9/1/94

MEMORANDUM:

SUBJECT: PP#3F4187. Thiazopyr (MON13200) in/on Cotton and Citrus Crops. Evaluation of Analytical Methods and of Residue Data. MRID#'s 426197-04, 426197-05, 426197-06, 426197-07, 426197-08, 426197-09, 426197-10, 426197-11, and 426197-12; 426414-00, 426414-01. CBTS#'s 11552, 11553, 11554, and 11555. DP Barcodes D189115, 189116, 189132, and 189136.

FROM: Jerry B. Stokes, Chemist
Chemistry Branch/Tolerance Support
Health Effects Division (7509C)

THRU: Richard Loranger, Ph.D., Acting Chief
Chemistry Branch/Tolerance Support
Health Effects Division (7509C)

TO: Joanne Miller/Eugene Wilson, PM 23
Fungicide/Herbicide Branch
Registration Division (7505C)

and

Albin Kocialski
Chemical Coordination Branch
Health Effects Division

Monsanto Company has submitted a petition (PP#3F4187) for the establishment of permanent tolerances for residues of the selective herbicide thiazopyr (ISO common name) [3-pyridine

1

carboxylic acid, 2-(difluoromethyl)-5-(4,5-dihydro-2-thiazolyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-, methyl ester] and its metabolites determined as 3-pyridine carboxylic acid, 5-(aminocarbonyl)-2-(difluoromethyl)-4-(2-methylpropyl)-6-trifluoromethyl-, methyl ester and 3-pyridine carboxylic acid, 2-(difluoromethyl)-4-(2-methylpropyl)-5-(((2-sulfoethyl) amino)carbonyl)-6-trifluoromethyl and expressed as parent equivalents as follows:

Commodity	Parts Per Million (ppm)
Citrus, whole fruit	0.05 ppm (group tolerance)
Cottonseed	0.05 ppm
Cotton, forage	0.2 ppm

Monsanto has previously petitioned for temporary tolerances (PP#2G4122) for the same residues in/on the above commodities at the same levels. The temporary tolerance petition was reviewed by CBTS (J. Garbus; CBTS Nos. 9899 and 9906, DP Barcodes D178499 and D178505, 6/2/93; CBTS No. 11817, DP Barcode D190954, 7/14/93; and CBTS No. 12126, DP Barcode D192487, 8/25/93) which recommended for the establishment of the temporary tolerances.

Data evaluation reports for the product chemistry, analytical methodology, storage stability studies, and magnitude of the residues (field trials and processed commodiites) have been provided by Dynamac Corporation under the supervision of CBTS, HED. Discussions of the nature of the residues in plants and animals, residues in meat, milk, and eggs, and rotational crops have been reviewed only by CBTS. These data evaluation reports have undergone secondary review and have been incorporated into this memo. Decisions on the adequacy of the submitted data and all conclusions are solely those of CBTS.

Conclusions:

1. Additional data are needed for Guideline 61-2. The petitioner must provide additional information for [redacted] as discussed in the Confidential Appendix.

2a. Additional data are needed for Guideline 61-3. The petitioner must explain the connection between the production of dithiopyr and the production of thiazopyr as discussed in the Confidential Appendix.

2b. The petitioner must provide additional information for the impurities #'s 105, 107, 109, 110, and 134 as discussed in the Confidential Appendix.

3a. The submitted data are adequate for Guideline 62-1. No additional data are needed for this petition review for the proposed uses on cotton and citrus.

However, if a Section 3 registration is established for thiazopyr uses on cotton and citrus, and when the commercial production begins, the petitioner must provide the Agency with 5 batch analyses of the TGAI and its impuriites. These data must be provided within a reasonable period after the commercial process is operating.

3b. The submitted data are not adequate for Guideline 62-2. The nominal concentration listed for the active ingredient in MRID# 246197-02 does not agree with the nominal concentration on the CSF dated 12/11/92. Please submit the correct value.

4a. Feeding and grazing restrictions are proposed for the use on cotton.

No feeding or grazing restrictions are proposed for cover crops in treated citrus orchards. A revised Section B must be submitted prohibiting the feeding or grazing of cover crops in treated citrus orchards. Alternatively, residue data and proposed tolerances can be submitted for grass cover crops in treated citrus orchards.

4b. A 9-month plant-back interval for all crops except cotton and an 18-month plant-back interval for grain sorghum, corn, and wheat are proposed. In the review of the temporary tolerance petition (PP#2G4122, J. Garbus, 6/2/93), CBTS concluded that the proposed label statements regarding rotational crops were acceptable for the purposes of an experimental use permit only. The 18-month plant-back

interval is not practical, and not acceptable for a permanant tolerance. The petitioner has submitted a confined rotational crop study (MRID #42275515) which was previously reviewed by EFGWB. CBTS must review rotational field trial residue data for these crops to determine if tolerances for thiazopyr residues must be established. [Note: The data responding to this deficiency has been received (Barcode DP D198931) and are currently in review.]

5. CBTS considers the metabolism of thiazopyr in plants and animals as adequately understood for these tolerance requests. The petitioner has proposed that tolerances be established for thiazopyr and those metabolites that can be converted to two common entities, referred to as the sulfonic diacid (SAA) and the amide acid (AA). The residues to be regulated will be determined by the HED Metabolism Committee.

6a. The proposed analytical enforcement methodology RES-041-92 does not determine the parent per se, but only those thiazopyr metabolites convertible to the AA chemophore; thiazopyr is converted to the SAA chemophore. This is not an acceptable proposed method for enforcement purposes. Therefore, CBTS requests that the petitioner submit enforcement methodology for the analysis of thiazopyr residues (parent plus metabolites) to include adequate validation data, chromatgraphic charts, and recovery data, and supported by an independent laboratory validation. A confirmatory method in a specificity study must be provided.

Since the field trial residue data were collected using Method RES-017-91, the petitioner must also submit bridging data (i.e., 10% of samples) using the reserve field trial samples (and several from the citrus and cottonseed processing studies, if availiable) with this new proposed method. (Note: The description of the method must also be clean of all confidential or business security stamps on the supplied copies.) The need for additional analytical methodology is dependent on the decision of the residues to be regulated as determined by the HED Metabolism Committee.

6b. If tolerances for livestock meat, meat by-products, and fat, and milk and eggs are not required for thiazopyr residues based upon the proposed use, analytical methodology for such

residues in these rac's may not be needed at this time. The need for additional analytical methodology is dependent on the decision of the residues to be regulated as determined by the HED Metabolism Committee and the results of residue data requested in conclusion 9 below for cotton gin byproducts. Also, if future uses show combined thiazopyr residues (>0.05 ppm) in these rac's, then additional analytical methodology, and tolerances, for livestock meat, meat byproducts, fat, milk, and/or eggs may be needed.

6c. CBTS requests that the company submit copies of the multi-residue testing results using the prescribed protocols without the company confidential or business security stamp on the submitted pages.

7a. The submitted data indicate that residues of thiazopyr and its metabolites convertible to SAA and AA are not likely to exceed the proposed tolerance of 0.05 ppm in/on citrus fruits harvested 32-98 days following a single soil broadcast application at 2 lb a.i./A using the 2 lb a.i./gal EC in both cases, or two sequential soil broadcast applications at 1 lb a.i./A/application for a maximum seasonal rate of 2 lb a.i./A. However, the need for additional residue data is dependent on the decision of the HED Metabolism Committee.

7b. The available data indicate that residues of thiazopyr and its metabolites convertible to SAA and AA are not likely to exceed the proposed tolerance of 0.05 ppm in/on cottonseed following a single preplant soil incorporated application of the 2 lb a.i./gal EC formulation at 1x and 2x the maximum seasonal rate, or a single preemergence soil surface application at 2x. The need for additional residue data is dependent on the decisions of the HED Metabolism Committee.

7c. CBTS data requirements for cotton forage have been changed; no data are needed for cotton forage; no tolerance should be established for cotton forage. However, data must be submitted for cotton gin byproducts (commonly called gin trash) which reflects the proposed use (See Conclusion 9, this memo). A revised Section F must be submitted which deletes cotton forage.

8a. The data indicate that residues of thiazopyr and its metabolites convertible to SAA and AA are not likely to concentrate in the pulp (finisher), peel (wet and dry), and juice that had been processed from citrus fruits treated with a single broadcast application of the thiazopyr EC formulation at 5x the proposed maximum seasonal rate. The residue data submitted for citrus are not adequate to support the proposed uses. Additional citrus processing data residues in citrus oil is currently in review (Barcode DP D203667). Residue data are still needed for citrus molasses. The need for additional residue data is dependent on the decisions of the HED Metabolism Committee.

8b. The available data indicate that residues of thiazopyr and its metabolites convertible to SAA and AA are not likely to concentrate in the meal, hulls, and crude oil resulting from the processing of cottonseed treated with a single preplant incorporated soil application of the thiazopyr EC formulation at 5x the proposed maximum seasonal rate. Based on these data, it is expected that thiazopyr residues of concern are also not likely to concentrate in soapstock and refined oil. The need for additional residue data is dependent on the decisions of the HED Metabolism Committee.

9. No feeding studies are submitted in this petition, PP#3F4147. The petitioner previously requested a waiver of feeding studies with thiazopyr in their petition for temporary tolerances (PP#2G4122). In the review of this temporary tolerance petition (J. Garbus, 6/2/93), CBTS concluded that the proposed uses would result in sufficiently low potential residues of thiazopyr and its metabolites of concern that feeding studies or temporary tolerances for meat, milk, poultry, and eggs would not be required. Based on the residue data submitted in this petition, potential residues in feed items could be sufficiently low to obviate the need for feeding studies or for tolerances in meat, milk, poultry, and eggs. However, since the CBTS has determined that cotton gin byproducts will be considered an animal feedstuff, then CBTS must review the additional residue data (requested above) from cotton gin byproducts before a decision on the need for feeding studies for ruminants can be made. CBTS would not be opposed to the establishment of tolerances with expiration dates based on the data requirements at the time

of this submission. The petitioner would have additional time to generate field residue data for cotton gin byproducts, propose a tolerance, and, if necessary, provide feeding studies in ruminants. Cotton gin byproducts is not a poultry feed item.

Likewise any decision on the need for enforcement methodology for residues of thiazopyr (and/or additional metabolites as determined by the HED Metabolism Committee) in livestock meat, meat byproducts, milk, and eggs will be determined after the additional residue data are submitted by the petitioner and subsequently reviewed by CBTS.

10. There are no CODEX, Canadian, or Mexican limits established for thiazopyr. Therefore, no compatability problem exists.

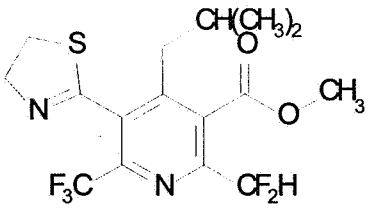
Recommendations:

CBTS recommends against the establishment of permanent tolerances for residues of the selective herbicide thiazopyr [3-pyridine carboxylic acid, 2-(difluoromethyl)-5-(4,5-dihydro-2-thiazolyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-, methyl ester] and its metabolites determined as 3-pyridine carboxylic acid, 5-(aminocarbonyl)-2-(difluoromethyl)-4-(2-methylpropyl)-6-trifluoromethyl-, methyl ester and 3-pyridine carboxylic acid, 2-(difluoromethyl)-4-(2-methylpropyl)-5-(((2-sulfoethyl)amino)carbonyl)-6-trifluoromethyl and expressed as parent equivalents in/on citrus, whole fruit, (0.05 ppm, group tolerance), cottonseed (0.05 ppm), and cotton, forage (0.2 ppm), because of **conclusions 1, 2a, 2b, 3b, 4a, 4b, 5, 6a, 6b, 6c, 7a, 7b, 7c, 8a, 8b, and 9.**

Detailed Considerations:

61-1. Product Identity and Disclosure of Ingredients

3-Pyridinecarboxylic acid, 2-(difluoromethyl)-5-(4,5-dihydro-2-thiazolyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-, methyl ester is the herbicide technical grade active ingredient (TGAI) in the 93% technical produced by Monsanto.



Other identifying characteristics and codes are:

Empirical Formula:	$C_{16}H_{17}F_5N_2O_2S_1$
Molecular Weight:	396.4
CAS Registry No.:	117718-60-2
EPA File Symbol No.:	524-UAE
Proposed Chemical Name:	thiazopyr
Company Product No.:	MON 13200

Monsanto submitted product identity data (MRID #42619701) and a Confidential Statement of Formula (CSF) dated 12/11/92 for the technical. (See Confidential Appendix for disclosure of the ingredients in the technical product.)

The submitted data are adequate for Guideline 61-1. No additional data are needed.

61-2. Description of Starting Materials and Manufacturing Process

Monsanto submitted (MRID #42619701) information concerning the suppliers and specifications of the starting materials along with a detailed description of the manufacturing process for the TGAI. Also included in the submission were the chemical equations for each step of the batch process, and details of purification and quality control measures taken to assure the consistent composition of the product. (See Confidential Appendix.)

Additional data are needed for Guideline 61-2 in regard to the starting material [redacted] (See Confidential Appendix.)

61-3. Discussion of Formation of Impurities

Monsanto submitted (MRID #42619701) a discussion of impurities formed during the production of the TGAI. The discussion included confirmed and theoretical impurities formed as a result of carryover of the starting materials and their impurities, intended and side reactions occurring during the manufacturing process, and cross-contamination impurities from the use of the manufacturing equipment for the manufacture of other products. (See Confidential Appendix.)

