, turnip tops, turnip roots, and summer squash controls fortified with tembotrione, M6, M5 or M2 at 0.010 ppm and 0.10 ppm ranged from 83% to 117% (mean = 101% ± 10%). The chromatograms of control samples of various crop matrices are free from interferences.

The total tembotrione residue data for the rotational crops of mustard greens, turnips and summer squash are presented by crop in Table C.3 and summarized in Table C.4. Total tembotrione residues were less than the LOQ of 0.010 ppm in rotated mustard green, turnip, and summer squash RACs at 90 to 120-day PBIs. Apparent residues in control samples of mustard greens, turnip tops, turnip roots, and summer squash were less than the LOQ for total tembotrione residues in all trials.

TABLE C.1. Summary of Concurrent Recoveries of Tembotrione and Metabolites from Rotational Crop Matrices.

Matrix	Analyte	Spike Level (mg/kg)	Sample size (n)	Recoveries (%)	Mean ± std. dev.
Mustard Greens	Tembotrione	0.01	1	93	NA[1]
		0.10	1	90	NA
	AE 0456148 (M6)	0.01	1	87	NA
		0.10	1	102	NA
	AE 1417268 (M5)	0.01	1	83	NA
		0.10	1	113	NA
	AE 1392936 (M2)	0.01	1	88	NA
		0.10	1	104	NA
Turnip Tops	Tembotrione	0.01	1	93	NA
		0.10	1	94	NA
	AE 0456148 (M6)	0.01	1	108	NA
		0.10	1	107	NA

TABLE C.1. Summary of Concurrent Recoveries of Tembotrione and Metabolites from Rotational Crop Matrices.

Matrix	Analyte	Spike Level (mg/kg)	Sample size (n)	Recoveries (%)	Mean ± std. dev.
	AE 1417268 (M5)	0.01	1	115	NA
		0.10	1	98	NA
	AE 1392936 (M2)	0.01	1	101	NA
		0.10	1	92	NA
Turnip Roots	Tembotrione	0.01	1	98	NA
		0.10	1	93	NA
	AE 0456148 (M6)	0.01	1	107	NA
		0.10	1	101	NA
	AE 1417268 (M5)	0.01	1	115	NA
		0.10	1	115	NA
	AE 1392936 (M2)	0.01	1	92	NA
		0.10	1	106	NA
Summer Squash	Tembotrione	0.01	1	93	NA
		0.10	1	91	NA
	AE 0456148 (M6)	0.01	1	92	NA
		0.10	1	106	NA
	AE 1417268 (M5)	0.01	1	117	NA
		0.10	1	117	NA
	AE 1392936 (M2)	0.01	1	92	NA
		0.10	1	114	NA

NA = not applicable

TABLE C.2. Summary of Storage Conditions.

Analyte	Matrix, (RAC)	Storage Temperature (°C)[1]	Actual study duration[2]	Limit of demonstrated storage stability (days)[3]
Tembotrione (Parent)	Mustard Greens	-25 to -15	303 days (10.0 months)	Tembotrione, M6, and M2 are stable for up to 11 months in frozen mustard greens, turnip roots, and summer squash and residues of M5 are stable in the same matrices for at least 12 months.
	Turnip Tops	-25 to -15	294 days (9.7 months)	
	Turnip Roots	-25 to -15	294 days (9.7 months)	
	Summer Squash	-25 to -15	326 days (10.7 months)	
AE 0456148 (M6)	Mustard Greens	-25 to -15	303 days (10.0 months)	
	Turnip Tops	-25 to -15	294 days (9.7 months)	
	Turnip Roots	-25 to -15	294 days (9.7 months)	
	Summer Squash	-25 to -15	326 days (10.7 months)	
AE 1217268 (M5)	Mustard Greens	-25 to -15	303 days (10.0 months)	
	Turnip Tops	-25 to -15	294 days (9.7 months)	

TABLE C.2. Summary of Storage Conditions.

Analyte	Matrix, (RAC)	Storage Temperature (°C)[1]	Aetual study duration[2]	Limit of demonstrated storage stability (days)[3]
AE 1392936 (M2)	Turnip Roots	-25 to -15	294 days (9.7 months)	
	Summer Squash	-25 to -15	326 days (10.7 months)	
	Mustard Greens	-25 to -15	303 days (10.0 months)	
	Turnip Tops	-25 to -15	294 days (9.7 months)	
	Turnip Roots	-25 to -15	294 days (9.7 months)	
	Summer Squash	-25 to -15	326 days (10.7 months)	

[1] Storage temperature from receipt at the Bayer Research Park through last sample extraction.
[2] Field sampling date through the sample extraction date. Samples were analyzed within 5 days of extraction.
[3] Refer to 46695602.der.doc.

TABLE C.3. Residues of Tembotrione in/on Rotational Crops.[1]

Trial Number NAFTA Zone City, State	Crop Variety	Commodity	% Dry Matter	Total Rate lb ai/A (kg ai/ha)	Harvest DAP[2] (days)	PBI[3] (days)	Total Tembotrione Residue[4] (ppm; parent equivalents)
RAAEX012-01H Zone 2 Tifton, GA	Mustard Greens/ Broad Leaf	Greens/ Leaves	ND[5]	0.165 (0.184)	54	107	<0.04 <0.04
RAAEX012-02H Zone 3 Molino, FL	Mustard Greens/ Giant Southern Curled	Greens/ Leaves	ND	0.166 (0.186)	51	117	<0.04 <0.04
RAAEX012-03H Zone 6 East Bernard, TX	Mustard Greens/ Tendergreen	Greens/ Leaves	ND	0.166 (0.186)	42	115	<0.04 <0.04
RAAEX012-01H Zone 2 Tifton, GA	Turnips/ Purple Top	Tops/Leaves	9	0.165 (0.184)	61	107	<0.04 <0.04
RAAEX012-02H Zone 3 Molino, FL	Turnips/ Purple Top White Globe	Tops/Leaves	7	0.166 (0.186)	51	117	<0.04 <0.04
RAAEX012-03H Zone 6 East Bernard, TX	Turnips/ Purple Top	Tops/Leaves	10	0.166 (0.186)	57	115	<0.04 <0.04
RAAEX012-01H Zone 2 Tifton, GA	Turnips/ Purple Top	Roots	9	0.165 (0.184)	61	107	<0.04 <0.04
RAAEX012-02H Zone 3 Molino, FL	Turnips/ Purple Top White Globe	Roots	8	0.166 (0.186)	51	117	<0.04 <0.04
RAAEX012-03H Zone 6 East Bernard, TX	Turnips/ Purple Top	Roots	8	0.166 (0.186)	57	115	<0.04 <0.04
RAAEX012-01H Zone 2 Tifton, GA	Summer Squash/ Destiny III	Fruit	ND	0.165 (0.184)	39	91	<0.04 <0.04

TABLE C.3. Residues of Tembotrione in/on Rotational Crops.[1]

Trial Number NAFTA Zone City, State	Crop Variety	Commodity	% Dry Matter	Total Rate lb ai/A (kg ai/ha)	Harvest DAP[2] (days)	PBI[3] (days)	Total Tembotrione Residue[4] (ppm; parent equivalents)
RAAEX012-02H Zone 3 Molino, FL	Summer Squash/ Summer Crookneck	Fruit	ND	0.166 (0.186)	51	117	<0.04 <0.04
RAAEX012-03H Zone 6 East Bernard, TX	Summer Squash/ Saffron Pro	Fruit	ND	0.166 (0.186)	45	104	<0.04 <0.04

[1] Additional rotational crops (mustard greens, turnips, and bell peppers) planted 273-349 days after the last application for the "spring" PBI were not analyzed since residues of AE 0.172747 and its metabolites M2, M5, and M6 were less than the LOQ in all RACs at the "fall" PBI.
[2] DAP = Days after planting.
[3] PBI = Plantback interval.
[4] The total tembotrione residue measured is the sum of the individual analytes total tembotrione, M5, M6, and M2. For the purpose of calculating the total residues (or any calculations), individual analyte residues that are reported as "<LOD" were assigned by the petitioner a finite value of ½ the value of the respective analyte LOD. Any total tembotrione residue measured to be less than the LOQ was reported as <0.010 ppm.
[5] ND = %DM not determined for this commodity.

TABLE C.4. Summary of Residue Data in Rotational Crops Following Treatment of the Primary Crop (Corn) with Tembotrione.

Commodity	Application Rate lb ai/A (kg ai/ha)	PBI (days)	Total Residue Levels (ppm)[1]						
			N	Min	Max	HAFT[2]	Median	Mean	Std. Dev.
Mustard Greens	0.165 – 0.166 (0.184 - 0.186)	107-117	6	<0.04	<0.04	<0.04	<0.04	<0.04	N/A
Turnip Tops	0.165 – 0.166 (0.184 - 0.186)	107-117	6	<0.04	<0.04	<0.04	<0.04	<0.04	N/A
Turnip Roots	0.165 – 0.166 (0.184 - 0.186)	107-117	6	<0.04	<0.04	<0.04	<0.04	<0.04	N/A
Summer Squash	0.165 – 0.166 (0.184 - 0.186)	91-117	6	<0.04	<0.04	<0.04	<0.04	<0.04	N/A

[1] Sum of residue contributions (expressed in parent equivalents) from parent, M5, M6, and M2.
[2] HAFT = Highest-Average Field Trial.

D. CONCLUSION

The rotational crop field trial data reflect the use of a SC formulation as one foliar spray application to the primary crop (corn at 36-inch height) plus one directed spray one week later for a total rate of 0.165-0.166 lb ai/A (0.184-0.186 kg ai/ha). The rotational crops (mustard greens, turnips and summer squash) were planted at 91- to 117-day plantback intervals.

