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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Memorandum

Subject: PP#7G3547; 45639-EUP-27;
Amitraz for Use on cotton;
Revised Section G; No MRID No.;
RCB No. 3402 and 3403.

From: Francis B. Suhre, Chemist *Francis B. Suhre*
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Thru: Edward Zager, Section Head *EZ*
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To: Dennis Edwards, PM-12
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The petitioner, NOR-AM Chemical Co., has responded to our previous review of PP#7G3547/45639-EUP-GL (F. Suhre, memo of 8-12-87) by providing a revised Section G (proposed experimental use). In addition, a metabolism study for amitraz was submitted in connection with (45639-EUP-YY).

The deficiencies from RCB's previous review of PP#7G3547 are restated below, followed by the petitioner's response and any additional comments by RCB.

Deficiency 1a ,restated from review dated 8-12-87

The metabolic nature of amitraz in cottonseed is not adequately understood. A metabolism study on cottonseed has not been submitted. In past reviews, we have concluded that the metabolic nature (s) of amitraz in lemons, pears, and cottonseed were not adequately understood (PP#2F2705, M. Firestone memo of 1-16-87; PP#8G2120, G. Makhijani, memo of 1-15-79; and PP5G3185, C. Deyrup, memo of 2-27-85).

Petitioner's Response to Deficiency 1a.

The petitioner responded by submitting a revised Section G (experimental protocol), reducing the acreage proposed for treatment from 7,100 to 1,300 acres. Furthermore, since the treatment sites are distributed over 10 states, and since the total acreage proposed for treatment (1,300 acres) represents <0.1% of the U.S. cotton production, the petitioner requested a waiver from the requirement of a cotton metabolism study.

The proposed treatment sites/acreage/dose, as listed in the revised Section G, are:

Site	Acres	lbs. ai
AK	100	100
AZ	300	300
CA	100	100
LA	100	100
MS	150	150
TX	150	150
AL	100	100
GA	150	150
SC	100	100
NC	50	50
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TOTAL	1300	1300

RCB's Comments

Since the metabolism study, " M77 AMITRAZ: The Fate of Amitraz in Cotton Late Season Application, A. Fortsch, 3/25/88," (MRID No. 405908-01), was provided to the Agency in support of 45639-EUP-YY, the petitioner's request for a waiver from the requirement of a cotton metabolism study is no longer germane; a review of this metabolism study follows:

[¹⁴C]-Amitraz (labeled in a single ring) [REDACTED]

[REDACTED] formulated into an emulsifiable concentrate containing 1 mg ai/mL with a specific activity of 2.0E 07 dpm/mg.

Cotton plants (Acala and Stoneville varieties, 6 each, grown under greenhouse conditions) were treated with [¹⁴C]-Amitraz at ca. 2 mg ai/plant, with a second treatment made 10 days after the first (total dose 0.8 lb. ai/A/season; approximately 1x the

proposed label dose). Two plants of each variety were harvested 2 hours after the second treatment, and the remaining plants were harvested at maturity (3 weeks after the second treatment for the Acala variety, and 5 weeks after the second treatment for the Stoneville variety). Harvested plants were separated into green parts (leaves, stems, and hulls; designated leaves), and bolls. Bolls were further separated into lint and seed. Portions of the mature plants were subjected to various extraction schemes, as summarized below:

Leaf fractions were washed with hexane, extracted with acetone/ Et_3N , concentrated, reconstituted with NaHCO_3 solution, and sequentially partitioned against non-polar (hexane), and medium polar (Diethyl Ether) solvents. Aliquots of these phases (hexane, diethyl ether, and aqueous) were analyzed for radioactivity by direct scintillation counting. Solids, remaining after extraction, were subjected: to Soxhlet extraction with acetonitrile, and methanol/water and analyzed by liquid scintillation counting; or analyzed by combustion techniques.

Lint fractions were: washed with hexane and extracted with acetone/ Et_3N ; washed with hexane and Soxhlet extracted with acetonitrile; washed with hexane and extracted with HCl ; or washed with hexane and steam distilled with NaOH . All solvents were analyzed for radioactivity by direct scintillation counting. Solids, remaining after extraction, were subjected to: acid and base hydrolysis, followed by extraction and liquid scintillation counting; or analyzed by combustion techniques.

Seed fractions were: washed with hexane and sequentially extracted with acetone/ Et_3N and hexane; washed with hexane and extracted with acetone/ Et_3N ; or sequentially washed with hexane and sulfuric acid, and extracted with hexane. All solvents were analyzed for radioactivity by direct scintillation counting. Solids, remaining after extraction, were subjected to: Soxhlet extraction with acetonitrile steam distillation, followed by extraction and liquid scintillation counting; or analyzed by combustion techniques.

The distribution of radioactivity in cotton plants is summarized in Table 1:

Table 1: Distribution of radioactivity in cotton plants, resulting from 2 treatments (10 day interval) at 0.4 lb. ai/A and harvested at maturity.

Plant Fraction	TRR, PPM Amitraz Equivalent (% TRR) Plant Variety/PHI	
	Acala/3 weeks	Stoneville/5 weeks
Leaves	4.07 (41%)	5.79 (40%)
Lint	5.49 (55%)	8.47 (58%)
Seeds	0.36 (4%)	0.31 (2%)

Identification of components in the TRR of each plant fraction was accomplished through additional separation (solvent partitioning, soxhlet extraction, hydrolysis, and distillation), followed by chromatographic (TLC and HPLC) comparison to reference standards. Results are summarized in Tables 2:

Table 2: Chemical elucidation of TRR in cotton leaves, lint, and seeds (Acala variety, 3 week PHI).