Additional data are needed for Guideline 61-3. The petitioner must explain the connection between the production of dithipyr and the production of thiazopyr. (See Confidential Appendix.)

62-1. Preliminary Analysis

Monsanto provided (MRID #42619702) the preliminary analysis data for five pilot plant batches of the technical. In addition, Monsanto has stated that no analyses for nitrosamines were performed because the conditions of the manufacturing process are not favorable for the formation of nitrosamines. (See Confidential Appendix.)

The submitted data are adequate for Guideline 62-1. No additional data are needed for this petition review for the proposed uses on cotton and citrus.

However, if a Section 3 registration is established for thiazopyr uses on cotton and citrus, and when the commercial production begins, the petitioner must provide the Agency with 5 batch analyses of the TGAI and its impuriites. These data must be provided within a reasonable period after the commercial process is operating.

62-2. Certification of Limits

Monsanto submitted data (MRID #42619702) and a CSF dated 12/11/92 which establish certified limits for the TGAI. (See Confidential Appendix.)

The submitted data are not adequate for Guideline 62-1. The nominal concentration listed for the active ingredient in MRID#

246197-02 does not agree with the nominal concentration on the CSF dated 12/11/92. Please submit the correct value.

62-3. Enforcement Analytical Methods

Monsanto submitted (MRID #42619702) a gas chromatography (GC) method (AM-152-92A) for the determination of thiazopyr (TGAI) in the technical. Standards and samples are prepared in toluene with the internal standard pentadecane, and injected onto a 30-m DB-5 column. The GC is equipped with a flame ionization detector (FID) and a cool on-column injector. The thiazopyr concentration is quantitated using the peak area response of the internal standard and multilevel calibration standards. The submitted validation data are presented in the following table.

Component	Precision [a]		Accuracy	
	Fortified levels	% Coeff. Variation	Fortified levels	% Recovery
thiazopyr	66-99%	0.52	15-51%	100

[a] Based on 6 assays; triplicate injections of duplicate sample weights.

Monsanto's enforcement analytical methods for the determination of the impurities of thiazopyr are discussed in the Confidential Appendix.

The submitted data are adequate for Guideline 62-3. No additional data are needed.

63-2 to 63-20. Physical and Chemical Characteristics

Data submitted by Monsanto (MRID #42619703) regarding the physical and chemical characteristics of the TGAI and PAI (pure active ingredient) are presented in Table 1. Data for the TGAI and PAI are required for GLN's 63-2 through 63-13.

Note: Some data from studies concerning storage stability and corrosion characteristics (GLN's 63-17 and 63-20) were submitted; the registrant indicated that additional data for these GLN's would be forthcoming by January 1993. This reviewer has not

received these data up to this time. This data is not needed for the TGAI.

Physical and chemical properties of the 93% technical (EPA File Symbol No. 524-UAE) purified active ingredient (98.1-99.9% PAI), and technical grade of the active ingredient (97.8% TGAI).

Guidelines Reference No., Name of Property		Description [Method] (Test Substance)
63-2	Color	white; Munsell color N 9.25/84.2% R [ASTM D-1535 80] (PAI) light tan; Munsell color 5Y(9/1) [ASTM D-1535 80] (TGAI)
63-3	Physical state	powdered solid (PAI) granular solid (TGAI)
63-4	Odor	slightly sulfurous (PAI) sulfurous (TGAI)
63-5	Melting point	79.0-80.3 C [capillary method; OECD Sect. 1, No. 102] (PAI) 77.3-79.1 C [capillary method; OECD Sect. 1, No. 102] (TGAI)
63-6	Boiling point	N/A; TGAI is a solid
63-7	Density, bulk density, or specific gravity	1.416 g/mL at ambient temperature [pycnometer] (PAI) 1.377 g/mL at 25 C [pycnometer] (TGAI)
63-8	Solubility	Solvent Solubility(g/100mL @20 C water 2.331×10^{-4} (PAI) water 2.49×10^{-4} (TGAI) methanol 28.7 (TGAI) hexane 3.06 (TGAI) [shake flask-method]

11

Guidelines Reference No., Name of Property		Description [Method] (Test Substance)
63-9	Vapor pressure	2.04 x 10^{-6} mm Hg at 25 C [gas-saturation method; OECD No. 104] (PAI)
63-10	Dissociation constant	N/A; does not readily dissociate
63-11	Octanol/water partition coefficient	7729 at ambient temperature; Log K_{ow} = 3.89 [shake-flask method; OECD No. 107] (PAI)
63-12	pH	5.72 at 24.5 C; 1% aqueous slurry [pH meter] (PAI) 5.39 at 25 C; 1% aqueous slurry [pH meter] (TGAI)
63-13	Stability	stable at 0 C for 48 hours and 54 C for 14 days; 19.8% loss of the active ingredient after 24 hours exposure to sunlight; insignificant weight loss of ca. 7.33 x 10^{-4} after 24 hours exposure to zinc coupons (TGAI)
63-14	Oxidizing/ reducing action	does not act as an oxidizing or reducing agent in the presence of zinc, potassium permanganate, water, or monoammonium phosphate (TGAI)
63-15	Flammability	flash point = 390 F [ASTM D-92] (TGAI)
63-16	Explodability	no exothermic activity at 25-550 C [differential scanning calorimetry; ASTM E-537 and ASTM E-92] (TGAI)
63-17	Storage stability	stable for 6 months at ambient conditions packaged in double-lined low density polyethylene bags; 1-year study still in progress (TGAI)
63-18	Viscosity	N/A; product is a solid
63-19	Miscibility	N/A; product is a solid

Guidelines Reference No., Name of Property		Description [Method] (Test Substance)
63-20	Corrosion characteristics	no package corrosion after 6 months storage at ambient conditions in double-lined low density polyethylene bags; (TGAI)

The submitted data are adequate for Guideline 63-1. No additional data are needed.

Proposed Uses:

Citrus

The 2 lb a.i./gal EC formulation (22.3 % a.i.) is proposed for preemergence surface applications to citrus crops as a single treatment at 1.0-1.5 lb a.i./A, for two sequential applications at 0.125-0.375 lb a.i./A/application with a 2- to 3-month retreatment interval, or for up to three sequential applications at 0.125-0.25 lb a.i./A/application with a 2- to 3-month retreatment interval. A maximum of 2 lb a.i./A may be applied per year. Ground applications are to be made in volumes from 20 to 50 gal/A with a minimum of 20 gal/A. Application may be made alone or as a tank mix with other herbicides. A 90-day PHI is proposed.

No feeding or grazing restrictions are proposed for cover crops in treated citrus orchards. A revised Section B must be submitted prohibiting the feeding or grazing of cover crops in treated citrus orchards. Alternatively, residue data and proposed tolerances can be submitted for grass cover crops in treated citrus orchards.

Cotton

The 2 lb a.i./gal EC formulation (22.3% a.i.) is proposed for use in all states except AZ and CA for a single treatment or for up to two sequential treatments as preplant incorporated or preemergence surface applications to cotton at 0.125-0.375 lb

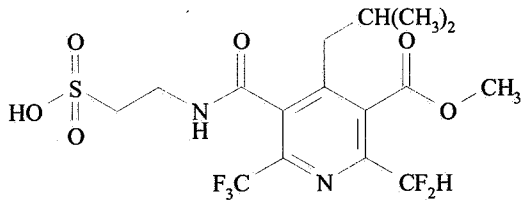
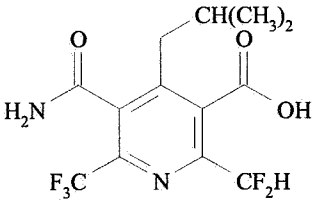
a.i./A/application. A maximum of 0.375 lb a.i./A may be applied per year. Use is limited to AZ and CA for preplant incorporated application to cotton at 0.375-0.5 lb a.i./A/application with a maximum rate of 0.5 lb a.i./A/year. Application may also be made in the fall and winter up to 180 days prior to planting. Ground applications are to be made in volumes from 20 to 50 gal/A with a minimum of 20 gal/A. Application may be made alone or as a tank mix with other herbicides. Feeding and grazing restrictions are proposed. A 9-month plant-back interval for all crops except cotton and an 18-month plant-back interval for grain sorghum, corn, and wheat are proposed.

The 18-month plant-back is not practical. Rotational residue data for these crops must be submitted for review to determine if tolerances for thiazopyr residues must be established. (See Rotational Crops section, this memo, for details) [Note: The data responding to this deficiency have been received and are currently in review (Barcode DP D198931)].

Nature of the Residue in Plants and Animals

In the review of the temporary tolerance petition (PP#2G4122, J. Garbus, 6/2/93), CBTS concluded that thiazopyr undergoes extensive and rapid degradation in plants and animals to a large number of polar metabolites, each present at low levels (<10% of TRR). The parent and most of the identified metabolites share a common moiety, 2-difluoromethyl-4-(2-methylpropyl)-6-trifluoromethyl pyridine carboxylate. The residues of concern are thiazopyr and its metabolites that can be converted to the sulfonic diacid (SAA), 2-difluoromethyl-4-(2-methylpropyl)-5-[(2-sulfoethyl)aminocarbonyl]-6-trifluoromethyl-3-pyridine carboxylic acid, methyl ester, and the amide acid (AA), 2-difluoromethyl-4-(2-methylpropyl)-5-aminocarbonyl-6-trifluoromethyl-3-pyridine carboxylic acid.

Chemical structures of **SAA** and **AA**.

	
SAA: 2-difluoromethyl-4-(2-methylpropyl)-5-[(2-sulfoethyl)aminocarbonyl]-6-trifluoromethyl-3-pyridine carboxylic acid, methyl ester	**AA:** 2-difluoromethyl-4-(2-methylpropyl)-5-aminocarbonyl-6-trifluoromethyl-3-pyridine carboxylic acid

Plant Metabolism Studies: [These studies were reviewed for the first time by J. Garbus (See memo of 06/02/93)].

Citrus: (MRID #422755-05)

Lemon trees grown in 5 gallon containers in a sandy loam soil were treated with thiazopyr (labelled at the C4 position of the pyridine moiety, specific activity: 28 mCi/mmol) at rates of 2 lb a.i./A (13 trees treated) and 4 lb a.i./A (26 trees treated). Foliage and immature fruit were collected at 133 and 124 days, respectively, after treatment, and mature fruits were harvested 236 days after treatment. Only the mature fruit were analyzed and fractionated for determination of residues.

The mature whole lemon fruit was divided into three parts; rind, pulp, and juice. The solid matrices were macerated, combusted and radioactivity determined by liquid scintillation counting; the lemon juice was counted directly. The following results were for both a 2 lb a.i./A and a 4 lb a.i./A treatments:

Plant Portion	Uptake% of Applied Radioactivity	% TRR	ppm, (Thiazopyr equivalents)
2 lb a.i./A			

rind	0.14	67	0.05
pulp	0.03	13	0.01
juice	0.04	20	0.01
fruit	0.21	100	0.02
4 lb a.i./A			
rind	0.13	68	
pulp	0.02	11	
juice	0.04	21	
fruit	0.19	100	

For the identification and characterization of metabolites, solid matrices (from the 4 lb a.i./A treatment) were extracted with acetonitrile/water and filtered (96-97% of the total radioactivity solvent soluble). The extracts were partitioned with methylene chloride into organic and aqueous phases. Organic phases were taken to dryness, dissolved in methanol for analyses by high pressure liquid chromatography (HPLC); aqueous phases were filtered, concentrated, and methylated, and analyzed by HPLC.

With the lemon rind 17% of the initial radioactivity was extracted into the organic phase; the aqueous phase contained 66% of the initial radioactivity. With the lemon pulp 45% of the initial radioactivity was extracted into the organic phase; the aqueous phase contained 52% of the initial radioactivity. With the lemon juice 26% of the initial radioactivity was extracted into the organic phase; the aqueous phase contained 71% of the initial radioactivity. The following table shows the distribution and identification of thiazopyr residues. (See Metabolite identification table, p. 19, this memo, for compound structures and numbers.)

Quantification of Thiazopyr and Its Metabolites in Lemons (ppb in parent equivalents) (4 lb a.i./A treatment)								
Chemical Residue	Rind		Pulp		Juice		Whole Fruit	
	% TRR	ppb	% TRR	ppb	% TRR	ppb	% TRR	ppb
thiazopyr (parent recovered)	0.22	0.31	ND	ND	ND	ND	0.22	0.05
Metabolite No.								
3	0.07	0.09	ND	ND	ND	ND	0.07	0.02
4	2.7	3.8	1.3	1.7	1.3	1.1	5.3	2.0
5	0.09	0.13	ND	ND	ND	ND	0.09	0.03
6	1.1	1.5	0.03	0.04	0.05	0.04	1.2	0.43
7	6.3	8.8	0.34	0.46	0.88	0.71	7.5	2.8
8	0.13	0.18	<0.02	<0.03	ND	ND	0.13	0.05
10	3.6	5.0	0.39	0.52	0.65	0.53	4.6	1.7
11	3.3	4.7	0.28	0.37	0.60	0.49	4.2	1.6
15	5.9	8.33	2.1	2.8	2.4	1.9	10	3.9
16	1.0	1.4	0.74	0.99	0.95	0.77	2.7	1.0
19	4.3	6.1	0.40	0.54	0.69	0.56	5.4	2.0
20	5.4	7.6	0.78	1.0	0.94	0.77	7.1	2.7

Total % TRR Identified /Quantified	34	--	6.3	--	8.4	--	49	--
% TRR Contained	68	--	13	--	19	--	100	--

ND: Not detected above LOD

81

The low C14 thiazopyr activity in this metabolism study suggests that thiazopyr metabolites containing the intact pyridine ring undergo negligible translocation from the soil to fruit. This study also shows that under actual field conditions at the maximum proposed label rate of 2.0 lb a.i./A, residues of thiazpoyr and its metabolites would be undetectable (<0.05 ppm). Mon 13200 is relatively nonpolar and is water-insoluble. Most of the metabolites in the lemon tissues were paritioned into the aqueous layer. Several metabolites (#15 and #16) were partially distributed in the organic and the aqueous layers. The levels of organic-soluble residues (MON-13200, #3, #5, #6, and #8) totaled <4% TRR.