Total tembotrione residues, the sum of the residues of tembotrione, M6, M5, and M2, was less than the limit of quantitation (0.04 ppm) in all rotated crops (mustard greens, turnip top, turnip root, and summer squash) planted at the 91- to 117-day PBI. An acceptable method was used for quantitation of residues in/on the rotated crop matrices, and adequate data are available to support sample storage intervals and conditions.

E. REFERENCES

46695537.der.doc
46695544.der.doc
46695602.der.doc

F. DOCUMENT TRACKING

RDI: RAB1 Chemists (1/25/07)
Petition Number: PP#5F7009
DP#s: 325349, 325663, and 331222
PC Code: 012801

Template Version June 2005

Tembotrione/AE 0172747/PC Code 012801/Bayer CropScience/264
DACO 7.4.5/OPPTS 860.1520/OECD IIA 6.5.4 and IIIA 8.5
Processed Food and Feed – Rotated Wheat

Primary Evaluator	George F. Kramer, Ph.D., Senior Chemist Registration Action Branch (RAB1) Health Effects Division (HED) (7509P)	Date: 18-JUL-2007
Approved by	P.V. Shah, Ph.D., Branch Senior Scientist RAB1/HED (7509P)	Date: 18-JUL-2007

This DER was originally prepared under contract by Dynamac Corporation (2275 Research Boulevard, Suite 300; Rockville, MD 20850; submitted 11/30/2006). The DER has been reviewed by HED and revised to reflect current *Office of Pesticide Programs* (OPP) policies.

STUDY REPORT:

46695611 Mackie, S. (2005) AE 0172747: Magnitude of Residues in Processed Wheat Fractions when used as a Rotational Crop after Field Corn that has had Exaggerated Rate Applications of AE 0172747 02 SC52 A1 (2003). [AE 0172747 02 SC52 A1: Request for Waiver from the Requirement for a Wheat Processing Study from a Rotational Crop of Wheat] Project Number: 03RAAEY001, RAAEY001, RAAEY001-01P. Unpublished study prepared by Bayer Corp. and Texas A & M Food Protein Research & and Bayer CropScience Midwest Field Technology Station. 77 p.

The petitioner has submitted an evaluation template for the study (Bayer CropScience DER for Study RAAEY001), which was used to generate this DER; selected sections were copied without alteration or were copied and modified to more specifically reflect the Agency's data evaluation requirements.

EXECUTIVE SUMMARY:

Bayer CropScience has submitted a processing study with tembotrione on wheat as a rotational crop. In one trial conducted in IL during the 2003 growing season, two foliar applications of AE 0172747 Herbicide, a suspension-concentrate (SC) formulation nominally containing 3.50 lb tembotrione ai/gallon (420 g ai/L), were made to the primary crop (field corn) at a seasonal rate of 0.82 lb ai/A (0.913 kg ai/ha). After normal harvest of the primary crop, the rotational crop winter wheat was planted in the test plot with a 107-day plantback interval (PBI). The winter wheat crop was allowed to grow according to good agricultural practices, and grain was harvested at commercial maturity (253 days after planting).

Samples of rotated wheat grain were analyzed for residues of the parent compound, tembotrione, and the metabolites AE 1392936 (M2), AE 1417268 (M5), and AE 0456148 (M6). The analytical method was entitled "AE 0172747: An Analytical Method for the Determination of Residues of AE 0172747, and its major metabolites AE 0456148, AE 1417268, and AE 1392936 in Plant Matrices Using LC/MS/MS." This method is acceptable for data collection based on adequate method validation and concurrent method recovery data. The limits of quantitation (LOQs) for tembotrione, M2, M5, and M6 were 0.010 ppm each in wheat grain. The calculated method limits of detection (LODs) were $\leq$0.003 ppm for each analyte in grain.

The maximum storage interval of wheat grain samples from harvest to analysis was 122 days (4 months). Adequate storage stability data for field corn commodities (refer to DER for MRID 46695601) are available to support the storage conditions and intervals of raw agricultural commodity (RAC) samples from the processing study.

Residues of tembotrione and each of its metabolites (M5, M6 and M2) were below the method LOQ (<0.010 ppm) in rotated wheat grain. Since all residues were <LOQ, the petitioner determined that processing of the bulk wheat grain samples to representative processed commodities was not necessary.

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the processed commodity residue data are classified as scientifically acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document [DP# 325349].

COMPLIANCE:

Signed and dated Good Laboratory Practice (GLP), Quality Assurance and Data Confidentiality statements were provided. No deviations from regulatory requirements were reported which would have an impact on the validity of the study.

A. BACKGROUND INFORMATION

Tembotrione, a new herbicide with broad use against mono- and dicotyledons in selected crops such as corn, is a 4-hydroxyphenylpyruvate deoxygenase (HPPD) inhibitor (bleacher). Details of the test compounds nomenclature (tembotrione and its three metabolites) and physiochemical properties of tembotrione are given in Tables A.1 and A.2.

TABLE A.1. Test Compound Nomenclature for Tembotrione and its Metabolites AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2).

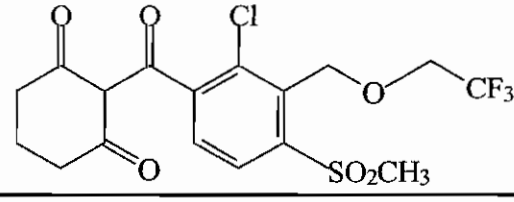
Compound: Tembotrione	Chemical Structure 
Common name	Tembotrione (Parent)
Company experimental name	AE 0172747
IUPAC name	2-{2-Chloro-4-mesyl-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl}cyclohexane-1,3-dione
CAS name	2-[2-Chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione
CAS #	335104-84-2
End-use product/EP	AE 0172747 Herbicide, EPA Reg No. 264-xxx

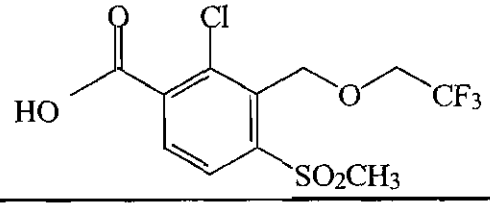
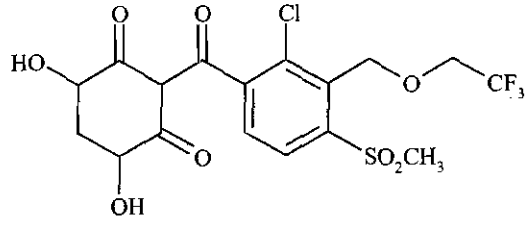
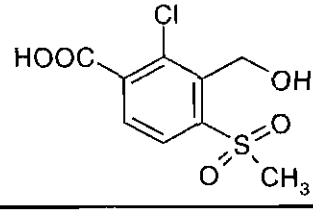
TABLE A.1. Test Compound Nomenclature for Tembotrione and its Metabolites AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2).	
Compound: AE 0456148	Chemical Structure 
Common name	Metabolite M6
Company experimental name	AE 0456148
IUPAC name	None provided
CAS name	2-chloro-4-mesyl-3-[(2,2,2-trifluroethoxy)methyl]benzoic acid
CAS #	None provided
Compound: AE 1417268	Chemical Structure 
Common name	Metabolite M5
Company experimental name	AE 1417268
IUPAC name	None provided
CAS name	2-[2-chloro-4-(methylsulfonyl)-3-[2,2,2-trifluoroethoxy)methyl]benzoyl]-4,6-dihydroxycyclohexan-1,3-dione
CAS #	None provided
Compound: AE 1392936	Chemical Structure 
Common name	Metabolite M2
Company experimental name	AE 1392936
IUPAC name	None provided
CAS name	2-chloro-3-hydroxymethyl-4-mesylbenzoic acid
CAS #	None provided

TABLE A.2. Physicochemical Properties of Technical Grade Tembotrione.		
Parameter	Value	Reference (MRID#)
Melting point	117 °C	46695402
pH @ 24 °C	3.63	

TABLE A.2. Physicochemical Properties of Technical Grade Tembotrione.

Parameter	Value	Reference (MRID#)
Density (g/mL @ 20 °C)	1.56	
Water solubility (mg/L @ 20 °C)	0.22 at pH4 28.3 at pH 7 29.7 at pH 9	
Solvent solubility (g/L at 20 °C) DMSO Methylene Chloride Acetone Ethyl Acetate Toluene Hexane Ethanol	 >600 >600 300-600 180.2 75.7 47.6 8.2	
Vapor pressure (Torr, 20 °C)	8.25×10^{-11}	
Dissociation constant (pK_a)	3.2	
Octanol/water partition coefficient (P_{ow} @ 23 °C) (P_{ow} @ 24 °C) (P_{ow} @ 23 °C)	 0.0430 at pH 9.0 0.0807 at pH 7.0 144.9 at pH 2.0	
UV/visible absorption spectrum (nm)	Primary: 205 Secondary: 284 Tertiary: 240	

B. EXPERIMENTAL DESIGN

In one trial conducted in IL during the 2003 growing season, two foliar applications of AE 0172747 Herbicide, a SC formulation nominally containing 3.50 lb tembotrione ai/gallon (420 g ai/L), were made to the primary crop (field corn) at a seasonal rate of 0.82 lb ai/A (0.913 kg ai/ha). After the normal harvest of the primary crop, the rotational crop winter wheat was planted in the test plot 107 days after the last application to corn. The winter wheat crop was allowed to grow according to good agricultural practices, and grain was harvested at commercial maturity (253 days after planting).

B.1. Application and Crop Information

TABLE B.1.1. Study Use Pattern.