Residue	% of TRR		
	Leaves	Lint	Seeds ^b
Amitraz	21.8	15.3	
BTS 27 271	9.7	15.9	0.4
BTS 27 919	25.8	29.7	16.3
BTS 24 868	6.9	8.1	13.2
BTS 28 037	3.8	0.6	
M 1	8.4	2.3	
M 2	0.8	9.1	
Total	80.4	83.8	29.9

a. chemical structures are provided in attachment #1; M-1 and M-2 are unknown metabolites.

b. reflects characterization of the radioactivity in the hexane-soxhlet extraction phase only (36.6% of the TRR). Radioactivity in the seed wash (18.2% of the TRR), acetonitrile/soxhlet extraction phase (10.7% of the TRR), and bound residues (34.5% of the TRR) was not chemically identified. The uncharacterized radioactivity reflects an amitraz tissue equivalent of 0.2 ppm.

The above data adequately delineates the terminal residues in or on cotton leaves and lint, but does not adequately delineate terminal residues in or on cottonseeds, where <40% of the TRR was chemically identified.

For the purpose of this temporary tolerance request (0.3 ppm in or on cottonseed), we will translate the metabolism data from cotton leaves and lint to cottonseeds; therefore, the amitraz residues of concern in and on cottonseed are the parent compound and its BTS 27 271 and BTS 27 919 metabolites, calculated as amitraz.

The petitioner should be advised that permanent tolerances for amitraz residues in or on cottonseed, will require additional characterization of the radioactivity in or on cottonseed.

Deficiency 1a. has been resolved (for the purpose of this temporary tolerance request only).

Deficiency 2, restated from review dated 8-12-87

We can draw no conclusions concerning the adequacy of the analytical method (Accession No. 263864, PP#4F3081) used for determining combined amitraz/metabolite residues in cottonseed. The petitioner must provide additional information with respect to the metabolic nature of amitraz in cottonseed before this deficiency can be resolved.

Petitioner's Response

The petitioner submitted a cotton metabolism study, which adequately describes (for the purpose of this temporary tolerance request) the metabolic nature of amitraz in cottonseed. Furthermore, the residue analytical method (Accession No. 263864, PP#4F3081) was validated by assaying several cottonseed samples from the metabolism study.

RCB's Comment

For the purpose of this temporary tolerance request, we consider deficiency 2 to be resolved.

Deficiency 4a, restated from memo of 8-12-87

We can draw no conclusions from the limited residue data submitted, concerning the adequacy of the proposed 0.3 ppm combined tolerance for amitraz/metabolite residues on cottonseed. The petitioner must provide additional information with respect to the metabolic nature of amitraz in cottonseed before this deficiency can be resolved. Additional residue data may be required.

Petitioner's Response Deficiency 4a

The petitioner responded by submitting a cotton metabolism study which (for the purpose of this temporary tolerance request) adequately describes the metabolic nature of amitraz in or on cottonseed.

RCB's Comment

The metabolic nature of amitraz in or on cottonseed is adequately understood (for the purpose of this temporary tolerance request). The residue of concern is the parent compound, per se, and its 2,4-dimethylaniline containing metabolites BTS 27 271 and BTS 27 919. Since these residues were detected by the residue chemistry method, we conclude that the residue data provided (Accession No. 402593-02) are adequate to support the requested tolerance.

Conclusions

1. All deficiencies (1a., 2 and 4a.) cited in our initial review of PP#7G3547 (F. Suhre, memo of 8-12-87) have been resolved.
2. Temporary tolerances for amitraz in or on cottonseed should be expressed in terms of the parent compound (amitraz) and its metabolites N-(2,4-dimethylphenyl)-N-methyl formamide and N-(2,4-dimethylphenyl)-N-methylmethanimidamide (both calculated as amitraz).

Recommendation

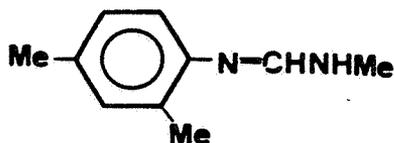
TOX considerations permitting, we recommend in favor of the temporary tolerance (0.3 ppm) for amitraz residues in or on cottonseed, as requested in PP#7G3547.

ATTACHMENT: Chemical structures of amitraz metabolites (1 page)

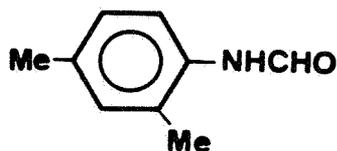
cc: R.F., S.F., Circu., PP#7G3547, Reviewer, RCB TAS Staff, PMSD/*F^sB*
RDI: EZ:5/11/88:RDS:5/11/88
TS-796:FBS:fbs:557-1883:CM#2:RM814:5/11/88

ATTACHMENT : AMITRAZ METABOLITES

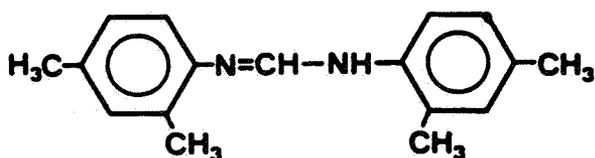
BTS 27 271 N-Methyl-N'-(2,4-dimethylphenyl)formamidine



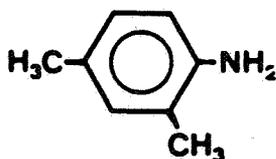
BTS 27 919 N-(2,4-Dimethylphenyl)-N-formyl-amine
(2,4-Dimethylformanilide)



BTS 28 037 N,N'-Bis(2,4-dimethylphenyl)formamidine



BTS 24 868 2,4-Dimethylaniline



Taken from MRID No. 405908-01