Cotton: (MRID# 422755-06)

Cotton plants, grown in sandy loam soil in individual greenhouse pots. The plants were divided into 4 treatment groups: untreated, treated with soil incorporation with unlabeled thiazopyr, soil incorporation treated with thiazopyr labeled in the pyridine or thiazoline rings, surface treatment with thiazopyr labeled in the pyridine or thiazoline rings. The pesticide was applied to each pot in an amount equivalent to 0.125 lbs a.i./A [Higher rates in the greenhouse caused phytotoxicity; the proposed maximum seasonal label rate is 0.375 lb a.i./A (0.5 lb a.i./A in AZ and CA)]. Cotton foliage was harvested at 56 days; cottonseed and cotton plant hay at 249 days after treatment. Residue levels were determined in plant matrices by combustion and the captured radioactivity was determined by LSC. Uptake of C14 thiazopyr was approximately 0.5% of the applied radioactivity. Residue levels for both ring labels were similar for both application methods. The results were as follows:

Matrix	Percentage of applied radioactivity	ppm, (Thiazopyr equivalents)
foliage (56 days)	0.20 - 0.41	0.063 - 0.083
hay (249 days)	0.33 - 0.45	0.037 - 0.039

cottonseed (249 days)	0.0 - 0.02	0.001 - 0.002

For the identification and characterization of metabolites, treated cotton foliage harvested at 59 days was extracted, and partitioned into organic and aqueous phases. Organic phases were taken to dryness, dissolved in methanol and subjected to HPLC; aqueous phases were filtered, concentrated, subjected to methylation and to HPLC. The very low level of C14 radioacitivity in cottonseed prohibited extraction and isolation of metabolites. The metabolism of thiazopyr in cotton was extensive, and parent remained in crop tissues. In a representative experiment, 93.1% of the total radioactivity of the leaves was extractable. The organic extract had 42% of the initial radioactivity, and of this, 13.2% was resolved into 11 discrete peaks. The aqueous phase had 57.8% of the initial radioactivity. HPLC resolved 29% of the initial extract radioactivity into 26 discernable peaks. In all, of over 40 peaks present, nine significant metaboites were identified and characterized. (See Metabolite identification table, p. 19, this memo, for compound structures and numbers). Recoveries of the identified peaks ranged from 0.1% to 9.4% of the TRR.

Quantification of Thiazopyr and Its Metabolites in Cotton (0.125 lb a.i./A treatment; C14-pyridine label)		
Chemical Residue	Forage (56 days)	
	% TRR	ppb
thiazopyr (parent recovered)	2.1	1.7
Metabolite No.		
3	7.2	6.0
5	3.1	2.6
6	7.1	5.9

7	7.6	6.3
8	3.0	2.5
10	2.2	1.8
11	9.4	7.8
18	6.1	5.1
Total % TRR Identified / Quantified	48	--
% TRR Contained	93	--

ND: Not detected above LOD

In summary, thiazopyr undergoes extensive and rapid degradation in plants to a large number of polar metabolites, all found at low levels (<10% of the TRR). Major routes of metabolism include sulfur oxidation, thiazoline ring opening and methyl ester hydroysis, and tranformation of the isobutyl side chain. About 30 metabolites have been positively or tentatively identified. The complete breakdown of thiazopyr to many low-level polar metabolities closely resembles the metabolic pathways observed in other crops and soil metabolism. For example in cotton, 8 metabolites are found, 13 in peanuts, and 12 in lemons. (See the comparsion table of metabolic pathways following the discussion of the metabolic pathways in the lactating goat and the laying hen).

The submitted metabolic data for plants are adequate. No additional data are needed for the proposed uses on cotton and citrus.

Animal Metabolism Studies: [These studies were reviewed for the first time by J. Garbus (See memo of 06/02/93)].

Lactating Goat: (MRID# 422755-07)

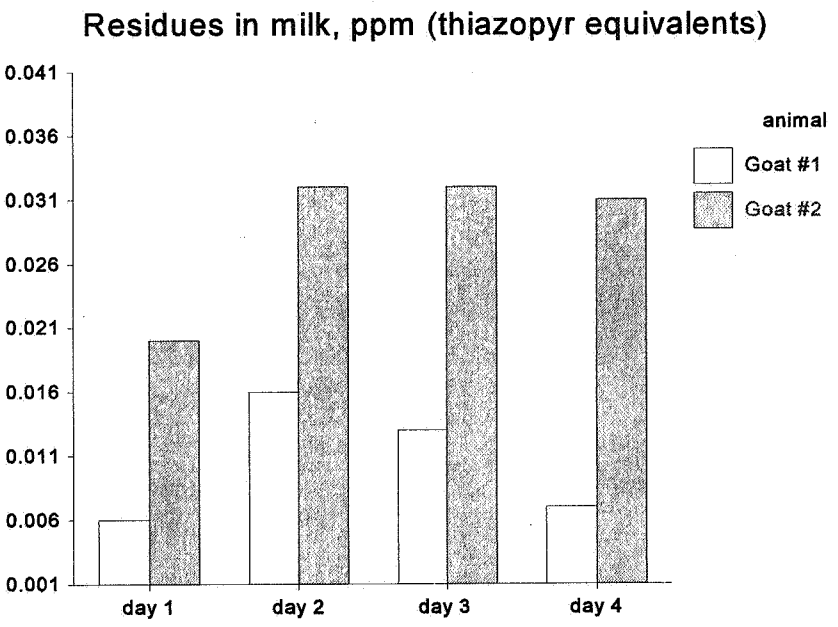
Two lactating goats were dosed orally for 4 consecutive days with 19.3 mg of C14/C13 thiazopyr (labeled with 13C and 14C in the C-4 position of the pyridine ring; specific activity, 16.1 mCi/mmole). One goat dosed with a placebo served as the control. The high dose goat is labelled goat #2 in this memo. The dosage administered to the animals was equivalent to 12 and 21 ppm in the diet, based on actual feed consumption. After four days the animals were sacrificed, aliquots of tissues, feces, milk, and urine were combusted and counted for radioactivity by LSC. Other aliquots were extracted with acetonitrile/water, partitioned, and after sample cleanup were analyzed by HPLC with radiometric detection to identify metabolites. (See Metabolite identification table, p. 19, this memo, for compound strutures and numbers).

% Total Recovery of Radioactivity		
Matrix	Goat #1	Goat #2

blood	<0.01	<0.01
feces	59.95	54.44
milk	0.06	0.12
tissues	0.41	1.86
urine	28.99	34.53
Total	89.41	90.45

Residues in Tissues, Fluids, and Milk (Percentages of dose, thiazopyr equivalents)				
Matrix	Goat #1		Goat #2	
	% of dose	ppm	% of dose	ppm
liver	0.30	0.193	0.48	0.375
kidney	<0.01	0.023	0.02	0.112
renal fat	<0.01	0.013	0.02	0.034
omental fat	<0.01	0.011	0.02	0.026
muscle	0.06	0.006	0.02	0.013
milk	0.06	0.02	0.12	0.013
bile	0.02	0.477	0.20	6.629

Based upon the following chart, it appears that the radiolabeled residues reached a plateau in milk by day 3.


Residues in milk, ppm (thiazopyr equivalents)
0.041
0.036
0.031
0.026
0.021
0.016
0.011
0.006
0.001
day 1
day 2
day 3
day 4
animal
Goat #1
Goat #2

The tissues of goat #2 were extracted and the extracts analyzed by HPLC. Total accountabilities ranged from 98 to 100, except for omental fat at 113%.

Thiazopyr and Its Metabolites Found in Tissues and Milk in Goat #2 (% of tissue radioactivity: ppm, thiazopyr equivalents)												
No.	liver		kidney		renal fat		omental fat		muscle		milk	
thiazopyr	1.9	0.007	-	ND	18	0.006	23	0.006	8.9	0.001	-	ND
2	-	ND	-	ND	-	-	-	-	9.8	0.001	-	ND
3	5.9	0.022	-	ND	8.5	0.003	12	0.003	-	ND	9.2	0.003
4	4.1	0.015	-	ND	-	-	-	-	-	ND	9.2	0.003
5	19	0.071	-	ND	7.8	0.003	11	0.003	-	ND	-	ND
6	-	ND	-	ND	6.2	0.002	13	0.003	-	ND	-	ND
8	-	ND	-	ND	9.2	0.003	21	0.005	-	ND	-	ND
14	3.7	0.014	-	ND	-	-	-	-	-	ND		ND
24	12	0.045	21	0.024	-	-	-	-	7.8	0.001	-	ND
25	6.0	0.023	-	ND	-	-	-	-	-	ND	-	ND
26	-	ND	31	0.035	-	-	-	-	24	0.003	44	0.015
29	-	ND	-	ND	-	-	-	-	10	0.001	-	ND
unext.	14	0.053	6.8	0.008	3.5	0.001	4.1	0.001	19	0.002	8.6	0.003
undefined	33	0.125	41	0.046	47	0.016	20	0.005	40	0.005	29	0.004

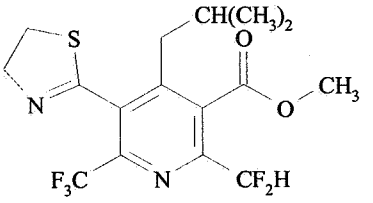
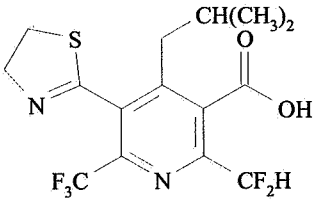
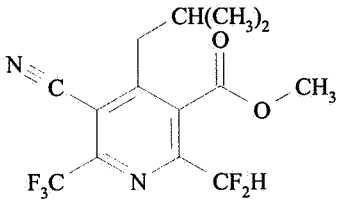
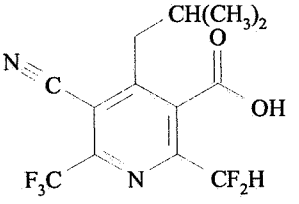
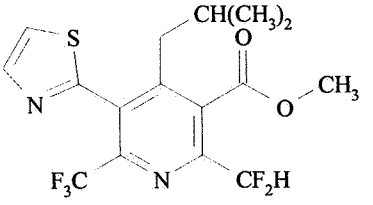
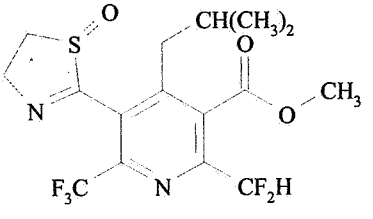
ND: not detected (Limit of detection: <0.0019 ppm)

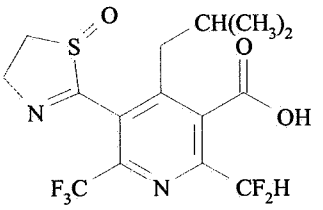
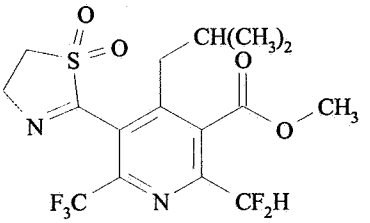
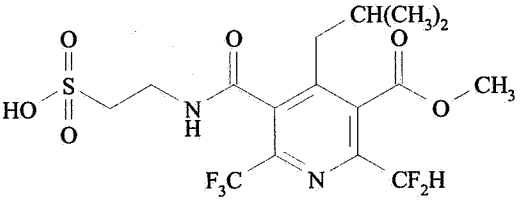
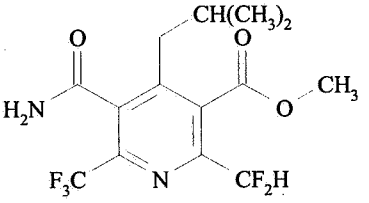
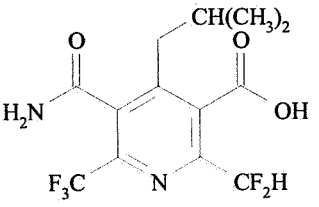
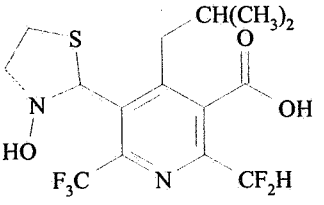
Unext.: unextracted radioactivity