Location: City, State NAFTA Zone Trial Number (RAAEY001-) Year	End-Use Product[1]	Application to Primary Crop						
		Method	Timing[2]	Rate lb ai/A (kg ai/ha)	RTI[3] (days)	Spray Volume GPA[4] (L/ha)	Total Rate lb ai/A (kg ai/ha)	Tank Mix Adjuvant[5]
Seymour, IL Zone 5 01P 2003	420 SC	Foliar	36	0.407 (0.456)	--	16.1 (151)	0.815 (0.913)	MSO & UAN
		Foliar	6 days later	0.408 (0.457)	6	15.8 (148)		

[1] The end-use product is a SC formulation of tembotrione and isoxadifen safener.
[2] Timing = Corn height in inches or 1 week later.
[3] RTI = Retreatment Interval.
[4] GPA = gallons per acre and L/ha = liters per hectare.
[5] Spray adjuvants methylated seed oil (MSO) and urea ammonium nitrate (UAN).

B.2. Sample Handling and Processing Procedures

Two bulk samples of rotated wheat grain (one untreated and one treated) were harvested by mechanical combine 253 days after planting, frozen within one hour of collection, and shipped frozen to Bayer CropScience (Stilwell, KS) by freezer truck. The frozen samples were subsequently shipped by freezer truck to Texas A&M University GLP Food Processing Center (Bryan, TX) for subsampling and if necessary, processing. The RAC subsamples were shipped back to Bayer CropScience via Federal Express on dry ice for analysis. Upon arrival at Bayer CropScience, samples were immediately transferred to frozen storage. To prepare samples for analysis, wheat grain subsamples were homogenized in dry ice. All samples were returned to frozen storage immediately following homogenization, and samples remained in frozen storage at all times except during subsampling for analysis.

The remaining bulk samples of wheat grain were not processed due to nonquantifiable residues in the RAC.

B.3. Analytical Methodology

Samples of rotated wheat grain were analyzed for residues of the parent compound, tembotrione, and the metabolites AE 1392936 (M2), AE 1417268 (M5), and AE 0456148 (M6). The analytical method used was an liquid chromatography/mass spectroscopy (LC/MS)/MS method entitled "AE 0172747: An Analytical Method for the Determination of Residues of AE 0172747, and its major metabolites AE 0456148, AE 1417268, and AE 1392936 in Plant Matrices Using LC/MS/MS." This method quantifies all analytes from a single sample using isotopically labeled internal standards.

Briefly, residues of tembotrione and its metabolites M2, M5, and M6 were extracted from crop matrices with acetonitrile:water (1:1, v:v) using accelerated solvent extraction. Internal standards of the deuterated analytes were added to the extract. For parent, M5, and M6 analysis, an aliquot of the extract was concentrated via Turbo-Vap. For M2 analysis, an aliquot of the

extract was loaded onto a strong anion-exchange solid-phase extraction (SPE) cartridge and eluted with oxalic acid. The SPE eluate was concentrated. The concentrates were reconstituted in 0.1% formic acid and filtered for LC/MS/MS analysis.

For the subject study, reference standards were prepared in tembotrione molar equivalents, therefore, quantitating residues as parent equivalents. Method validation was performed prior to sample analysis with field corn grain (refer to DER for MRID 46695537), and concurrent recoveries were performed during sample analysis to demonstrate acceptable method performance.

The LOQ for tembotrione, M2, M5, and M6 was 0.010 ppm for each analyte in wheat grain. The LOQ is defined as the lowest fortification level of an analyte at which acceptable recovery data was achieved.

The calculated LODs for grain (based on field corn) were 0.0011 ppm for tembotrione, 0.0029 ppm for M6, 0.0025 ppm for M5, and 0.0017 ppm for M2. The LOD was calculated by multiplying the standard deviation of recovery measurements at the LOQ by $t_{0.99}$ (where $t_{0.99}$ is the one-tailed statistic at the 99% confidence level for n-1 replicates) and adding the average residue found in the untreated control samples.

C. RESULTS AND DISCUSSION

Sample storage conditions and intervals are summarized in Table C.2. The maximum storage interval of wheat grain samples from harvest to analysis was 122 days (4 months). The submitted storage stability data on field corn RAC commodities (refer to DER for MRID 46695601) indicate that tembotrione, M2, M5, and M6 residues are stable (<30% decomposition) during frozen storage for at least 13 months prior to analysis with one exception. Residues of M5 in grain showed some apparent degradation with time; however, based on the results of the corn metabolism studies with tembotrione, M5 is not found in significant amounts in grain (<0.010 ppm). These data adequately support the storage conditions and intervals of RAC samples from the processing study.

The analytical method (LC/MS/MS) was successfully validated for the analysis of tembotrione residues and its metabolites M2, M5, and M6 in/on various plant matrices. Recoveries of tembotrione, M6, M5, and M2 from wheat grain were measured concurrently with each set of samples to verify method performance. The concurrent recovery data are summarized in Table C.1. The data demonstrate acceptable method performance during sample analysis. Concurrent method recoveries from wheat grain fortified with tembotrione, M6, M5 or M2 at 0.01 ppm were 88%, 85%, 96%, and 104%, respectively. No apparent residues were found in untreated wheat grain.

Residue data from the rotated wheat processing study are reported in Table C.3. Residues of tembotrione and each of its metabolites (M5, M6 and M2) were below the method LOQ (<0.010 ppm) in rotated wheat grain. Therefore, no processing of the bulk wheat grain samples to representative processed commodities was performed, and the study was terminated.

TABLE C.1. Summary of Concurrent Recoveries of Tembotrione, M5, M6, and M2 from Wheat Grain.

Matrix	Analyte	Spike Level (mg/kg)	Sample Size (n)	Recoveries (%)	Mean Recovery (%)± std dev[1]
Grain	Tembotrione	0.01	1	88	NA
	AE 0456148 (M6)	0.01	1	85	NA
	AE 1417268 (M5)	0.01	1	96	NA
	AE 1392936 (M2)	0.01	1	104	NA

[1] The standard deviation is not applicable for a sample size (n) of less than three.

TABLE C.2. Summary of Storage Conditions.

Residue Components	Matrix	Storage Temp. (°C)	Actual Storage Duration[1]	Interval of Demonstrated Storage Stability[2]
Tembotrione AE 0456148 (M6) AE 1417268 (M5) AE 1392936 (M2)	Rotated wheat grain	< -15	120-122 days (4 months)	Tembotrione, M6, and M2 are stable for up to 13 months in frozen field corn grain. M5 is stable in frozen field corn grain for up to 188 days but declined by 17% after 371 days (61% average corrected recovery).

[1] Actual study duration = number of days between harvest and analysis date. Samples were analyzed within 1 day of extraction.
[2] Field corn RAC storage stability data; refer to the 860.1380 DER for MRID 46695601.

TABLE C.3. Residue Data from the Rotational Crop (Wheat) Processing Study with Tembotrione.

RAC	Proeessed Commodity	Total Rate lb ai/A (kg ai/ha)	PBI[1] (days)	Sum of Total Tembotrione Residues: Parent + M5 + M6 + M2 = Total [2] (ppm in parent equivalents)	Processing Factor
Wheat Grain	RAC	0.815 (0.914)	107	<LOD + <LOD + 0.004 + <LOD = <0.006 [3]	--
	Bran	Not analyzed			
	Flour				
	Middlings				
	Shorts				
	Germ				

[1] PBI = Plantback interval.
[2] Total tembotrione residue is the sum of the individual analytes (quantitated as parent equivalents) as calculated by the petitioner; individual analyte residues reported as "<LOD" were assigned a finite value of ½ the respective analyte LOD. The LOD values for tembotrione (parent), M5, M6, and M2 were 0.0008 ppm, 0.0025 ppm, 0.0016 ppm, and 0.0018 ppm, respectively, in wheat grain.
[3] Average of triplicate subsamples.

D. CONCLUSION

The submitted field trial data reflect the use of two foliar broadcast applications of the SC formulation for a total rate of 0.82 lb ai/A (0.913 kg ai/ha) to the primary crop (field corn). After normal harvest of the primary crop, the rotational crop winter wheat was planted in the test plot at a PBI of 107 days. Residues of tembotrione and each of its metabolites (M5, M6 and M2)

were nonquantifiable in rotated wheat grain harvested at commercial maturity (253 days after planting). Since all residues were <LOQ, the petitioner determined that processing of the bulk wheat grain samples to representative processed commodities was not necessary. An acceptable method was used for quantitation of residues in rotated wheat grain and adequate data are available to support sample storage intervals and conditions.

E. REFERENCES

46695537.der.doc
46695601.der.doc

F. DOCUMENT TRACKING

RDI: RAB1 Chemists (1/17/07)
Petition Number: PP#5F7009
DP#s: 325349, 325663, and 331222
PC Code: 012801

Template Version June 2005

Tembotrione/AE 0172747/PC Code 012801/Bayer CropScience/264
DACO 7.4.3/OPPTS 860.1850/OECD IIA 6.6.3, 6.8.7 and IIIA 8.6
Confined Accumulation in Rotational Crops – Swiss Chard, Turnip, and Wheat

Primary Evaluator	George F. Kramer, Ph.D., Senior Chemist Registration Action Branch (RAB1) Health Effects Division (HED) (7509P)	Date: 18-JUL-2007
Approved by	P.V. Shah, Ph.D., Branch Senior Scientist RAB1/HED (7509P)	Date: 18-JUL-2007

This DER was originally prepared under contract by Dynamac Corporation (2275 Research Boulevard, Suite 300; Rockville, MD 20850; submitted 10/31/2006). The DER has been reviewed by HED and revised to reflect current Office of Pesticide Programs (OPP) policies.

STUDY REPORT:

46695612 J.K. Rupprecht. (15 August 2005). The Accumulation of [U-^{14}C-phenyl]-AE 0172747 in Confined Rotational Crops. Guideline No. OPPTS 860.1850, Bayer Report No. MEAEX007. Unpublished study prepared by Bayer CropScience. 85 pages.

