9-7-95

MEMORANDUM

SUBJECT: Thidiazuron Metabolism. Issues to be Presented to the Metabolism Committee on September 18, 1995.

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THRU: Edward Zager, Branch Chief
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TO: Metabolism Committee
Health Effects Division (7509C)

Tolerances (40 CFR 180.403) are established for the combined residues of the defoliant thidiazuron (N-phenyl-N'-1,2,3-thiadiazol-5-ylurea) and its aniline containing metabolites in or on cottonseed at 0.4 ppm and in meat, milk, poultry and eggs ranging from 0.05 ppm to 0.2 ppm as outlined in the attached TIS report. No food additive tolerances are established. A feed additive tolerance is established for the combined residues of thidiazuron and its aniline containing metabolites in cottonseed hulls at 0.8 ppm.

No Codex MRL's are established; therefore, no compatibility questions exist for thidiazuron.

The Phase IV Review for thidiazuron (Chemical No. 120301, Case No. 4092) was completed 2/2/93. In this review it was concluded that the analytical method was not adequate for data collection or enforcement because of the nonspecificity of the method, i.e. it will detect any aniline-containing moiety. Since aniline is endogenous, an accurate residue determination is not attainable using this method. Metabolism studies submitted indicate that a specific method determining the parent, thidiazuron per se may be appropriate.

Nature of the Residue in Plants

The metabolism of thidiazuron in plants has been adequately defined through the study of thidiazuron ^{14}C-radiolabeled in the phenyl and thiazoyl rings and applied to cottonseed. Several studies have been conducted, the results of which are shown in Tables 1 to 3 below.

Table 1. Metabolites in Cotton from the Application of ^{14}C-Thidiazuron labeled in the phenyl ring[1]

Residue Identified	Leaves (21.88 ppm)		Seeds (0.04 ppm)	
	% TRR	PPM	%TRR	PPM
thidiazuron	29	6.31	60	0.02
photoproduct	13	2.76	7	<0.008
bound residue	38	8.27	<12	<0.008
origin	13	2.77	15	<0.008
unknown I	6	1.36	6	<0.008
unknown II	2	0.41	ND	<0.008

1. ^{14}C-thidiazuron was applied at a rate of 0.2 lb ai/A (1x).

Table 2. Metabolites in Cotton for the Application of Thidiazuron labeled in the thidiazolyl and phenyl rings.[1]

Metabolite	Thiadiazolyl-labeled (2.96 ppm)		Phenyl-labeled (3.92 ppm)	
	TRR (ppm)	Percent TRR	TRR (ppm)	Percent TRR
Thidiazuron	2.23	75.2	3.07	78.4
Photoproduct	0.04	1.5	0.02	0.4
Not Identified	0.69	23.3	0.83	21.2

1. ^{14}C-thidiazuron was applied at a rate of 0.2 lb ai/A (1x).

Table 3. Metabolites Found in Cotton Foliage after Application of ^{14}C-Thidiazuron labeled in the phenyl ring	
Residues	% TRR
Thidiazuron	79.2
Photoproduct	0.2
Origin	2.1
Other products	0.6
Not Extracted	0.3
Unaccounted	17.6%
Total	100
1. Ten mls of ^{14}C-thidiazuron was brushed on the leaves.	

Nature of the Residue in Animals

The nature of the residue in animals is adequately understood.

Ruminant metabolism: [^{14}C-aniline] thidiazuron was fed to a lactating cow at a rate of 10 ppm for seven days. The animal was sacrificed within 24 hours of administration of the final dose. Radioactivity found was 0.05 ppm, 0.1 ppm, 1.5 ppm, and 1.0 ppm in fat, muscle, kidney and liver, respectively. Radioactivity reached a plateau in milk on the second day (0.2 ppm). Analysis was performed using HPLC and TLC.

Poultry metabolism. [^{14}C-aniline] thidiazuron was fed once daily to six hens for fourteen days at a rate of 8 ppm. Radioactivity did not plateau in eggs during this period. All tissues were first treated with protease and β-glucuronidase prior to extraction. Radioactivity found was 0.02 ppm, 0.27 ppm, 1.11 ppm, 0.66 ppm, 0.10 ppm, 0.10 ppm and 0.34 ppm in fat, gastrointestinal tract, gastro-intestinal tract contents, liver, muscle, skin and blood, respectively.

Identification and characterization of residues in livestock are shown in Tables 4 and 5.

Table 4. Metabolites in Ruminant Tissues and Milk from A Lactating Cow Dosed with ^{14}C-thidiazuron labeled in the phenyl ring.

Metabolite	Liver (1.0 ppm)		Kidney (1.5 ppm)		Muscle (0.1 ppm)		Fat (0.05 ppm)		Milk (0.2 ppm)	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Thidiazuron	2	0.02	3	0.04	58	0.058	---	---	31	0.062
Phenylurea	13	0.13	15	0.23	2	0.002	10	0.005	3	0.006
4-hydroxythidiazuron	4	0.04	6	0.09	1	0.001	2	0.001	49	0.098
phenylurea conjugate	15	0.15	18	0.27	---	---	7	0.004	<3	<0.006
4-hydroxythidiazuron conjugate	36	0.36	11	0.16	13	0.013	46	0.023	<3	<0.006
Polar Fraction	22	0.22	23	0.35	---	---	11	0.005	11	0.022
Total	92	0.92	76	1.14	74	0.073	76	0.038	<100	<0.2

Table 5. Metabolites in Poultry and Eggs from a Laying Hen with ^{14}C-thidiazuron labeled in the phenyl ring.

	Liver (0.66 ppm)		Muscle (0.10 ppm)		Fat (0.02 ppm)		Eggs (0.15 ppm)	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Thidiazuron	---	---	2	0.002	2	0.0004	20	0.03
Phenylurea	9	0.059	8	0.008	9	0.0018	16	0.024
4-hydroxy thidiazuron	5	0.033	3	0.003	4	0.0008	---	---
Component G (phenylurea conjugate)	14	0.092	18	0.018	11	0.0022	---	---
Component H (4-hydroxythidiazuron conjugate)	64	0.422	22	0.022	56	0.0112	22	0.033
Polar Fraction	3	0.020	17	0.017	11	0.0022	13	0.02
Total	95	0.626	70	0.07	93	0.0186	71	0.107

Questions to the Committee

1. Thidiazuron is currently regulated as the parent and its aniline containing moieties. In light of data presented above, should the parent only be regulated in plants and livestock?

cc: Reviewer(F. Fort), Reg. Std. File, RF, SF, Circ.
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