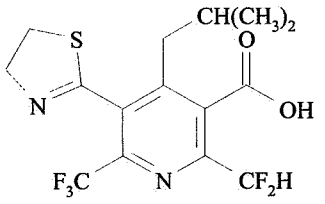
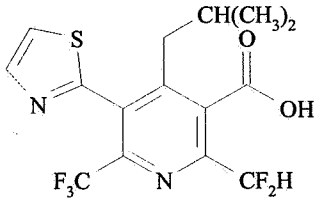
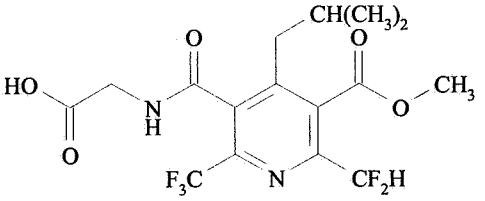
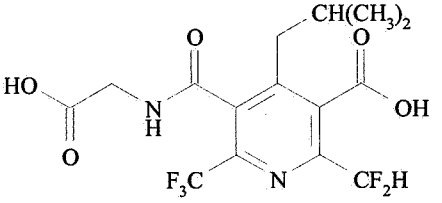
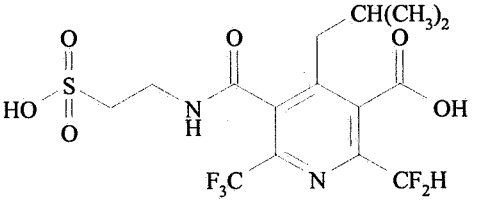
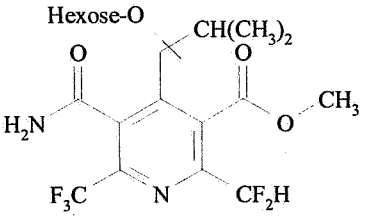
Undefined: Residues undefined/residues lost in extraction interfaces

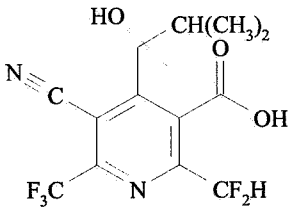
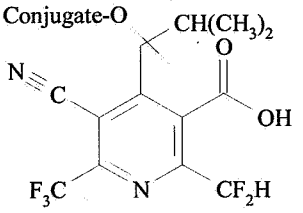
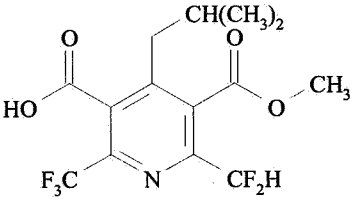
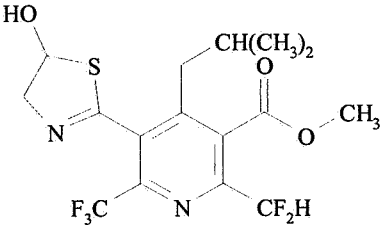
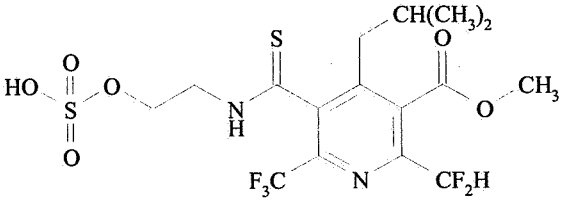
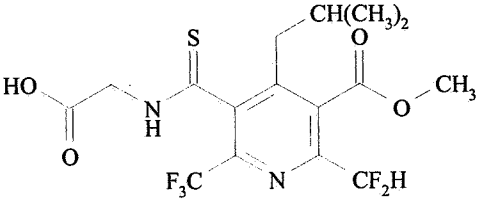
25

Simplified Names/Chemical Structures of Thiazopyr and its Metabolites.

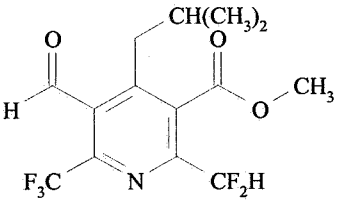
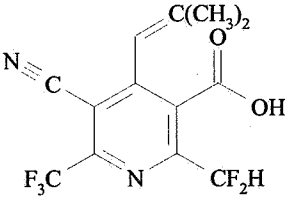
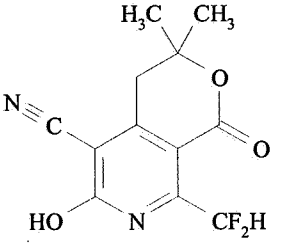
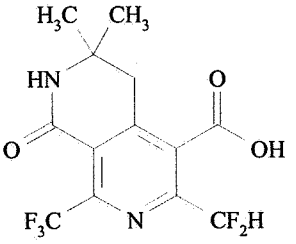
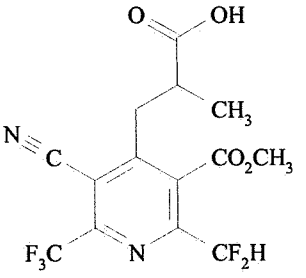
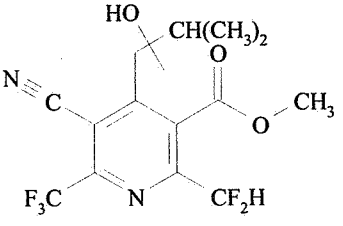
Compound Number	Simplified Name [a]	Structure
1	thiazopyr; MON-13200	
2	monoacid	
3	nitrile ester	
4	nitrile acid	
5	thiazole ester	
6	sulfoxide ester	

Compound Number	Simplified Name [a]	Structure
7	sulfoxide acid	
8	sulfone ester	
9	sulfonic acid ester	
10	amide ester	
11	amide acid	
12	NA [b]	

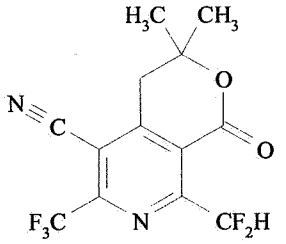
Compound Number	Simplified Name [a]	Structure
13	NA	
14	thiazole acid	
15	glycine amide ester	
16	glycine amide acid	
17	sulfonic diacid	
18	amide ester, hexose conjugate	

Compound Number	Simplified Name [a]	Structure
19	hydroxy nitrile acid	
20	nitrile acid conjugate	
21	NA	
22	NA	
23	sulfate ester	
24	glycine thioamide ester	

29

Compound Number	Simplified Name [a]	Structure
25	aldehyde ester	
26	unsaturated nitrile acid	
27	NA	
28	NA	
29	nitrile acid ester	
30	hydroxy nitrile ester	

30

Compound Number	Simplified Name [a]	Structure
31	nitrile lactone	

[a] Assigned by Monsanto for ease of discussion of metabolism studies.

[b] NA: Not assigned a simplified name by company.

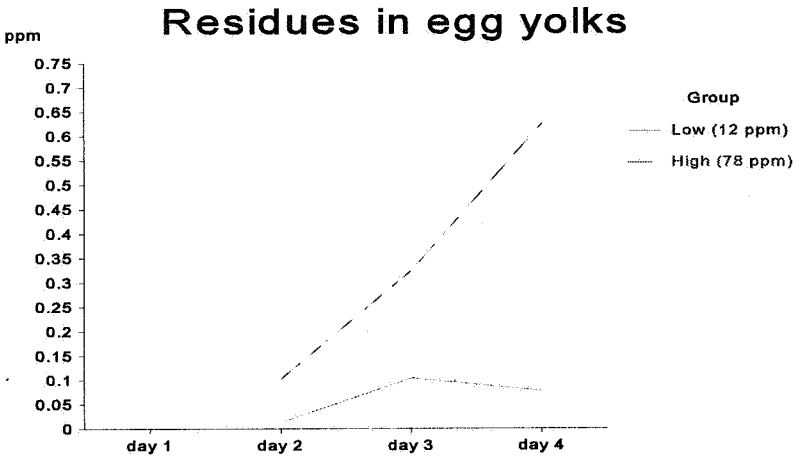
The metabolism of thiazopyr in a lactating ruminant is similar to that found in plants in that thiazopyr undergoes degradation to a large number of polar metabolites, all found at low levels. Milk contained 3 identifiable metabolites, liver had 7 metabolites including the parent, kidney had 2, and renal and omental fat had 5, and muscle had 5. In all, parent plus 11 individual metabolites were identified in goat tissues and milk. Of these, 6 were identical to plant metabolites and 2 others were very similar. The major residues in ruminant muscle and milk are thiazopyr and its unsaturated nitrile acid (compound #26). The major residues in fat are thiazopyr and its sulfone ester metabolite (compound #8). (See the comparsion table of metabolic pathways (thiazopyr in plants, animals, and soil) following the discussion of the metabolic pathway in poultry).

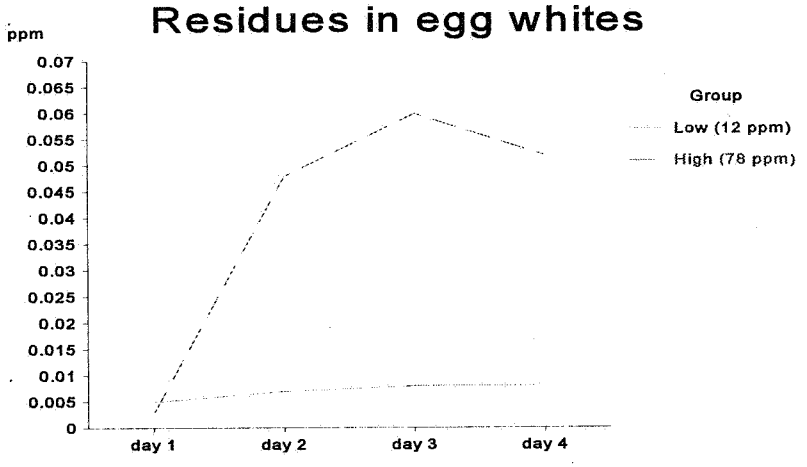
Poultry: (MRID# 422755-08)

Laying hens were dosed orally for 4 days with either 1.3 mg (Group #'s 6 and 7) or 10.4 mg (Group #4) of labeled thiazopyr (14C/13C in the C-4 position of the pyridine ring; specific activity either 15.7, 16.14 or 7.93 mCi/mol, depending upon the particular lot used for dosing). The administered dosages based on actual feed consumption, was equivalent to 12 and 78 ppm in the diet in the low and high dose diet, respectively. After four days the animals were sacrificed, aliquots of tissues, excreta, and eggs were combusted and counted for radioactivity by LSC. Other aliquots were extracted with acetonitrile/water, partitioned, and analyzed after sample cleanup by HPLC with radiometric detection to identify metabolites. (See Metabolite identification table, p. 19, this memo, for compound structures and numbers).

Residues in Poultry Tissues and Excreta (Percentages of dose, thiazopyr equivalents)						
Matrix	Group #6, low dose (12 ppm)		Group #7, low dose (12 ppm)		Group #4. high dose (78 ppm)	
	% of dose	ppm	% of dose	ppm	% of dose	ppm
liver	0.17	0.222	0.24	0.298	0.12	1.112
kidney	<0.01	0.047	0.01	0.052	0.01	0.501
abdominal fat	0.03	0.123	0.06	0.173	0.09	1.417
skin with fat	0.03	0.049	0.08	0.097	0.05	0.488
muscle, thigh	0.01	0.010	0.01	0.008	0.02	0.086
muscle, breast	0.01	0.004	0.01	0.005	0.01	0.033
egg yolk	0.03	0.124	0.04	0.132	0.03	1.06
egg white	0.02	0.027	0.02	0.026	0.02	0.163
blood	<0.01	0.016	<0.01	0.021	<0.01	0.097
GI tract	0.19	0.134	0.21	0.153	0.19	0.933
excreta	94.31	-	90.08	-	92.73	-
Totals	95	-	91	-	93	-

Residues in eggs over the collection period are shown in the charts below. As shown by the charts, the residues in the low dose groups plateaued by day 4. In the high dose birds the residues had not plateaued by day 4. As normal egg formation requires 7 days, the low dose may not really be a plateau, but a variation of residues from day to day.





Tissues of group 3 hens were extracted and the extracts subjected to HPLC. Total accountabilities ranged from 92 to 114% (ave: 104%).

Thiazopyr and Its Metabolites Found in Tissues and Eggs in Poultry Dosed Orally at 12 ppm/day (Groups #'s 6 and 7) (% of tissue radioactivity: ppm, thiazopyr equivalents)												
No.	liver		kidney		skin with fat		abdominal fat		muscle		egg yolk	
thiazopyr	0.5	0.002	-	ND	2.7	0.003	2.7	0.005	1.5	0.0001	2.0	0.002
3	1.4	0.004	2.3	0.001	59	0.057	69	0.119	16	0.0011	24	0.018
5	6.7	0.020	-	ND	7.6	0.007	7.9	0.014	1.9	0.0001	2.8	0.002
29	41	0.122	57	0.029	4.2	0.004	-	-	9.9	0.0007	11	0.008
31	-	-	-	-	3.4	0.003	7.0	0.012	3.2	0.0002	-	-
10	2.5	0.008	4.2	0.002	-	-	-	-	1.4	0.0001	-	-
26	-	-	-	-	-	-	-	-	-	-	7.7	0.006
unext.	23	0.068	30	0.015	7.2	0.007	8.6	0.015	19	0.0013	31	0.023
undefined	25	0.075	9	0.005	16	0.016	5	0.009	47	0.003	22	0.016

ND: not detected (Limit of detection: <0.0019 ppm)
Unext.: unextracted radioactivity
Undefined: Residues undefined/residues lost in extraction interfaces

Comparsion chart of metabolic pathways for plants and animals.