The petitioner has submitted an evaluation template for the study (Bayer CropScience DER for Study MEAEX007), which was used to generate this DER; selected sections were copied without alteration or were copied and modified to more specifically reflect the Agency's data evaluation requirements.

EXECUTIVE SUMMARY:

Bayer CropScience has submitted a confined rotational crop study with [phenyl-U-^{14}C]tembotrione (specific activity = 140.9 μCi/mg). The radiolabeled test substance was combined with nonlabeled tembotrione and diluted with acetonitrile (ACN), then applied to bare sandy loam soil at a rate equivalent to 0.189 lb ai/A (212 g ai/ha). Rotational crops, Swiss chard, turnips, and spring wheat, were planted 90 days after soil treatment.

Total radioactive residues (TRR), determined by summing extractable and nonextractable residues in wheat grain and by combustion/liquid-scintillation counting (LSC) in remaining matrices, accumulated at ≥0.01 ppm in all rotated crop matrices. TRR were 0.134 ppm in Swiss chard, 0.050 and 0.013 ppm, respectively, in turnip tops and roots, and 0.031, 0.246, 0.188, and 0.178 ppm, respectively, in wheat forage, hay, straw, and grain.

Approximately 74-97% TRR were extracted from rotational crop matrices using ACN/water; additional residues (~10-13% TRR) were extracted from wheat hay and straw by refluxing with methanol/water. The nonextractable residues of wheat straw and grain were also subjected to mild acid or base hydrolysis procedures which released ~5% TRR (acid hydrolysis) or ~11-13% TRR (base hydrolysis). Nonextractable residues following extraction and hydrolysis procedures accounted for ≤0.009 ppm in all rotational crop matrices except wheat hay, in which nonextractable residues accounted for 7.3% TRR (0.018 ppm). These procedures adequately extracted the majority of residues from rotational crop matrices. Extraction values were normalized; reported accountabilities before normalization were 85.5% for Swiss chard and 77.4% and 91.8%, respectively for turnip tops and roots. In wheat matrices, accountabilities

before normalization were 98.2%, 92.0%, and 94.2%, respectively, for wheat forage, hay, and straw. TRR in wheat grain were determined by summing extractable and nonextractable residues; therefore, accountability was 100%. Residues were identified and quantitated by high-performance liquid chromatography (HPLC), thin-layer chromatography (TLC), and HPLC/mass spectrometry (MS) and HPLC/MS/MS analyses.

Total identified residues ranged ~22-25% TRR in turnip tops and roots, and 80-91% TRR in remaining matrices. The parent, tembotrione, was not identified in any rotational crop commodity. The major identified residue in all rotational crop matrices was metabolite AE 0456148 (M6), which accounted for 90.6% TRR (0.121 ppm) in Swiss chard, 22.0% and 15.5% TRR (0.011 and 0.002 ppm) in turnip tops and roots, respectively, 51.0% TRR (0.016 ppm) in wheat forage, 70.6% TRR (0.173 ppm) in wheat hay, 59.7% TRR (0.112 ppm) in wheat straw, and 86.4% TRR (0.154 ppm) in wheat grain. The only other identified metabolite was AE 1392936 (M2), which was not found in Swiss chard, turnip tops, or wheat grain, but accounted for 9.4% TRR (0.001 ppm) in turnip roots, 35.1% TRR (0.011 ppm) in wheat forage, and 20.2% and 20.3% TRR (0.050 and 0.038 ppm) in wheat hay and straw, respectively. The petitioner characterized a number of unknowns in Swiss chard and turnip matrices. These unknowns, designated A1-A10, were generally determined at individual levels ≤8.4% TRR and ≤0.006 ppm; however, unknowns A2 and A3 were present at 15.0% and 15.7% TRR (0.007 and 0.008 ppm) in turnip tops, and unknowns A1 and A2 were present at 21.3% and 25.5% TRR (0.003 ppm each) in turnip roots, where they constituted the major components of the residue. Unknowns designated R1 and R2 were found in the methanol reflux extract of wheat straw at ≤0.003 ppm. Because no individual unknown accounted for 0.010 ppm, no further analysis is required.

The petitioner did not provide the dates of sample extraction and profiling, but did provide storage intervals for the RACs and extracts. Based on these data, sample extraction and metabolite profiling were completed within ≤97 days of collection. Because samples were stored for <6 months prior to analysis, supporting storage stability data are not required.

The metabolic profile of tembotrione in confined rotational crops involves cleavage of the complete cyclohexyl moiety from the parent compound leaving the benzoic acid moiety of the molecule, AE 0456148, and to a lesser extent subsequent cleavage of the ether bond to form AE 1392936. Both AE 0456148 and AE 1392936 are significant soil degradates, hence, the presence of these degradates in the confined rotational crops is consistent with the uptake of these metabolites from soil by the rotational crops. The metabolic pathway seen in this study is consistent with the pathway observed in the corn metabolism study (refer to DER 46695530.der.doc).

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the confined rotational crop residue data, using [phenyl-U-^{14}C]tembotrione as the test substance, are classified as scientifically acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document [DP# 325349].

COMPLIANCE:

Signed and dated Good Laboratory Practices (GLP), Quality Assurance and Data Confidentiality statements were provided. No deviations from regulatory requirements were reported.

A. BACKGROUND INFORMATION

Tembotrione, a new herbicide with broad use against mono- and dicotyledons in selected crops such as corn, is a 4-hydroxyphenylpyruvate deoxygenase (HPPD) inhibitor (bleacher). The test compound nomenclature and physiochemical properties of the test compound are presented in Tables A.1 and A.2, respectively.

TABLE A.1. *Test Compound Nomenclature for Tembotrione.*

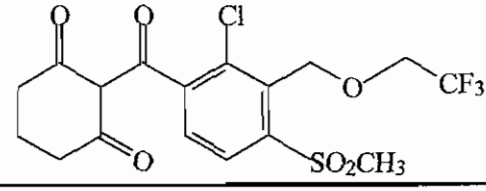
Compound: Tembotrione	Chemical Structure 
Proposed common name	Tembotrione
Company experimental name	AE 0172747
IUPAC name	2-{2-chloro-4-mesyl-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl}cyclohexane-1,3-dione
CAS name	2-[2-chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]-1,3-cyclohexanedione
CAS #	335104-84-2
End-use product/EP	*AE 0172747 Herbicide, EPA Reg No. 264-xxx*

TABLE A.2. Physicochemical Properties of Technical Grade Tembotrione.

Parameter	Value	Reference (MRID#)
Melting point	117 °C	46695402
pH @ 24 °C	3.63	
Density (g/mL @ 20 °C)	1.56	
Water solubility (mg/L @ 20 °C)	0.22 at pH4 28.3 at pH 7 29.7 at pH 9	
Solvent solubility (g/L at 20 °C) DMSO Methylene Chloride Acetone Ethyl Acetate Toluene Hexane Ethanol	 >600 >600 300-600 180.2 75.7 47.6 8.2	
Vapor pressure (Torr, 20 °C)	8.25×10^{-11}	
Dissociation constant (pK_a)	3.2	

TABLE A.2. Physicochemical Properties of Technical Grade Tembotrione.		
Parameter	Value	Reference (MRID#)
Octanol/water partition coefficient (P_{ow} @ 23 °C) (P_{ow} @ 24 °C) (P_{ow} @ 23 °C)	 0.0430 at pH 9.0 0.0807 at pH 7.0 144.9 at pH 2.0	
UV/visible absorption spectrum (nm)	Primary: 205 Secondary: 284 Tertiary: 240	

B. EXPERIMENTAL DESIGN

B.1. Test Site and Crop Information

The test system was a stainless steel tank with a surface area of 1.39 m^2 (76.2 cm by 182.9 cm; 61.0 cm deep) which was prepared by placing approximately 15 cm of gravel in the bottom and filling with sandy loam to within several cm of the top (Table B.1.1). The composition of the soil with respect to relative distribution of sand, silt, and clay was not reported. Prior to treatment and during the soil aging period, the tank was moved between a greenhouse and a covered outdoor patio area; once the crops were planted, the tank remained in the greenhouse.

Plants were maintained according to good agricultural practices. Swiss chard, turnips and spring wheat were planted 90 days after a bare soil treatment with [phenyl-U-^{14}C]tembotrione (Table B.1.2.). The plot was irrigated manually as needed, in a controlled fashion to minimize splashing the foliage with treated soil. Weeds were removed from the test plots by hand. Pesticides were used when necessary to achieve maximum crop growth. Because the in-life portion of the study was conducted in a greenhouse, there were no unusual meteorological occurrences during the study.

TABLE B.1.1. Test Site Information.							
Testing environment and location	Soil characteristics[1]						
	Type	% Sand	% Silt	% Clay	%OM	pH	CEC
Stainless steel tank maintained in a greenhouse following planting	Sandy Loam	Not reported			2.4	7.4	9.3 meq/100 g

[1] OM = Organic matter, CEC = Cation-exchange capacity.

TABLE B.1.2. Crop Information.					
Crop; crop group	Variety	Plantback intervals (days)	Growth stage at harvest	Harvested Matrix	Harvesting procedure
Swiss chard; Vegetable, leafy, except brassica, group 4	Luccullus	90	Mature	Leaves	Excised with scissors, cutting at the base of the plant
Turnip; Vegetable, root and tuber, group 1 & Vegetable, leaves of root and tuber, group 2	Purple Top	90	Mature	Tops and roots	Harvested by hand, tops were then separated from the roots

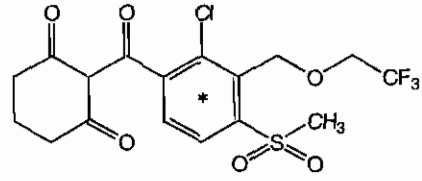
TABLE B.1.2. Crop Information.