Compd. No.	aerobic soil	anaerobic soil	cotton/peanut	citrus	rotational crops	rat	lactating goat	laying hen	bluegill sunfish
1:Thiazopyr	✓	✓	✓	✓	✓	✓	✓	✓	✓
2	✓	✓					✓		
3	✓	✓	✓	✓	✓	✓	✓	✓	✓
4	✓			✓	✓		✓		✓
5	✓	✓	✓	✓	✓	✓	✓	✓	✓
6	✓	✓	✓	✓	✓		✓		
7	✓	✓	✓	✓	✓				
8	✓		✓	✓	✓		✓		✓
9	✓	✓	✓ (peanut only)		✓				
10	✓	✓	✓	✓	✓			✓	✓
11	✓	✓	✓	✓	✓				
12		✓							
13		✓							
14			✓(peanut only)			✓	✓		
15			✓(peanut only)	✓					
16			✓(peanut only)	✓	✓				
17			✓(peanut only)						
18			✓						
19				✓					
20				✓					
21					✓				

93

Comparsion chart of metabolic pathways for plants and animals.

22						✓			
23						✓		✓	
24						✓	✓		✓
25						✓	✓		
26						✓	✓	✓	
27						✓			
28						✓			
29							✓	✓	
30								✓	
31								✓	

The metabolism of thiazopyr in laying hens is similar to that found in plants in that thiazopyr undergoes degradation to a large number of polar metabolites, all found at low levels. Liver had 5 metabolites including the parent(4 of which were found as plant metabolites, while kidney had 3 (2 of which are plant metabolites). Egg yolk had 5 (3 of which are plant metabolites) and muscle had 6 (4 of which are plant metabolites). In all, 8 individual metabolites were identified in hen tissue, eggs, and excreta. Of these, 4 were identical to plant metabolites. The major terminal residues in poultry are thizaopyr and its nitrile acid ester metabolite (compound #29).

CBTS considers the metabolism of thiazopyr in plants and animal as adequately understood. The petitioner has proposed that tolerances be established for thiazopyr those metabolites that can be converted to two common entities, referred to as the sulfonic diacid (SAA) and the amide acid (AA). The residues to be regulated will be determined by the HED Metabolism Committee.

Residue Analytical Methods

Tolerance enforcement method:

In the review of the temporary tolerance petition (PP#2G4122, J. Garbus, 6/2/93), CBTS noted that the residue analytical method proposed with the petition (Method RES-017-91) appeared to be suitable for generating the residue data reported as the result of field trials with thiazopyr. However, CBTS considered the method to be too complex and lengthy for use as an enforcement method, but was forwarded to the Beltsville laboratory (ACL) for judgement. ACL concurred.

Monsanto Company (MRID #42619712) has now submitted a simplified proposed enforcement method, Method RES-041-92, and an independent laboratory validation data for the determination of thiazopyr residues of concern in/on citrus and cotton raw agricultural commodities.

In Method RES-017-91, thiazopyr and its major metabolites (nitrile ester, #3; sulfoxide ester, #6 ; sulfoxide acid, #7; amide ester, AE (#10); and amide acid, AA (#11) are transformed into sulfonic diacid (SAA) and amide acid (AA) chemophores. The AA chemophore is derivatized to its methyl ester (AE) and then

quantitated. The petitioner notes that the AA chemophore metabolites account for the largest portion of the metabolite profile, and based on endogenous validations and metabolism studies, the concentration of the AA chemophore is approximately equal to or greater than the SAA chemophore in cotton and citrus. Also, the petitioner asserts that in cotton and citrus RAC studies, no residues of either chemophore were found to be greater than the lower limit of method validation (LLOMV) which is set at 0.025 ppm. Therefore, a rapid screening procedure for the AA chemophore would eliminate the need to routinely monitor for the SAA chemophore. If residue levels of the AA chemophore were above the LLOMV, then additional analyses for the SAA chemophore would be conducted using the more complex residue data collection method RES-017-91. The proposed enforcement method RES-041-92 submitted in this petition addresses this point. Residues in/on samples of cottonseed are extracted with methanol:deionized water (70:30; v:v) containing sodium bicarbonate, and residues in/on samples of citrus fruits are extracted with methanol:0.2 N hydrochloric acid (70:30; v:v). The extracts are filtered and then sequentially acid- and base-hydrolyzed in a microwave reaction vessel at 80 psi with 6 N hydrochloric acid and 30% hydrogen peroxide, and with 25% sodium hydroxide to convert compound #3 to the AA. The sample is acidified with 6 N hydrochloric acid, the methanol is removed by evaporation, and the sample is resuspended in acidified methanol. The extract is then partitioned three times with 80% ethyl acetate:isooctane. The organic phase is dried over sodium sulfate and the residues are derivatized to AE in methanol with trimethylsilyldiazomethane in hexane. The reaction is quenched with 88% formic acid and the mixture is cleaned using a solid-phase extraction (SPE) column. The AE analyte is eluted from the column with 80% ethyl acetate in isooctane and quantified by GC/MS. The validated limit of detection is 0.025 ppm for cottonseed and citrus commodities. The petitioner provided representative chromatograms and sample calculations.

The independent method validation of Method RES-041-92 was conducted by Arthur D. Little, Inc. (Cambridge, MA). Untreated control samples of ginned cottonseed and whole grapefruit were fortified with #3 at 0.025 and 0.100 ppm (as parent equivalents); the #3 metabolite was used since it required vigorous conditions to be converted to AA. The recoveries of AA from samples of cottonseed and grapefruit using Method RES-041-92 are presented

in Table 1. Apparent residues of AA were nondetectable (<0.025 ppm) in/on two untreated control samples each of cottonseed and grapefruit.

Table 1. Method recoveries of AA from duplicate samples of cottonseed and citrus commodities fortified with #3 and analyzed using method RES-041-92.

Commodity	Fortified level (ppm)	Percent recovery [a]
Cottonseed	0.025	70, 89
	0.100	53, 73
Grapefruit	0.025	97, 99
	0.100	60, 86

[a] Each recovery value represents one sample.

This method was forwarded to the Beltsville laboratory (ACL) for evaluation, but both ACL and CBTS agreed that the method as proposed would not be sufficient since the samples could not be fortified with thiazopyr for the validation test. The major problem with this proposed methodology is that the parent cannot be analyzed using this procedure, but only with those thiazopyr metabolites convertabile to the AA chemophore; thiazopyr is converted to the SAA chemphore. After several telephone discussions with a Monsanto laboratory analyst, Janet Obert (314-537-6201), it was discovered that Monsanto in the very near future will be submitting another enforcement method in which all residues are converted to one common chemophore, a triacid with the fluorinated pyridine ring still intact. Esterification of this triacid and analysis by GC/MS show conversion of <70% of the thiazopyr residues. Based on this information, CBTS has decided to withdraw its initial request (See memo of 3/9/94, E. Greer, ACS, ACB) for the a PMV of Method RES-041-92.

Therefore, the petitioner must submit enforcement methodology for the analysis of thiazopyr residues to include adequate validation data, chromatgraphic charts, and recovery data, and supported by an independent laboratory validation. A confirmatory method in a specificity study must be provided. Since the field trial residue data were collected using Method RES-017-91, the

petitioner must also submit bridging data (i.e., 10% of samples) using the reserve field trial samples (and several from the each citrus and cottonseed processing studies, if avaliable) with this new proposed method.

Since tolerances for livestock meat, meat by-products, and fat, and milk and eggs are not required for thiazopyr residues based upon the proposed use (See Meat, Milk, and Eggs section, this memo) analytical methodology for such residues in these rac's will not be needed at this time. The need for additional analytical methodology is dependent on the decision of the residues to be regulated as determined by the HED Metabolism Committee and the results of residue data requested in conclusion 9 below for cotton gin byproducts.However, if future uses show combined thiazopyr residues (<0.025 ppm) in these rac's, then analytical methodology will be needed in additional to tolerances for these rac's.

Residue data collection method:

Monsanto Company (MRID #42619712) submitted validation data for the GC/MS and HPLC/UV proposed residue data collection method (RES-017-91) for the determination of thiazopyr residues of concern in/on citrus and cotton raw agricultural commodities. Thiazopyr and its metabolites are converted to SAA or AA using acid and base hydrolyses. SAA is determined by HPLC/UV; AA is determined by derivatization to its methyl ester (AE) with subsequent quantification by GC/MS.

A brief description of Method RES-017-91 follows. Residues in/on samples of cottonseed are extracted with methanol:deionized water (70:30; v:v) containing sodium bicarbonate, and residues in/on samples of citrus fruits and cotton forage are extracted with methanol:0.2 N hydrochloric acid (70:30; v:v). The extracts are filtered and 6 N hydrochloric acid and 30% hydrogen peroxide are added. Approximately 3% of the reaction mixture is used for conversion of the thiazopyr metabolites to AA as previously described (See Tolerance enforcement method, this memo). To improve method performance, an internal standard of deuterated AE is added just prior to injection onto the GC/MS. The remainder of the reaction mixture is used for conversion of residues of thiazopyr and its metabolites to SAA by the following procedure. The sample is refluxed for 3 hours, base-hydrolyzed with 25%

sodium hydroxide, and refluxed for an additional 2.5 hours. Following distillation to remove the methanol, the sample is neutralized with glacial acetic acid, diluted with deionized water, and cleaned on an AG1-X8 ion exchange column. Oily crop samples are partitioned with methylene chloride prior to dilution with deionized water and column cleanup. After eluting the analytes with acidified methanol, and drying the eluate by rotary evaporation, and 0.025 M potassium dihydrogen phosphate is added to the samples, and the buffer solublized residues are quantified by HPLC/UV.

Untreated control samples of cottonseed and grapefruit were fortified with the #3 metabolite, representing the AA chemophore, and the parent compound, representing the SAA chemophore, at 0.025-0.250 ppm. The recoveries of AA and SAA are presented in Table 2. Apparent residues of AA and SAA were nondetectable (<0.025 ppm) in/on two untreated control samples of each commodity of cottonseed and grapefruit.

Table 2. Method recoveries of AA and SAA from duplicate samples of cottonseed and citrus fruit commodities fortified with #3 and thiazopyr and analyzed using Method RES-017-91.

		Percent recovery [a]	
Commodity	Fortified level (ppm)	AA	SAA
Cottonseed	0.025	94, 112	69, 96
	0.100	73, 93	62, 96
	0.250	80, 86	97, 98
Grapefruit	0.025	69, 71	52, 71
	0.100	71, 78	73, 89
	0.250	77, 78	71, 71

[a] Each recovery value represents one sample.

Samples of citrus fruit commodities from the submitted storage stability (MRID #42619706) and field residue (MRID #'s 42619705 and 42641401) studies were analyzed for residues of thiazopyr and its metabolites convertible to AA, SAA, glycine amide ester (metabolite #15), and thiazole ester (metabolite #5) using method

RES-017-91. The lower limit of method validation for #15 and #5 is 0.025 ppm each. Determination of #15 accounts for residues of glycine amide acid (metabolite #16) as well, and determination of #5 accounts for residues of thiazole acid (metabolite #14) as well. Metabolites #15, #16, #5, and #14 are not converted to either the SAA or AA chemophores using method RES-017-91, but these metabolites can be determined using a slight modification of the GC/MS analysis for the AA chemophore. The GC/MS analysis of the AA chemphore involves the conversion of the AA (amide acid) to AE (amide ester). Likewise #16 (GAA: glycine amide acid) is converted to #15 (GAE: glycine amide ester), and #14 (TA: triazole acid) to #5 (TE: triazole ester). AE, GAE, and TE are quantitated using multiple ion detection: AE, 314, 317, 334, and 337 ions; GAE, 386 ion; and TE, 334 ion. Each sample was analyzed separately for the AE chemphore and the GAE/TE metabolites. Based upon the metabolism studies, the #15/#16 pair can represent a combined residue total of 12%, while the #5/#14 pair is <2%.

Samples of cotton commodities from the submitted storage stability (MRID #'s 42619710 and 42619711) and field residue studies (MRID #'s 42619707, 42619708, and 42619709) were analyzed for residues of thiazopyr and its metabolites convertible to AA and SAA using method RES-017-91. Concurrent method recoveries of AA, SAA, #15, and #5 from citrus fruit commodities fortified with #3, thiazopyr, #15, and #5 are presented in Table 3, and of AA and SAA from cotton commodities fortified with #3 and thiazopyr are presented in Table 4.

Table 3. Concurrent method recoveries of AA, SAA, #15, and #5 from samples of **citrus fruit** and its processed commodities fortified with #3, thiazopyr, #15, and #5 (MRID #'s 42641401, 42619705, and 42619706).

	Fortified	Percent Recovery (Number of Samples)			
Commodity	Level (ppm)	AA	SAA	#15 [a]	#5 [b]
MRID #42641401					
Citrus fruits	0.023-0.025	56-124 (16)	70-95 (14)	53-87 (6)	76-94 (6)
	0.046-0.050	59-104 (12)	67-110 (14)	64-102 (6)	78-106 (6)

	Fortified	Percent Recovery (Number of Samples)			
Commodity	Level (ppm)	AA	SAA	#15 [a]	#5 [b]
	0.093-0.100	68-90 (16)	69-98 (9)	59-89 (6)	81-104 (6)
	0.250	64-85 (7)	69-110 (14)	--	--
MRID #42619705					
Oranges	0.025	60-94 (3)	83-92 (3)	--	--
	0.100	71-85 (3)	83-90 (3)	--	--
Grapefruit	0.025	78 (1)	87 (1)	--	--
	0.100	73 (1)	79 (1)	--	--
Lemons	0.025	81, 90 (2)	75 (1)	--	--
	0.100	73, 80 (2)	87 (1)	--	--
Orange juice	0.025	64, 89 (2)	64-121 (3)	--	--
	0.100	66-80 (3)	72-98 (3)	--	--
Grapefruit juice	0.025	62 (1)	102 (1)	--	--
	0.100	74 (1)	95 (1)	--	--
Lemon juice	0.025	57, 61 (2)	--	--	--
	0.100	64,69 (2)	85 (1)	--	--
Lemon wet peel	0.025	90 (1)	138 (1)	--	--
	0.100	82 (1)	92 (1)	--	--
Lemon dry peel	0.025	80 (1)	146 (1)	--	--
	0.100	69 (1)	70 (1)	--	--
MRID #42619706					
Oranges	0.2	54-82 (3) [c]	79-86 (4)	--	--

[a] Percent recovery is adjusted for the percent recovered from a control sample run through the method and spiked with #15 just before analysis.

[b] Percent recovery is adjusted for the percent recovered from a control sample run through the method and spiked with #5 just before analysis.

[c] Percent recovery is adjusted for the percent recovered from a control sample run through the method and spiked with AE just before analysis.

Table 4. Concurrent method recoveries of AA and SAA from samples of cottonseed and its processed commodities fortified with #3 and thiazopyr (MRID #'s 42619707, 42619708, and 42619709).

		Percent Recovery (Number of Samples)	
Commodity	Fortified level (ppm)	AA	SAA
MRID #42619707			
Cotton forage	0.025	74-99 (4)	72-105 (4)
	0.040	89 (1)	83 (1)
	0.050	74-93 (3)	79-94 (3)
	0.080	69-89 (3)	73, 81 (2)
	0.100	73-88 (3)	63-84 (3)
	0.150	78, 89 (2)	76 (1)
	0.200	--	79, 106 (2)
Cottonseed	0.025	99-119 (4)	59-83 (3)
	0.050	86-110 (4)	66-100 (4)
	0.080	87 (1)	75 (1)
	0.100	78-105 (4)	75-117 (4)
	0.150	80 (1)	78 (1)
	0.200	87, 93 (2)	84, 86
MRID #42619708			
Cotton forage	0.025	66-122 (10)	53-95 (10)
	0.050	52-100 (10)	63-94 (10)
	0.080	97 (1)	72-94 (4)
	0.100	78-108 (9)	64-122 (9)

		Percent Recovery (Number of Samples)	
Commodity	Fortified level (ppm)	AA	SAA
	0.200	61-98 (8)	68-117 (6)
Cottonseed	0.025	67-149 (10)	56-137 (10)
	0.040	79-88 (4)	81-128 (4)
	0.050	68-84 (5)	75-102 (6)
	0.080	55-86 (3)	74-94 (3)
	0.100	65-90 (8)	74-118 (9)
	0.150	56, 83 (2)	43, 109 (2)
	0.200	61-100 (5)	87-110 (5)
MRID #42619709			
Cottonseed	0.025	51, 75 (2)	81, 100 (2)
	0.100	97, 97 (2)	83-94 (3)
Hulls	0.025	101 (1)	64 (1)
	0.100	93, 97 (2)	71, 83 (2)
	0.200	85 (1)	64 (1)
Meal	0.025	128 (1)	72 (1)
	0.100	106 (1)	85 (1)
Crude oil	0.025	76, 107 (2)	86, 87 (2)
	0.100	77, 82 (2)	98, 99 (2)
MRID #42619710			
Cotton forage	0.2	86, 91 (2) [a]	71, 80 (2)
Cottonseed	0.2	68-81 (4) [a]	79-96 (4)
MRID #42619711			
Cottonseed meal	0.4	112 (1) [a]	84 (1)
	1.0	89 (1) [a]	87 (1)
Cottonseed crude oil	0.1	81 (1) [a]	106 (1)
	0.4	84 (1) [a]	99 (1)

[a] Percent recovery is adjusted for the percent recovered for a control sample run through the method and spiked with AE just before analysis.

The submitted analytical methodology (RES-017-91) is an adequate residue data collection method for the proposed uses on cotton and citrus. **However, this methodology is not adequate as an enforcement method.**

Radiovalidation of Method RES-017-91: (MRID#426197-12)

Subsamples of cotton forage, cottonseed, and whole lemons from the metabolism studies were analyzed using data collection residue analytical Method RES-017-91. The petitioner provided representative chromatograms. The total radioactive residues (TRR) in samples from the metabolism study were determined by combustion/liquid scintillation spectroscopy, and then the samples were analyzed by Method RES-017-91, and the radioactivity in each of the AA and SAA chemophore peaks was determined. Samples of cottonseed from the cotton metabolism study did not contain sufficient levels of radioactivity to accurately quantify levels of SAA and AA metabolites. In samples of cotton forage analyzed using Method RES-017-91, AA metabolites accounted for 30.3% of TRR and SAA metabolites accounted for 17.3% of TRR. Therefore, the petitioner concluded that ca. 48% of TRR was determined using the data collection residue analytical method.

In the lemon metabolism study, 23% of TRR consisted of SAA/AA metabolites, 13% consisted of #16/#15 metabolites, and 0.1% consisted of #14/#5 metabolites. Using Method RES-017-91, the SAA/AA metabolites accounted for 27% of TRR, the #16/#15 metabolites accounted for 14% of TRR, and the #14/#5 metabolites accounted for 1.5% of TRR.

Multi-Residue Methodology

The parent compound was analyzed using Protocols C, D, and E. Tomatoes, analyzed using Protocol D, were fortified with 0.1 and 0.5 ppm parent thiazopyr. Tomatoes and peanuts fortified at 0.05 and 0.5 ppm with parent were analyzed using Protocol E. **Note:** The company must submit copies of the multi-residue testing results using the prescribed protocols without the company confidential or business security stamp on the submitted pages. CBTS had forwarded this information to FDA (See memo of 3/1/94, J. Stokes) but it was returned (See memo of 3/25/94, M. Wirtz, FDA) because the mult-residue information cannot be accepted by

FDA with a confidential stamp on the copy of the method description.

Storage Stability Data

Monsanto Company submitted data (MRID #42619706, 42619710, and 42619711) depicting the frozen storage stability of residues of thiazopyr and its metabolites convertible to AA and SAA in/on oranges, cotton forage, cottonseed, and the selected processed fractions cottonseed meal and cottonseed crude oil. The petitioner noted that the reports for cotton commodities are interim reports and that the storage stability studies for these commodities are continuing. Untreated control samples of each crop were separately fortified with thiazopyr and the #3 metabolite [representative compounds of the sulfonic diacid (SAA) and amide acid (AA) class of metabolites, respectively] at 0.2-0.4 ppm. Fortified samples were stored frozen at <-20 C for up to 531 days for oranges, 522 days for cotton forage, 543 days for cottonseed, 552 days for cottonseed meal, and 522 days for cottonseed crude oil.

Concurrent method recoveries of thiazopyr and the #3 metabolite from untreated samples fortified at the same levels as the storage stability samples were conducted at the time of analysis (See Residue Analytical Methods, this memo). Apparent residues of AA and SAA metabolites were nondetectable (<0.025 ppm each) in/on eight unfortified samples of oranges, two unfortified samples of cotton forage, four unfortified samples of cottonseed, three unfortified samples of cottonseed meal, and four unfortified samples of cottonseed crude oil. Apparent residues of AA metabolites were 0.0554 ppm on one unfortified sample of cottonseed meal. Samples were analyzed by Monsanto Company (St. Louis, MO) for residues of AA metabolites using GC/MS and for residues of SAA metabolites using HPLC with UV detection (Method RES-017-91). The storage stability of residues of thiazopyr and its AA and SAA metabolites in/on fortified samples of oranges, cotton forage, cottonseed, cottonseed meal, and cottonseed crude oil is presented in Table 5. The petitioner provided representative chromatograms and sample calculations. The submitted storage stability data indicate that residues of thiazopyr and its metabolites convertible to AA and SAA are stable under frozen storage conditions for up to 531 days for oranges, 522 days for cotton forage, 543 days for cottonseed, 552

days for cottonseed meal, and 522 days for cottonseed crude oil. No storage stability data for residues of AA and SAA metabolites in citrus fruit processed commodities were submitted.

Citrus fruit samples from the field residue study were stored frozen at -20 C for up to 524 days prior to analysis. Cottonseed and cotton forage samples from the field residue studies were stored frozen at -20 C for up to 836 days and 935 days, respectively, prior to analysis. Samples of cottonseed and its processed fractions from the residue field trials were stored frozen for up to 986 days prior to analysis.

Table 5. Storage stability of residues of AA and SAA in/on oranges, cotton forage, cottonseed, and the processed commodities cottonseed meal and cottonseed crude oil fortified with #3 and thiazopyr at 0.2-0.4 ppm and stored frozen at <-20 C (MRID #'s 42619706, 42619710, and 42619711).

		Percent Recovery [a]	
Storage interval (days)	Fortified level (ppm)	AA	SAA
Oranges (MRID #42619706)			
		Average % recovery:[b] 73	Average % recovery: 82
58	0.2	101, 125	96, 100
149	0.2	121	96, 104
237	0.2	115, 133	96, 100
330	0.2	103, 110	80, 88
420	0.2	109, 116	79, 90
531	0.2	109, 111	83, 90
Cotton forage (MRID #42619710)			
		Average % recovery: 88	Average % recovery: 76
188	0.2	105, 110	106, 117
368	0.2	105, 105	90, 98
459	0.2	99, 86	90, 102

		Percent Recovery [a]	
Storage interval (days)	Fortified level (ppm)	AA	SAA
522	0.2	93, 95	81, 98
Cottonseed (MRID #42619710)			
		Average % recovery: 74	Average % recovery: 88
189	0.2	99, 114	86, 100
209	0.2	118	90
369	0.2	67, 86	73, 75
389	0.2	91	65
460	0.2	97, 107	83, 85
480	0.2	103	81
523	0.2	87, 94	67, 80
543	0.2	80	67
Cottonseed meal (MRID #42619711)			
		Average % recovery: 101	Average % recovery: 85
79	0.4	101	-- [c]
170	0.4	115	90
258	0.4	105	81
351	0.4	109	102
441	0.4	115	98
552	0.4	125	92
Cottonseed crude oil (MRID #42619711)			
		Average % recovery: 83	Average % recovery: 102
49	0.4	109	92
140	0.4	110	89
228	0.4	87	87
321	0.4	102	89
411	0.4	111	96
522	0.4	102	88

[a] Storage stability recoveries corrected for average concurrent method recovery.
[b] Average concurrent method recovery.
[c] The petitioner noted that this sample was lost.

The submitted storage stability data for field and processed samples are adequate for the proposed uses on cirus and cotton. No additional storage stability data are needed for either citrus or cotton.

Magnitude of the Residue

Citrus Fruits

Monsanto Company submitted data (MRID #42641401) from 20 tests conducted in AZ(3), CA(8), and FL(9) depicting residues of thiazopyr, its AA and SAA metabolites, and its glycine amide ester (#15) and thiazole ester (#5) metabolites, including glycine amide acid (#16) and thiazole acid (#14), in/on grapefruit, lemons, and oranges following a single soil broadcast application of the 2 lb a.i./gal EC formulation at 2 lb a.i./A or two sequential soil broadcast applications each at 1 lb a.i./A/application with a 3 month retreatment interval. The total seasonal application rate was 2 lb a.i./A (1x the maximum proposed seasonal application rate). Applications were made using ground equipment at 28-46 gal/A. Citrus fruits were harvested 89-98 days (~3 months) after the final application and stored frozen at -31 to -7 C. One site samples were harvested at 32-92 days PHI. Samples were shipped frozen (temperature unspecified) to Monsanto (St. Louis, MO) and stored frozen for 178-524 days prior to analysis.

Citrus fruits were analyzed for residues of AA metabolites using GC/MS and for residues of SAA metabolites using HPLC with UV detection (Method RES-017-91). The limits of detection and quantitation for AA metabolites were 0.003 ppm and 0.037 ppm, respectively. The limits of detection and quantitation for SAA metabolites were 0.013 ppm and 0.017 ppm, respectively. Apparent residues of AA and SAA metabolites in/on 40 untreated samples of citrus fruits were nondetectable (<0.003 ppm and <0.013 ppm, respectively). Four samples each of oranges and grapefruit from FL and four samples of lemons from CA were analyzed for residues of #15 (and #16) and #5 (and #14) using a slight modification of the GC/MS portion of Method RES-017-91. (See Residue Analytical Methods, this memo). Residues of #15 and #5 were nondetectable (<0.025 ppm each). Residues of AA and SAA metabolites in/on treated citrus fruits are presented in Table 6. Residues were not corrected for concurrent method recoveries.

Geographic representation is adequate since the test states of AZ, FL, and CA together accounted for virtually all (ca. 99%) of the 1991 U.S. grapefruit, lemon, and orange production (Agricultural Statistics 1992, USDA).

The available data indicate that residues of thiazopyr and its metabolites convertible to AA and SAA are not likely to exceed the proposed tolerance of 0.05 ppm in/on citrus fruits harvested 32-98 days following a single soil broadcast application of the 2 lb a.i./gal EC formulation at 2 lb a.i./A or two sequential soil broadcast applications at 1 lb a.i./A/application for a maximum seasonal rate of 2 lb a.i./A.

Table 6. Residues of thiazopyr and its metabolites convertible to AA and SAA in/on oranges, grapefruit, and lemons following a single soil broadcast application at 2 lb a.i./A or two sequential soil broadcast applications each at 1 lb a.i./A/application of the 2 lb a.i./gal EC formulation (MRID #42641401).