Crop; crop group	Variety	Plantback intervals (days)	Growth stage at harvest	Harvested Matrix	Harvesting procedure
Wheat; Grain, cereal, group 15 & Grain, cereal, forage, fodder, and straw, group 16	Butte 86 HRS	90	6-8" stage	Forage	Excised with scissors, cutting at the base of the plant
			Boot to soft dough stage	Hay	Excised with scissors, cutting at the base of the plant
			Mature	Grain and straw	Excised with scissors, cutting at the base of the plant, straw separated from the grain

B.2. Test Materials

The radiolabeled test substance was combined with nonlabeled tembotrione and diluted with ACN. The test material characteristics are presented in Table B.2.1.

TABLE B.2.1. Test Material Characteristics.

Chemical structure	
Radiolabel position	[phenyl-U-^{14}C]tembotrione
Lot No.	BECH 1579
Purity	Radiochemical purity: 98-100.0% by HPLC
Specific activity [1]	Test substance: 5.21 MBq/mg (140.9 µCi/mg) Application solution: 53.0 µCi/mg

[1] Bq = Disintegrations/second.

B.3. Study Use Pattern

The application solution was applied as a broadcast spray directly to bare soil using a hand-held, pump-action sprayer, at a rate equivalent to 0.189 lb ai/A (212 g ai/ha). Rotational crops Swiss chard, turnip, and wheat were planted 90 days after treatment. The study use pattern is summarized in Table B.3.1.

TABLE B.3.1. Use Pattern Information.

Chemical name	[phenyl-U-^{14}C]tembotrione
Application method	The radiolabeled test substance was mixed with unlabeled test substance and diluted with ACN, then applied directly to bare soil.
Application rate	0.189 lb ai/A (212 g ai/ha)
Number of applications	One
Timing of application	90 days prior to planting Swiss chard, turnips and wheat.
DAT[1] (days)	N/A; application to bare soil

[1] DAT = Days after treatment

B.4. Identification/Characterization of Residues

B.4.1. Sample Handling and Preparation

The petitioner noted that, when necessary, harvested crops were briefly air-dried and brushed lightly to remove any adhering soil prior to placing into plastic bags. Swiss chard and wheat forage were homogenized on the day of harvest; all other samples were stored frozen prior to homogenization. Samples of Swiss chard, turnip tops and roots, and wheat forage and straw were homogenized in the presence of dry ice; samples of wheat hay and grain were homogenized in the presence of liquid nitrogen using a mortar and pestle. The homogenized samples were stored frozen prior to extraction.

Samples of Swiss chard, turnip tops and roots, and wheat forage, hay, straw, and grain were extracted three times with ACN/water (4:1, v:v), then centrifuged. The supernatants were combined, concentrated to dryness or near dryness under a gentle stream of nitrogen, then reconstituted in ACN:0.1% acetic acid (1:9, v:v) and reserved for HPLC and/or TLC analysis.

The nonextractable residues of wheat hay and straw were extracted at reflux overnight with methanol:water (4:1, v:v). Following cooling, the suspension was filtered, and the resulting filter cake was rinsed three times with methanol. The filtrate and rinses were combined, concentrated to dryness under a nitrogen stream, and redissolved in ACN:0.1% acetic acid (1:9, v:v). The resulting solution was filtered and reserved for HPLC and TLC analysis.

Separate subsamples of the nonextractable residues of wheat straw and grain following methanol/water reflux were subjected to acid or base hydrolysis with 1 M HCl or 1 M NaOH at reflux for 18-18.5 hours to release bound residues. After each procedure, the mixture was cooled and centrifuged, and the pellet was rinsed with water and centrifuged three more times. The respective hydrolysates and rinses were combined.

Representative flow charts of the extraction procedures are presented in the following figures: Figure 1 for Swiss chard, turnip tops and roots, and wheat forage and grain; Figure 2 for wheat hay; Figure 3 for wheat straw; and Figures 4a and 4b for the hydrolysis of nonextractable residue of wheat straw and grain.

Figure 1. Extraction procedures for Swiss chard, turnip tops and roots, and wheat forage and grain.

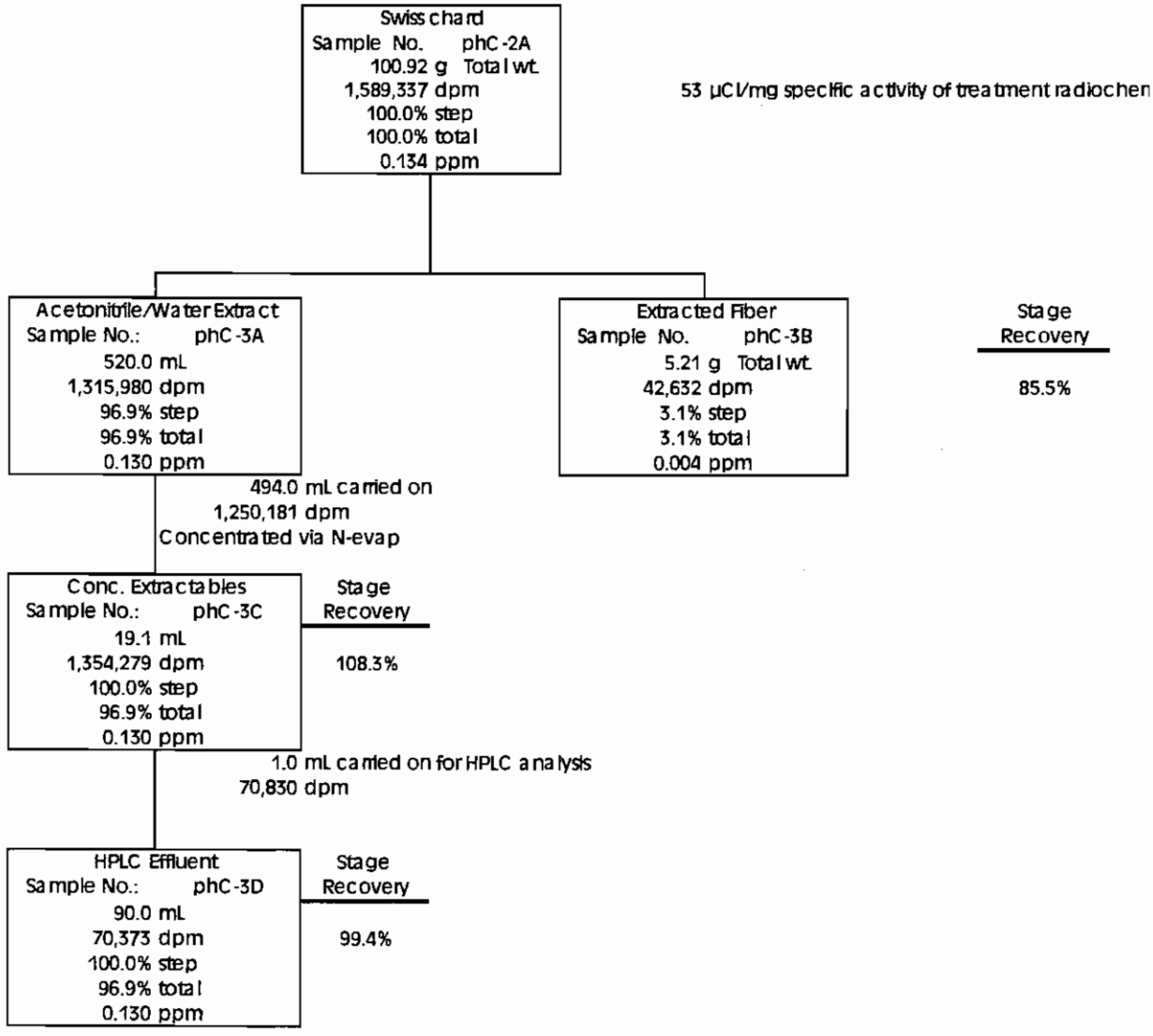


Figure 2. Extraction procedures for wheat hay.

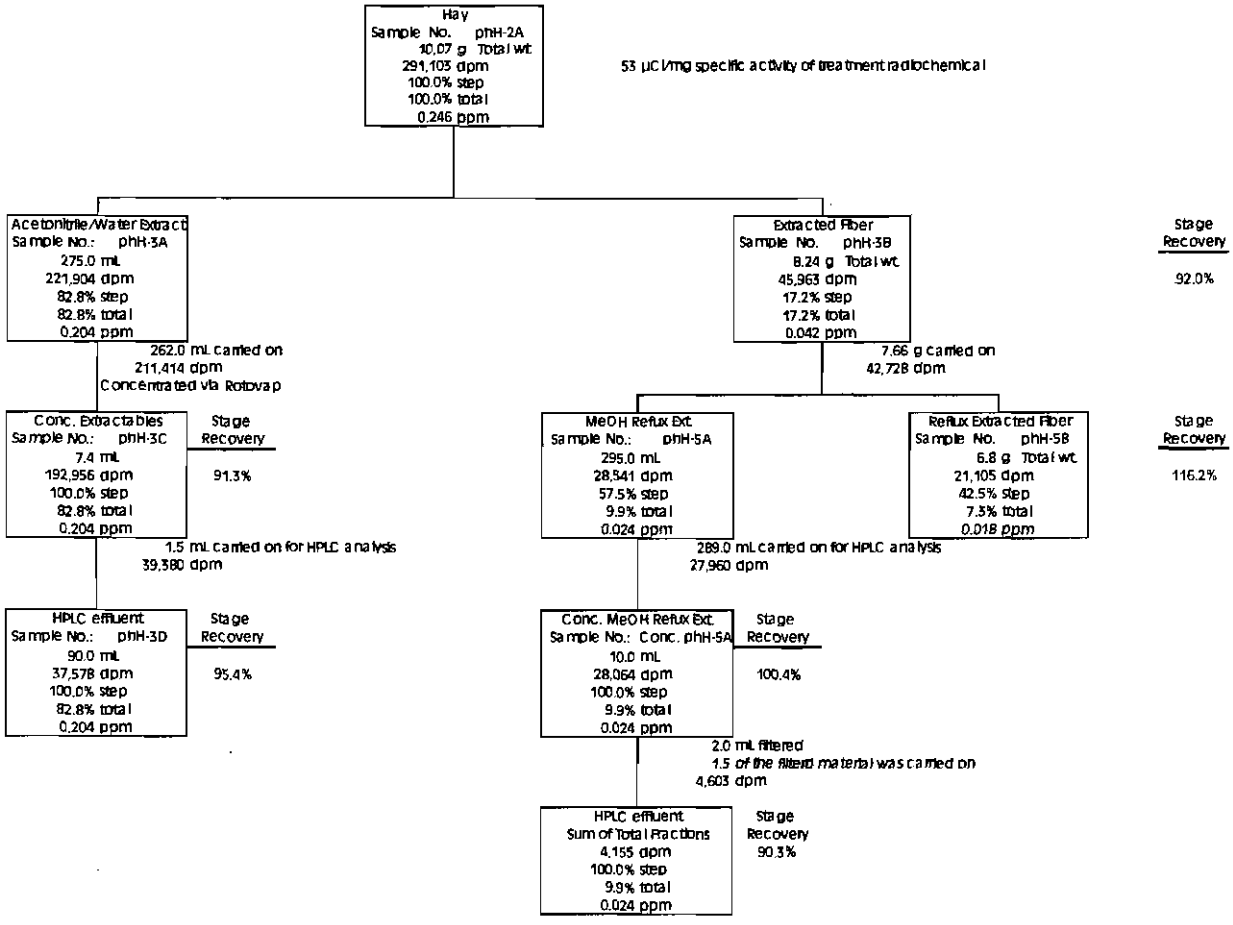


Figure 3. Extraction procedures for wheat straw.

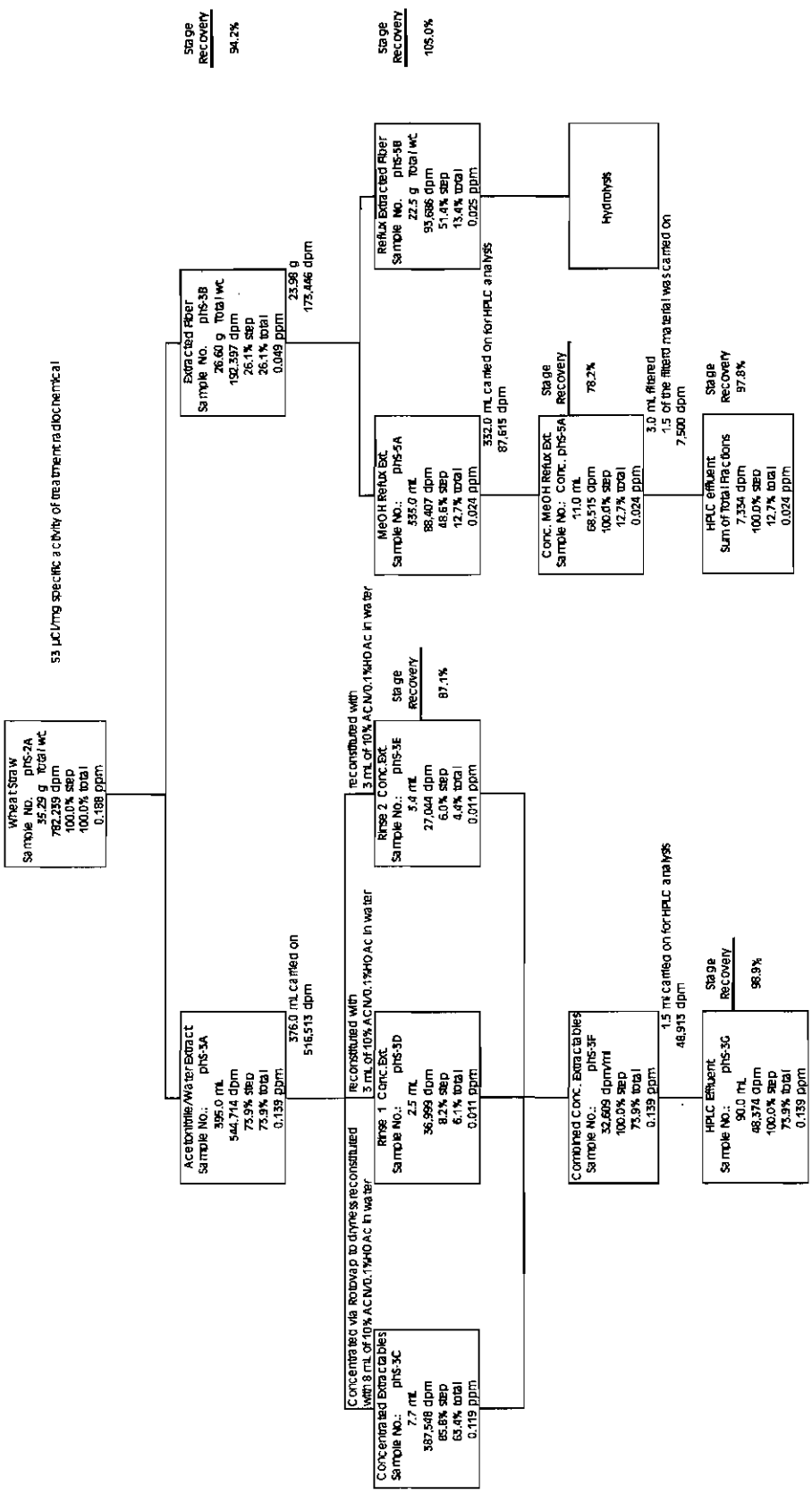


Figure 4a. Acid hydrolysis of nonextractable residues for wheat straw and grain.

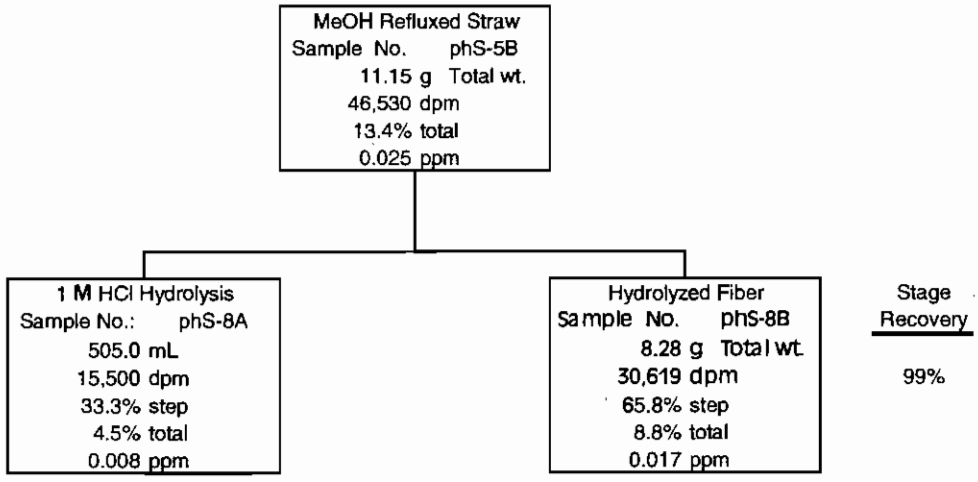
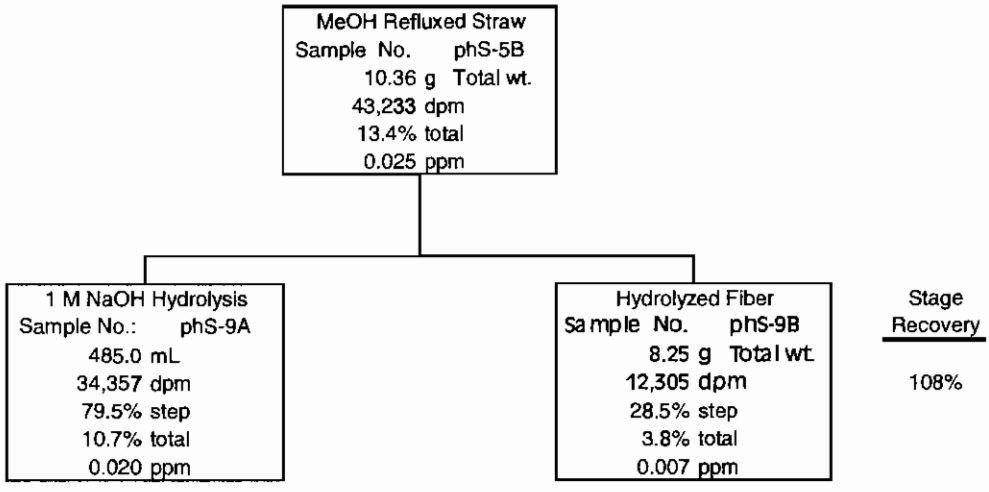


Figure 4b. Base bydrolysis of nonextractable residues for wheat straw and grain.



B.4.2. Analytical Methodology

TRR were determined by combustion/LSC in all rotational crop matrices except wheat grain. Due to the low yield of wheat grain, the sample was not combusted prior to extraction to allow the maximum amount of sample for extraction; TRR in wheat grain were determined by summing extractable and nonextractable residues. Extracts and hydrolysates were radioassayed by LSC, and nonextractable residues were radioassayed by combustion/LSC. The reported limits of quantitation (LOQs) for TRR determinations were ~0.002 ppm for solid and liquid samples.