Total Rate (lb a.i./A)	Number of Appl.	PHI [a] (Days)	Test Sites (no. of samples)	Residues in ppm		
				AA [b]	SAA [c]	Combined Residues
Oranges						
2	1	90-98	FL (12)	<0.003-0.0042	<0.013	<0.016-<0.0172

2	2	90-98	FL (12)	<0.003-0.0052	<0.013	<0.016-<0.0182
2	1	32-92	CA (8)	<0.003-0.0039	<0.013	<0.016-<0.0169
2	2	32-92	CA (8)	<0.003	<0.013	<0.016
2	1	65	AZ (2)	<0.003	<0.013	<0.016
2	2	65	AZ (2)	<0.003	<0.013	<0.016
Control	--	--	FL, CA, AZ (22)	<0.003	<0.013	<0.016
Grapefruit						
2	1	90-98	FL (6)	<0.003-0.0051	<0.013	<0.016-0.0181
2	2	90-98	FL (6)	<0.003-0.006	<0.013	<0.016-0.019
2	1	89, 91	CA (4)	<0.003	<0.013	<0.016
2	2	89, 91	CA (4)	<0.003	<0.013	<0.016
2	1	91	AZ (2)	<0.003	<0.013	<0.016
2	2	91	AZ (2)	<0.003	<0.013	<0.016
Control	--	--	FL, CA, AZ (12)	<0.003	<0.013	<0.016
Lemons						
2	1	55, 85	CA (4)	<0.003-0.0042	<0.013	<0.016-0.0172
2	2	55, 85	CA (4)	<0.003-0.0108	<0.013	<0.016-0.0238
2	1	91	AZ (2)	<0.003, 0.0043	<0.013	<0.013, <0.0173
2	2	91	AZ (2)	<0.003	<0.013	<0.016
Control	--	--	CA, AZ (6)	<0.003	<0.013	<0.016

[a] Preharvest interval.
[b] The limit of detection for AA is 0.003 ppm.
[c] The limit of detection for SAA is 0.013 ppm.

The submitted residue data are adequate for the proposed use on citrus. No additional residue data are needed. The proposed tolerances are adequately supported by the above residue data.

Citrus Fruit Processed Commodities

Monsanto Company submitted data (MRID #42619705) depicting the potential for concentration of residues of thiazopyr and its metabolites convertible to AA and SAA in citrus processed commodities. In five tests conducted in CA(1) and FL(4), citrus fruits (oranges, grapefruit, and lemons) were harvested 89-92 days following a single soil broadcast application of the 2 lb a.i./gal EC formulation at 10 lb a.i./A/application (5x the proposed maximum seasonal rate) using ground equipment.

Treated and control samples from the FL and CA sites were harvested and delivered to the University of Florida, Citrus Research Center and Education Center (Lake Alfred, FL) or to California State Polytechnic University (Pomona, CA), respectively, for processing. Samples were cooled (4-7 C) prior to processing. Citrus fruits were processed and untreated fruits, washed fruits, finisher pulp, wet peel, dry peel, juice, molasses, and cold-pressed oil were collected using a simulated commercial procedure. The processed fractions were shipped frozen (temperature unspecified) by freezer trucks to the analytical laboratory (Monsanto Company, St. Louis, MO). Samples were stored frozen at -24 to -23 C for up to 428 days for oranges, 369 days for grapefruit, 504 days for lemons, 511 days for orange juice, 414 days for grapefruit juice, 651 days for lemon juice, and 531 days for wet and dry lemon peel prior to analysis. Untreated control and treated samples were analyzed for residues of AE and SAA using Method RES-017-91, which has a lower limit of method validation of 0.025 ppm for both AE and SAA.

Residues of AA metabolites were nondetectable (<0.025 ppm) in/on 6 samples of whole oranges, 2 samples of whole grapefruit, 4 samples of whole lemons, 6 samples of orange juice, 2 samples of grapefruit juice, 3 samples of lemon juice, 2 samples of lemon wet peel, and 2 samples of lemon dry peel; residues of AA metabolites were 0.064 ppm in one sample of lemon juice. Residues of SAA metabolites were nondetectable (<0.025 ppm) in/on 6 samples of whole oranges, 2 samples of whole grapefruit, 2 samples of whole lemons, 6 samples of orange juice, 2 samples of grapefruit juice, 2 samples of lemon juice, 2 samples of lemon wet peel, and 2 samples of lemon dry peel. Apparent residues of AA and SAA metabolites were nondetectable (<0.025 ppm each) in/on

6 samples of whole oranges, 2 samples of whole grapefruit, 4 samples of whole lemons (2 samples for SAA analysis), 6 samples of orange juice, 2 samples of grapefruit juice, 4 samples of lemon juice (2 samples for SAA analysis), 2 samples of lemon wet peel, and 2 samples of lemon dry peel. Analyses of the molasses was not performed because residues less than the level of quantitation (<0.025 ppm) of AA and SAA were found in whole citrus and peel. **Note:** Residue data for processed citrus oil has recently been submitted and are currently in review (Barcode DP D203667). Residue data for citrus molasses is still needed.

The data indicate that residues of thiazopyr and its metabolites convertible to AA and SAA are not likely to concentrate in the pulp (finisher), peel (wet and dry), and juice that had been processed from citrus fruits treated with a single broadcast application of the thiazopyr EC formulation at 5x the proposed maximum seasonal rate.

The submitted field residue data are adequate for the proposed use on citrus. Final conclusions on the citrus processing must await completion of the review on the recently submitted daat on citrus oil. The proposed tolerances on citrus, except oil, are adequately supported by the above residue data.

Cottonseed

Monsanto Company submitted data (MRID #42619707) from four tests conducted in AZ(2) and CA(2) depicting residues of thiazopyr and its metabolites convertible to AA and SAA in/on cottonseed and cotton forage following a single preplant soil incorporated application of the 2 lb a.i./gal EC formulation at 0.5 lb a.i./A or 1.0 lb a.i./A or a single preemergence soil surface application at 0.5 lb a.i./A. Applications were made using ground equipment in 11-30 gal/A. Cotton forage and cottonseed were harvested 143-236 days and 279-323 days, respectively, after the last application. Cottonseed was ginned after harvest and stored frozen at ≤-17 C. Samples of cotton forage and cottonseed were shipped frozen at ≤-17 C in freezer trucks to Monsanto (St. Louis, MO) and stored frozen for 571-713 days and 460-560 days, respectively, prior to analysis.

Cotton forage and cottonseed were analyzed for residues of AA metabolites by GC/MS and for residues of SAA metabolites by HPLC

with UV detection (Method RES-017-91). The lower limit of method validation was 0.025 ppm for both AA and SAA. Apparent residues of AA and SAA metabolites in/on 16 untreated control samples each of cotton forage and cottonseed were nondetectable (<0.025 ppm each). Residues of AA and SAA metabolites in/on treated samples of cotton forage and cottonseed are presented in Table 7. Residue values have not been corrected for concurrent method recoveries.

The available data indicate that residues of thiazopyr and its metabolites convertible to AA and SAA are not likely to exceed the proposed tolerances of 0.2 ppm in/on cotton forage and 0.05 ppm in/on cottonseed harvested 143-323 days following a single preplant soil incorporated application at 0.5 lb a.i./A or 1.0 lb a.i./A, or a single preemergence soil surface application at 0.5 lb a.i./A of the 2 lb a.i./gal EC formulation.

Monsanto Company also submitted data (MRID #42619708) from ten tests conducted in AZ(1), AR(1), CA(2), LA(1), MS(1), OK(1), and TX(3) depicting residues of thiazopyr and its metabolites convertible to AA and SAA in/on cottonseed and cotton forage following a single preplant soil incorporated application of the 2 lb a.i./gal EC formulation at 0.3 lb a.i./A (1x) or 0.6 lb a.i./A (2x) or a single preemergence soil surface application at 0.6 lb a.i./A (2x). Applications were made using ground equipment in 9-21 gal/A. Cotton forage and cottonseed were harvested 48-66 days and 121-198 days, respectively after application. Cottonseed was ginned after harvest and stored frozen at ≤-17 C. Samples of cotton forage and cottonseed were shipped frozen at ≤-17 C in freezer trucks to Monsanto (St. Louis, MO) and stored frozen for 632-719 days and 515-620, respectively, prior to analysis.

Cotton forage and cottonseed were analyzed for residues of AA metabolites by GC/MS and for residues of SAA metabolites by HPLC with UV detection (Method RES-017-91). The lower limit of method validation is 0.025 ppm for both AA and SAA. Apparent residues of AA and SAA metabolites in/on 40 untreated control samples each of cotton forage and cottonseed were nondetectable (<0.025 ppm each). Residues of AA and SAA metabolites in/on treated samples of cotton forage and cottonseed are presented in Table 8. Residues value have not been corrected for concurrent method recoveries.

57

Table 7. Residues of thiazopyr and its metabolites convertible to AA and SAA in/on cotton forage and cottonseed following a single preplant soil incorporated application of the 2 lb a.i./gal EC formulation at 0.5 lb a.i./A or 1.0 lb a.i./A, or a single preemergence soil surface application at 0.5 lb a.i./A (MRID #42619707).

Test Sites	Total Rate (lb a.i./A)	Treatment Type [a]	PHI [b] (days)	Residues, ppm [c]		
				AA	SAA	Combined Residues [d]
Cotton forage						
AZ	0.5	PPI	236	0.038, 0.040	<0.025	0.038, 0.040
	1.0	PPI	236	0.144, 0.151	<0.025	0.151, 0.161
	0.5	PRE	235	0.046, 0.047	<0.025	0.049, 0.049
	Control	--	--	<0.025	<0.025	<0.025
AZ	0.5	PPI	197	0.042, 0.044	<0.025	0.050, 0.051
	1.0	PPI	197	0.056, 0.060	<0.025	0.068, 0.073
	0.5	PRE	197	0.052, 0.053	<0.025 (1)	0.058 (1)
	Control	--	--	<0.025	<0.025	<0.025
CA	0.5	PPI	169	0.049, 0.050	<0.025	0.068, 0.071
	1.0	PPI	169	0.073, 0.074	<0.025	0.092, 0.093
	0.5	PRE	169	0.093, 0.099	0.030	0.123, 0.129
	Control	--	--	<0.025	<0.025	<0.025
CA	0.5	PPI	143	<0.025	<0.025	<0.025
	1.0	PPI	143	0.035, 0.036	<0.025	0.042, 0.043
	0.5	PRE	143	0.029, 0.030	<0.025	0.029, 0.033
	Control	--	--	<0.025	<0.025	<0.025

Test Sites	Total Rate (lb a.i./A)	Treatment Type [a]	PHI [b] (days)	Residues, ppm [c]		
				AA	SAA	Combined Residues [d]
Cottonseed						
AZ	0.5	PPI	304	<0.025	<0.025	<0.025
	1.0	PPI	304	<0.025	<0.025	<0.025
	0.5	PRE	303	<0.025	<0.025	<0.025
	Control	--	--	<0.025	<0.025	<0.025
Cottonseed						
AZ	0.5	PPI	323	<0.025	<0.025	<0.025
	1.0	PPI	323	<0.025	<0.025	<0.025
	0.5	PRE	323	<0.025	<0.025	<0.025
	Control	--	--	<0.025	<0.025	<0.025
CA	0.5	PPI	279	<0.025	<0.025	<0.025
	1.0	PPI	279	<0.025	<0.025	<0.025
	0.5	PRE	279	<0.025	<0.025	<0.025
	Control	--	--	<0.025	<0.025	<0.025
CA	0.5	PPI	319	<0.025	<0.025	<0.025
	1.0	PPI	319	<0.025	<0.025	<0.025
	0.5	PRE	319	<0.025	<0.025	<0.025
	Control	--	--	<0.025	<0.025	<0.025

[a] PPI = preplant soil incorporated; PRE = preemergence.

[b] Preharvest interval.

[c] Two samples at each rate and treatment type, unless noted in parentheses. The reported lower limit of method validation was 0.025 ppm for AE and SAA.

[d] Raw data results were used to determine combined residues rather than the sum of quantification limits.

Table 8. Residues of thiazopyr and its metabolites convertible to AA and SAA in/on cotton forage and cottonseed following a single preplant soil incorporated application of the 2 lb a.i./gal EC formulation at 0.3 lb a.i./A or 0.6 lb a.i./A, or a single preemergence soil surface application at 0.6 lb a.i./A (MRID #42619708).