Initial profiling of sample extracts was conducted using reverse phase HPLC on a system equipped with a C-18 column, a variable wavelength UV detector (254 nm), a radioactivity detector, and a fraction collector; a gradient mobile phase of 0.1% aqueous acetic acid/ACN was used. Similar HPLC systems were used for the isolation and purification of metabolites (using gradient mobile phases of water and ACN) and to confirm the ionization properties of metabolite AE 1392936 (gradient mobile phase of water/ACN, each containing 0.1% trifluoroacetic acid).

Metabolites were identified/confirmed by LC/MS, LC/MS/MS, or normal phase TLC analyses. TLC analyses were conducted using silica gel plates and a solvent system of toluene:ethyl acetate:ammonia (6:5:1, v:v:v). LC/MS and LC/MS/MS analyses were conducted using negative ion electrospray on a system equipped with a quadrapole mass spectrometer and an HPLC system equipped with reverse phase C8 column and using a mobile phase of 0.1% formic acid/methanol. The reference standards used in the study are presented in Appendix I.

C. RESULTS AND DISCUSSION

The storage conditions and intervals for rotational crop commodities and extracts are presented in Table C.1. The petitioner did not provide the dates of sample extraction and profiling, but did provide storage intervals for the RACs and extracts. Based on these data, sample extraction and metabolite profiling were completed within ≤97 days of collection. Because samples were stored for <6 months prior to analysis, supporting storage stability data are not required.

Total radioactive residues, determined by summing extractable and nonextractable residues in wheat grain and by combustion/LSC in remaining matrices, accumulated at ≥0.01 ppm in all rotated crop matrices planted 90 days following application of [phenyl-U-^{14}C]tembotrione directly to bare soil. TRR were 0.134 ppm in Swiss chard, 0.050 and 0.013 ppm, respectively, in turnip tops and roots, and 0.031, 0.246, 0.188, and 0.178 ppm, respectively, in wheat forage, hay, straw, and grain.

The extraction profiles and distribution of the radioactivity in rotational crop commodities are presented in Tables C.2.2.1 (Swiss chard and turnip matrices) and C.2.2.2 (wheat matrices). Approximately 74-97% TRR were extracted from rotational crop matrices using ACN/water; additional residues (~10-13% TRR) were extracted from wheat hay and straw by reflux with methanol. The nonextractable residues of wheat straw and grain were also subjected to mild acid or base hydrolysis procedures which released ~5% TRR (acid hydrolysis) or ~11-13% TRR (base hydrolysis). Nonextractable residues following extraction and hydrolysis procedures accounted for ≤0.009 ppm in all rotational crop matrices except wheat hay, in which nonextractable residues accounted for 7.3% TRR (0.018 ppm). Extraction values were normalized; reported accountabilities before normalization were 85.5% for Swiss chard and 77.4% and 91.8%, respectively for turnip tops and roots. In wheat matrices, accountabilities before normalization were 98.2%, 92.0%, and 94.2%, respectively, for wheat forage, hay, and straw. TRR in wheat grain were determined by summing extractable and nonextractable residues; therefore, accountability was 100%.

The characterization and identification of residues in rotational crop matrices are summarized in Tables C.2.3.1 (Swiss chard and turnip matrices) and C.2.3.2 (wheat matrices). Total identified residues ranged ~22-25% TRR in turnip tops and roots, and 80-91% TRR in remaining matrices. The parent, tembotrione, was not identified in any rotational crop commodity. The major identified residue in all rotational crop matrices was metabolite AE 0456148 (M6), which accounted for 90.6% TRR (0.121 ppm) in Swiss chard, 22.0% and 15.5% TRR (0.011 and 0.002 ppm) in turnip tops and roots, respectively, 51.0% TRR (0.016 ppm) in wheat forage, 70.6% TRR (0.173 ppm) in wheat hay, 59.7% TRR (0.112 ppm) in wheat straw, and 86.4% TRR (0.154 ppm) in wheat grain. The only other identified metabolite was AE 1392936 (M2), which was not found in Swiss chard, turnip tops, or wheat grain, but accounted for 9.4% TRR (0.001 ppm) in turnip roots, 35.1% TRR (0.011 ppm) in wheat forage, and 20.2% and 20.3% TRR (0.050 and 0.038 ppm) in wheat hay and straw, respectively. The petitioner characterized a number of unknowns in Swiss chard and turnip matrices. These unknowns, designated A1-A10, were generally determined at individual levels ≤8.4% TRR and ≤0.006 ppm; however, unknowns A2 and A3 were present at 15.0% and 15.7% TRR (0.007 and 0.008 ppm) in turnip tops, and unknowns A1 and A2 were present at 21.3% and 25.5% TRR (0.003 ppm each) in turnip roots, where they constituted the major components of the residue. Unknowns designated R1 and R2 were found in the methanol reflux extract of wheat straw at ≤0.003 ppm. Because no individual unknown accounted for 0.010 ppm, no further analysis is required.

Metabolite AE 0456148 was identified in Swiss chard and wheat hay and straw by LC/MS and LC/MS/MS; identification in turnip tops and roots, and wheat forage, hay, straw, and grain was confirmed by retention time comparison with a reference standard on HPLC analysis and by TLC co-chromatography. Metabolite AE 1392936 was identified by HPLC retention time comparison and by TLC co-chromatography in turnip roots wheat forage, hay, and straw.

C.1. Storage Stability

All samples were stored frozen (<-20 °C) immediately after harvest, and remained frozen except during sub-sampling for extraction and analysis; extracts were stored at <2 °C. The petitioner did not provide the dates of sample extraction and profiling, but did provide storage intervals for the RACs and extracts (Table C.1). Based on these data, sample extraction and metabolite profiling were completed within ≤97 days of collection. Because samples were stored for <6 months prior to analysis, supporting storage stability data are not required.

TABLE C.1. Summary of Storage Conditions

Matrix	Plant-back interval (days)	Storage Temp. (°C)	Actual Storage Duration (days)[1]	Interval of Demonstrated Storage Stability
RACs				
Swiss Chard	90	<-20	1	Not required
Turnip Tops	90	<-20	6	Not required
Turnip Roots	90	<-20	7	Not required
Wheat Forage	90	<-20	4	Not required
Wheat Hay	90	<-20	22	Not required
Wheat Straw	90	<-20	20	Not required

TABLE C.1. Summary of Storage Conditions				
Matrix	Plant-back interval (days)	Storage Temp. (°C)	Actual Storage Duration (days)[1]	Interval of Demonstrated Storage Stability
Wheat Grain	90	<-20	15	Not required
Extracts				
Swiss Chard	90	<2	3	Not required
Turnip Tops	90	<2	7	Not required
Turnip Roots	90	<2	90	Not required
Wheat Forage	90	<2	4	Not required
Wheat Hay	90	<2	22	Not required
Wheat Straw	90	<2	20	Not required
Wheat Grain	90	<2	15	Not required

[1] Assumed to be the interval from harvest to extraction for RACs and the interval from extraction to profiling for extracts.

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

TABLE C.2.1. TRR in Matrices.		
Matrix	Plant-back interval (days)	ppm
Swiss Chard Leaves	90	0.134
Turnip Leaves	90	0.050
Turnip Roots	90	0.013
Wheat Forage	90	0.031
Wheat Hay	90	0.246
Wheat Straw	90	0.188
Wheat Grain	90	0.178

TABLE C.2.2.1. Distribution of the Parent and the Metabolites in Rotational Swiss Chard and Turnip Tops *and Roots* Planted 90 Days Following Application of [phenyl-U-14C]Tembotrione to Soil at 0.189 lb ai/A (212 g ai/ha).

Metabolite Fraetion	Swiss chard		Turnip tops		Turnip roots	
	TRR = 0.134 ppm		TRR = 0.050 ppm		TRR = 0.013 ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm
ACN/water	96.9	0.130	81.7	0.041	91.5	0.012
AE 0456148	90.6	0.121	22.0	0.011	15.5	0.002
AE 1392936	--	--	--	--	9.4	0.001
A1	--	--	--	--	21.3	0.003
A2	--	--	15.0	0.007	25.5	0.003
A3	--	--	15.7	0.008	--	--
A4	4.2	0.006	--	--	--	--
A5	--	--	8.2	0.004	7.9	0.001
A6	--	--	7.5	0.004	--	--
A7	--	--	8.4	0.004	--	--
A8	--	--	1.9	0.001	--	--
A9	2.1	0.003	--	--	--	--
A10	--	--	3.0	0.001	--	--
Nonextractable	3.1	0.004	18.3	0.009	8.5	0.001

TABLE C.2.2.2. Distribution of the Parent and the Metabolites in Rotational Wheat Matrices Planted 90 Days Following Application of [phenyl-U-14C]Tembotrione to Soil at 0.189 lb ai/A (212 g ai/ha).[1]

Metabolite Fraction	Wheat forage		Wheat hay		Wheat straw		Wheat grain	
	TRR = 0.031 ppm		TRR = 0.246 ppm		TRR = 0.188 ppm		TRR = 0.178 ppm	
	%TRR	ppm	% TRR	ppm	%TRR	ppm	%TRR	ppm
ACN/water	86.2	0.026	82.8	0.204	73.9	0.139	86.4	0.154
AE 0456148	51.0	0.016	65.7	0.161	56.0	0.105	86.4	0.154
AE 1392936	35.1	0.011	17.2	0.042	17.9	0.034	--	--
Methanol Reflux			9.9	0.024	12.7	0.024		
AE 0456148			4.9	0.012	3.7	0.007		
AE 1392936			3.0	0.007	2.4	0.004		
R1			--	--	1.5	0.003		
R2			--	--	1.0	0.002		
Nonextractable	13.8	0.004	7.3	0.018	13.4	0.025	13.6	0.024
1. HCl hydrolysate					4.5	0.008	4.8	0.009
Nonextractable					8.8	0.017	8.8	0.016
2. NaOH hydrol.					10.7	0.020	12.7	0.023
Nonextractable					3.8	0.007	0.9	0.002

[1] Shading indicates that the extraction step and/or characterization analysis was not conducted for the matrix in question.