Test Sites	Total Rate (lb a.i./A)	Treatment Type [a]	PHI [b] (days)	Residues, ppm [c]		
				AA	SAA	Combined Residues [d]
Cotton forage						
AZ	0.3	PPI	66	<0.025	<0.025	<0.025
	0.6	PPI	66	<0.025	<0.025	<0.025
	0.6	PRE	66	<0.025	<0.025	<0.025
	Control	--	--	<0.025	<0.025	<0.025
AR	0.3	PPI	56	<0.025	<0.025	<0.025
	0.6	PPI	56	<0.025	<0.025	<0.025
	0.6	PRE	48	<0.025	<0.025	<0.025
	Control	--	--	<0.025	<0.025	<0.025
CA	0.3	PPI	62	0.051, 0.052	<0.025	0.070, 0.072
	0.6	PPI	62	0.074, 0.076	<0.025	0.092, 0.095
	0.6	PRE	62	0.099, 0.100	0.032, 0.034	0.131, 0.134
	Control	--	--	<0.025	<0.025	<0.025
CA	0.3	PPI	57	<0.025	<0.025	<0.025
	0.6	PPI	57	<0.025	<0.025	<0.025

Test Sites	Total Rate (lb a.i./A)	Treatment Type [a]	PHI [b] (days)	Residues, ppm [c]		
				AA	SAA	Combined Residues [d]
	Control	--	--	<0.025	<0.025	<0.025
LA	0.3	PPI	49	<0.025	<0.025	<0.025
	0.6	PPI	49	<0.025, 0.026	<0.025	<0.025, 0.026
	Control	--	--	<0.025	<0.025	<0.025
Cotton forage						
MS	0.3	PPI	53	<0.025, 0.028	<0.025	<0.025, 0.028
	0.6	PPI	53	0.031, 0.034	<0.025	0.039, 0.043
	0.6	PRE	53	0.034	<0.025	0.044, 0.048
	Control	--	--	<0.025	<0.025	<0.025
OK	0.3	PPI	54	<0.025	<0.025	<0.025
	0.6	PPI	54	0.075, 0.079	0.027, 0.029	0.102, 0.108
	Control	--	--	<0.025	<0.025	<0.025
TX	0.3	PPI	58	<0.025	<0.025	<0.025
	0.6	PPI	58	<0.025	<0.025	<0.025
	0.6	PRE	58	<0.025	<0.025	<0.025
	Control	--	--	<0.025	<0.025	<0.025
TX	0.3	PPI	63	<0.025	<0.025	<0.025
	0.6	PPI	63	<0.025	<0.025	<0.025
	Control	PRE	--	<0.025	<0.025	<0.025

Test Sites	Total Rate (lb a.i./A)	Treatment Type [a]	PHI [b] (days)	Residues, ppm [c]		
				AA	SAA	Combined Residues [d]
TX	0.3	PPI	50	<0.025	<0.025	<0.025
	0.6	PPI	50	<0.025	<0.025	<0.025
	Control	PRE	--	<0.025	<0.025	<0.025
Cottonseed						
AZ	0.3	PPI	198	<0.025	<0.025	<0.025
	0.6	PPI	198	<0.025	<0.025	<0.025
	0.6	PRE	198	<0.025	<0.025	<0.025
	Control	--	--	<0.025	<0.025	<0.025
AR	0.3	PPI	143	<0.025	<0.025	<0.025
	0.6	PPI	143	<0.025	<0.025	<0.025
	0.6	PRE	135	<0.025	<0.025	<0.025
	Control	--	--	<0.025	<0.025	<0.025
CA	0.3	PPI	166	<0.025	<0.025	<0.025
	0.6	PPI	166	<0.025	<0.025	<0.025

Test Sites	Total Rate (lb a.i./A)	Treatment Type [a]	PHI [b] (days)	Residues, ppm [c]		
				AA	SAA	Combined Residues [d]
	0.6	PRE	166	<0.025	<0.025	<0.025
	Control	--	--	<0.025	<0.025	<0.025
CA	0.3	PPI	166	<0.025	<0.025	<0.025
	0.6	PPI	166	<0.025	<0.025	<0.025
	Control	--	--	<0.025	<0.025	<0.025
LA	0.3	PPI	144	<0.025	<0.025	<0.025
	0.6	PPI	144	<0.025	<0.025	<0.025
	Control	--	--	<0.025	<0.025	<0.025
Cottonseed						
MS	0.3	PPI	121	<0.025	<0.025	<0.025
	0.6	PPI	121	<0.025	<0.025	<0.025
	0.6	PRE	121	<0.025	<0.025	<0.025
	Control	--	--	<0.025	<0.025	<0.025
OK	0.3	PPI	176	<0.025	<0.025	<0.025
	0.6	PPI	176	<0.025	<0.025	<0.025
	Control	--	--	<0.025	<0.025	<0.025

42

Test Sites	Total Rate (lb a.i./A)	Treatment Type [a]	PHI [b] (days)	Residues, ppm [c]		
				AA	SAA	Combined Residues [d]
TX	0.3	PPI	170	<0.025	<0.025	<0.025
TX	0.6	PPI	170	<0.025	<0.025	<0.025
	0.6	PRE	170	<0.025	<0.025	<0.025
	Control	--	--	<0.025	<0.025	<0.025
TX	0.3	PPI	128	<0.025	<0.025	<0.025
	0.6	PPI	128	<0.025	<0.025	<0.025
	Control	--	--	<0.025	<0.025	<0.025
TX	0.3	PPI	132	<0.025	<0.025	<0.025
	0.6	PPI	132	<0.025	<0.025	<0.025
	Control	--	--	<0.025	<0.025	<0.025

[a] PPI = preplant incorporated and PRE = preemergence.

[b] Preharvest interval.

[c] Two samples at each rate and treatment type. The reported lower limit of method validation was 0.025 ppm for AA and SAA.

[d] Raw data results were used to determine combined residues rather than the sum of quantification limits.

Geographic representation is adequate. The test states of AZ(6%), AR(9%), CA(15%), LA(8%), MS(13%), OK(1%), and TX(27%) accounted for ca. 80% of the 1991 U.S. cottonseed production (Agricultural Statistics 1992, USDA).

The available data indicate that residues of thiazopyr and its metabolites convertible to AA and SAA are not likely to exceed the proposed tolerance of 0.05 ppm in/on cottonseed following a single preplant soil incorporated application of the 2 lb a.i./gal EC formulation at 1x and 2x the maximum seasonal rate, or a single preemergence soil surface application at 2x.

CBTS data requirements for cotton forage have been changed; no data are needed for cotton forage; no tolerance will be established for cotton forage. A revised Section F must also be submitted that reflects the removal of the proposed tolerance for cotton forage.

Data must be submitted for cotton gin byproducts (commonly called gin trash: the plant residue from ginning cotton, and consists of burrs, leaves, stems, lint, immature seeds, and sand and/or dirt) which reflects the proposed use. The need for a feed additive tolerance will be determined after review of the submitted residue data. A revised Section F must be also submitted if a tolerance is needed.

The data requirements for cotton gin byproducts were not imposed at the time of this submission, therefore we will not hold up a recommendation for the proposed tolerances on cotton once the remaining deficiencies are satified. The petitioner would have additional time to generate field residue data for cotton gin byproducts, and if necessary, provide feeding stuides in ruminants and propose tolerances. Cotton gin byproducts is not a poultry feed item.

Cottonseed Processed Commodities

Monsanto Company submitted data (MRID #42619709) depicting the potential for concentration of residues of thiazopyr and its metabolites convertible to AA and SAA in cottonseed processed commodities. In two tests conducted in CA(1) and TX(1), cottonseed was harvested 156-189 days following a single preplant incorporated soil application of the 2 lb a.i./gal EC formulation at 0.3 lb a.i./A, 0.6 lb a.i./A, and 1.5 lb a.i./A (1x, 2x, and 5x the maximum

proposed seasonal rate, respectively) using ground equipment at 15-16 gal/A.

Treated and control samples were harvested, stored frozen at ≤-17 C, and shipped in a freezer truck to the Food Protein Research and Development Center of Texas A&M University (College Station, TX) for processing. Cottonseed was processed into hulls, meal, crude oil, refined oil, and soapstock using a simulated industrial procedure. The processed fractions were then packed in dry ice and shipped to the analytical laboratory (Monsanto Company, St. Louis, MO). Samples were stored frozen (temperature unspecified) for up to 842 days for cottonseed, 772 days for cottonseed hulls, 986 days for cottonseed meal, and 945 days for cottonseed crude oil prior to analysis. Untreated and treated samples were analyzed for residues of AA and SAA metabolites using Method RES-017-91, which has a lower limit of method validation of 0.025 ppm for both AA and SAA.

Apparent residues of AA and SAA metabolites were nondetectable (<0.025 ppm) in each untreated control sample. Residues of AA and SAA metabolites in/on 24 treated cottonseed samples were nondetectable (<0.025 ppm each). Residues of AA and SAA metabolites were nondetectable (<0.025 ppm each) in/on 24 treated samples each of hulls and crude oil, and 16 samples of meal. The petitioner noted that the processed fractions soapstock and refined oil were not analyzed because residues were not detected in/on cottonseed or the selected processed fractions hulls, meal, and crude oil.

The available data indicate that residues of thiazopyr and its metabolites convertible to AA and SAA are not likely to concentrate in the meal, hulls, and crude oil that had been processed from cottonseed treated with a single preplant incorporated soil application of the thiazopyr EC formulation at 5x the proposed maximum seasonal rate. Based on these data, it is expected that thiazopyr residues of concern are also not likely to concentrate in soapstock and refined oil.

The submitted processing residue data are adequate for the proposed use on cotton. No additional residue data are needed.

Rotational Crops

In the review of the temporary tolerance petition (PP#2G4122, J. Garbus, 6/2/93), CBTS concluded that the proposed label statements

regarding rotational crops are acceptable for the purposes of an experimental use permit. The petitioner has submitted a confined rotational crop study (MRID #42275515) which was reviewed previously by EFGWB. The petitioner has proposed a 9-month plant-back for crops other than cotton, except for sorghum, corn, or wheat which have a 18-month plant-back.

In the review of the temporary tolerance petition (PP#2G4122, J. Garbus, 6/2/93), CBTS concluded that the proposed label statements regarding rotational crops were acceptable for the purposes of an experimental use permit only. The 18-month plant-back interval is not practical, and not acceptable for a permanant tolerance. The petitioner has submitted a confined rotational crop study (MRID #42275515) which was reviewed by EFGWB. CBTS must review rotational field trial residue data for these crops to determine if tolerances for thiazopyr residues must be established. [**Note:** The data responding to this deficiency has been received and is currently in review (BarcodeDP D198931).]

Meat, Milk, Poultry, and Eggs

Feeding studies

No feeding studies are submitted in this petition, PP#3F4147. The petitioner previously requested a waiver of feeding studies with thiazopyr in their petition for temporary tolerances (PP#2G4122). In the review of this temporary tolerance petition (J. Garbus, 6/2/93), CBTS concluded that the proposed uses would result in sufficiently low potential residues of thiazopyr and its metabolites of concern that feeding studies or temporary tolerances for meat, milk, poultry, and eggs would not be required. Feeding studies and enforcement methodology will be needed for any future tolerance requests for livestock feed items containing significant residues.

The petitioner has requested a waiver of feeding studies in this petition, PP#3F4147, based on the following arguments.

A hypothetical diet for dairy cattle that maximizes potential exposure to residues of thiazopyr in/on the commodities of this petition is the following:

Proposed diet for dairy cattle			
RAC	% in diet	Residue*, ppm	Dietary burden
cotton forage	40	0.34	0.136
cottonseed	7	<0.1	0.007
citrus pulp, dried	33	<0.2	0.066
citrus pulp, wet	10	<0.2	0.02
citrus molasses	10	<0.2	0.02
Total			0.249

* Residues in cottonseed and citrus were below the limit of quantification of 0.05 ppm. In cotton forage a maximum of 0.17 ppm was found. However the analytical method determines about 50% of the residues in cotton as shown by radioactive studies and 25% in citrus. The assumed residue values have been calculated taking this into consideration.

In the animal metabolism study, lactating goats were dosed at rate of 12 (240X) or 24 ppm (480X). At these dosages, the maximum total radioactivity found in animal tissues was 0.193 and 0.375 ppm, respectively, in liver. From these results, the calculated maximum tissue levels in dairy cattle fed the hypothetical diet would be 0.004 and 0.0045 ppm. This calculated values are below the analytical limit of detection.

A hypothetical diet for poultry that maximizes potential exposure to residues of thiazopyr for rac's of this petition is as follows:

Proposed diet for dairy cattle			
RAC	% in diet	Residue*, ppm	Dietary burden
cottonseed meal	10	<0.1	0.01
cottonseed soapstock	5	<0.1	0.005
citrus RAC's	0	-	-
Total			0.249

* Residues in cottonseed and citrus were below the limit of quantification of 0.05 ppm. In cotton forage a maximum of 0.17 ppm was found. However the analytical method determines about 50% of the residues in cotton as shown by radioactive studies

and 25% in citrus. The assumed residue values have been calculated taking this into consideration.

In the poultry metabolism study, laying hens were dosed at rate of 12 (240X) or 78 (1560X) ppm. At these dosages, the maximum total radioactivity found in animal tissues was 0.298 and 1.417 ppm, in liver and abdominal fat, respectively. From these results, the calculated maximum tissue levels in poultry fed the hypothetical diet would be 0.0004 and 0.0003 ppm, respectively. These calculated values are below the analytical limit of detection.

Based on the residue data submitted in this petition, potential residues in feed items could be sufficiently low to obviate the need for feeding studies or for tolerances in meat, milk, poultry, and eggs. However, since the CBTS has determined that cotton gin byproducts will be considered an animal feedstuff, then CBTS must review the additional residue data (requested above) from cotton gin byproducts before a decision of can be made on the need for feeding studies for ruminants for the proposed use of thiazopyr on cotton.

CBTS would not be opposed to the establishment of tolerances with expiration dates based on the data requirements at the time of this submission. The petitioner would have additional time to generate field residue data for cotton gin byproducts, propose a tolerance, and, if necessary, provide feeding studies in ruminants. Cotton gin byproducts is not a poultry feed item.

Likewise any decision on the need for enforcement methodology for residues of thiazopyr (and/or additional metabolites as determined by the HED Metabolism Committee) in livestock meat, meat byproducts, and milk, will be determined after the additional residue data are submitted by the petitioner and subsequently reviewed by CBTS.

Other Considerations:

There are no CODEX, Canadian, or Mexican limits established for thiazopyr. Therefore, no compatability problem exists.

cc with Confidential Attachment: J. Stokes (CBTS); PP#3F4147; R.F.

cc without Confidential Attachment: Circu
RDI:Perrico:08/16/94:MFlood:08/26/94
7509C:CBTS:CM#2:Rm803:JStokes:js:305-7561:09/01/94