TABLE C.2.3.1. Summary of Characterization and Identification of Radioactive Residues in Rotational Swiss Chard and Turnip Tops and Roots Planted 90 Days Following Application of [phenyl-U-14C]Tembotrione to Soil at 0.189 lb ai/A (212 g ai/ha).

Compound	Swiss chard		Turnip tops		Turnip roots	
	TRR = 0.134 ppm		TRR = 0.050 ppm		TRR = 0.013 ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm
AE 0456148 (M6)	90.6	0.121	22.0	0.011	15.5	0.002
AE 1392936 (M2)	--	--	--	--	9.4	0.001
A1	--	--	--	--	21.3	0.003
A2	--	--	15.0	0.007	25.5	0.003
A3	--	--	15.7	0.008	--	--
A4	4.2	0.006	--	--	--	--
A5	--	--	8.2	0.004	7.9	0.001
A6	--	--	7.5	0.004	--	--
A7	--	--	8.4	0.004	--	--
A8	--	--	1.9	0.001	--	--
A9	2.1	0.003	--	--	--	--
A10	--	--	3.0	0.001	--	--
Total identified	90.6	0.121	22.0	0.011	24.9	0.003
Total characterized	6.3	0.009	59.7	0.029	54.7	0.007
Total extractable	96.9	0.130	81.7	0.041	91.5	0.012
Unextractable[1]	3.1	0.004	18.3	0.009	8.5	0.001
Accountability[2]	100		100		100	

[1] Residues remaining after exhaustive extractions.

[2] Accountability = (Total extractable + Total unextractable)/(TRR from combustion analysis; see TABLE C.2.1) * 100. Extraction values were normalized; reported accountabilities before normalization were 85.5% for Swiss chard, and 77.4% and 91.8%, respectively, for turnip tops and roots.

TABLE C.2.3.2. Summary of Characterization and Identification of Radioactive Residues in Rotational Wheat Matrices Planted 90 Days Following Application of [phenyl-U-14C]Tembotrione to Soil at 0.189 lb ai/A (212 g ai/ha).

Compound	Wheat forage		Wheat hay		Wheat straw		Wheat grain	
	TRR = 0.031 ppm		TRR = 0.246 ppm		TRR = 0.188 ppm		TRR = 0.178 ppm	
	%TRR	ppm	% TRR	ppm	%TRR	ppm	%TRR	ppm
AE 0456148 (M6)	51.0	0.016	70.6	0.173	59.7	0.112	86.4	0.154
AE 1392936 (M2)	35.1	0.011	20.2	0.050	20.3	0.038	--	--
R1	--	--	--	--	1.5	0.003	--	--
R2	--	--	--	--	1.0	0.002	--	--
Base hydrolysate	--	--	--	--	10.7	0.020	12.7	0.023
Total identified	86.2	0.026	90.8	0.223	80.0	0.150	86.4	0.154
Total characterized	0	0	0	0	13.2	0.025	12.7	0.023
Total extractable	86.2	0.026	92.7	0.228	97.3	0.183	99.1	0.177
Unextractable (PES)[1]	13.8	0.004	7.3	0.018	3.8	0.007	0.9	0.002
Accountability[2]	100		100		100		100	

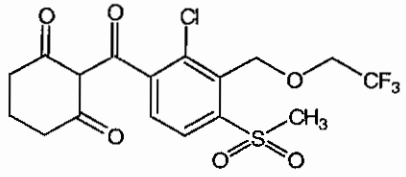
[1] Residues remaining after exhaustive extractions.

[2] Accountability = (Total extractable + Total unextractable)/(TRR from combustion analysis; see TABLE C.2.1) * 100. Initial extraction values were normalized; reported accountabilities before normalization were 98.2%, 92.0%, 94.2%, respectively, for wheat forage, hay, and straw. TRR in wheat grain were determined by summing extractable and nonextractable residues, therefore, accountability was 100%.

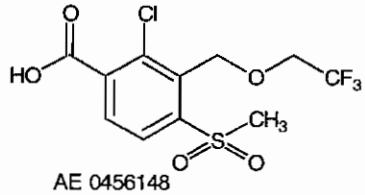
C.3. Proposed Metabolic Profile

The metabolic profile of tembotrione in confined rotational crops involves cleavage of the complete cyclohexyl moiety from the parent compound leaving the benzoic acid moiety of the molecule, AE 0456148, and to a lesser extent subsequent cleavage of the ether bond to form AE 1392936. Both AE 0456148 and AE 1392936 are significant soil degradates, hence the presence of these degradates in the confined rotational crops is consistent with the uptake of these metabolites from soil by the rotational crops. The metabolic pathway seen in this study is consistent with the pathway observed in the corn metabolism study (refer to DER 46695530.der.doc).

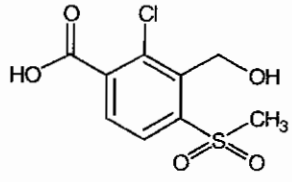
FIGURE C.3.1. Proposed Metabolic Profile of Tembotrione in Rotational Swiss Chard, Turnips, and Wheat



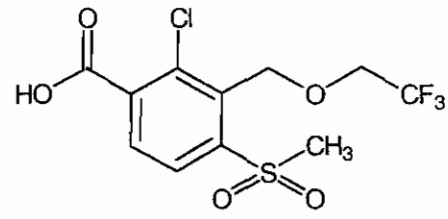
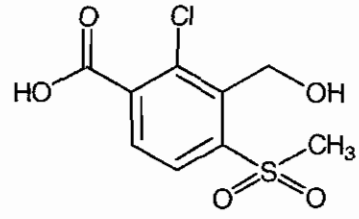
AE 0172747



AE 0456148



AE 1392936

TABLE C.3.1. Identification of Compounds from the Confined Rotational Crop Study.		
Common name/code Figure C.3.1 ID No.	Chemical name	Chemical structure
Descyclohexadione Tembotrione/ AE 0456148 (M6)	2-chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoic acid	
Tembotrione Hydroxyacid/ AE 1392936 (M2)	2-chloro-3-hydroxymethyl-4-mesylbenzoic acid	

D. CONCLUSION

The extent and nature of the residue uptake by crops planted 90 days post-application in soil treated with [phenyl-U-^{14}C]tembotrione at 0.189 lb ai/A (212 g ai/ha) was determined. TRR were 0.134 ppm in Swiss chard, 0.050 ppm in turnip tops, 0.013 ppm in turnip roots, 0.031 ppm wheat forage, 0.246 ppm in wheat hay, 0.188 ppm in wheat straw, and 0.178 ppm in wheat grain.

The principal residues identified were AE 0456148 and AE 1392936. The majority of the residue was identified in all analyzed matrices (~80-91% of the TRR), with the exception of turnip tops and turnip roots where 22.0% and 24.9% of the TRR were identified, respectively, due to low overall residues. The largest single unidentified residue in any matrix accounted for 0.008 ppm. The metabolic profile in this study was consistent with profiles observed in the corn metabolism study and the soil degradation studies.

The metabolic profile of tembotrione in confined rotational crops involves cleavage of the complete cyclohexyl moiety from the parent compound leaving the benzoic acid moiety of the molecule, AE 0456148, and to a lesser extent subsequent cleavage of the ether bond to form AE 1392936. Both AE 0456148 and AE 1392936 are significant soil degradates, hence, the presence of these degradates in the confined rotational crops is consistent with the uptake of these metabolites from soil by the rotational crops.

E. REFERENCES

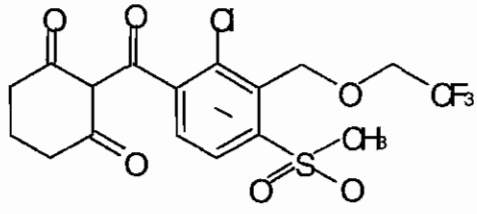
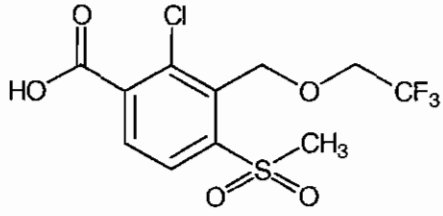
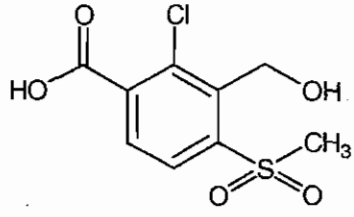
46695530.der.doc

F. DOCUMENT TRACKING

RDI: RAB1 Chemists (1/17/07)
Petition Number: PP#5F7009
DP#s: 325349, 325663, and 331222
PC Code: 012801

Template Version June 2005

APPENDIX I. Chemical Names and Structures of Reference Standards Used in the Confined Rotational Crop Study.

Common name; Company code	Chemieal name	Chemical structure
Tembotrione/AE 0172747	1,3-cyclohexanedione, 2-[2-chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl]	
Descyclohexadione Tembotrione/AE 0456148 (M6)	2-ehloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoic acid	
Tembotrione Hydroxyacid/ AE 1392936 (M2)	2-chloro-3-hydroxymethyl-4-mesylbenzoic acid	

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Chemical: Tembotrione

PC Code:
012801

HED File Code: 11500 Petition Files Chemistry
Memo Date: 7/18/2007
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DPD325663
DPD331222
DPD332977
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