

2/21/96

MEMORANDUM

SUBJECT: PP#5F4546, Evaluation of Analytical Method and Residue Data for New Use Pattern on Lettuce. Tolerances for the Inadvertent Residues of Cyromazine in/on Cotton, Alfalfa, and Sudangrass. Chemical# 121301, DP Barcode: D216971, CBTS#: 15802, MRID#:436944-01

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Ciba Crop Protection Division, Ciba-Geigy Corp. requests the establishment of tolerances for inadvertent residues of the insecticide/ insect growth regulator cyromazine (N-cyclopropyl-1,3,5-triazine-2,4,6-triamine) and its metabolite melamine (1,3,5-triazine-2,4,6-triamine) calculated as cyromazine at 2 ppm on cottonseed, alfalfa hay, and sudangrass hay, 1 ppm on alfalfa and sudangrass forage, and 0.2 ppm on alfalfa seed after rotation from head lettuce.

Tolerances have been established for cyromazine in/on other RACs; including head lettuce at 5 ppm, celery at 10 ppm, curcubit vegetables at 2 ppm, and leafy vegetables (except brassica, including leaf lettuce) at 10 ppm (40 CFR §180.414). Separate tolerances for both cyromazine and melamine are established at 0.05 ppm for poultry fat, meat, and meat byproducts from chicken layer hens and chicken breeder hens only. A petition to establish tolerances for the inadvertent residues of cyromazine

on sweet corn and radishes is currently in reject status awaiting an ILV and revised Section F (PP#6F3332, 2/13/95).

No Registration Standard for cyromazine has been issued.

Conclusions

1. The product chemistry of cyromazine has been adequately described. No further data are required for this proposed use.
2. The proposed use directions in Section B are inadequate. The proposed use pattern states that rotation is permitted to sweetcorn and radishes in addition to cotton, alfalfa, and sudangrass. Until the requirements allowing the rotation to sweetcorn and radishes have been met, the rotation to sweetcorn and radishes must be deleted from the label.
3. The metabolism of cyromazine in plants is adequately understood. No further data are required for this proposed use. Based on data from other crops, the residues of concern are cyromazine and its metabolite, melamine. Total residues are expressed as parent.
4. The metabolism of cyromazine in animals is adequately understood. No additional animal metabolism data are necessary for this proposed use. The residues of concern are cyromazine and its metabolite, melamine. An additional metabolite 1-methyl-cyromazine has also been found in liver and kidney. Total residues are expressed as parent.
5. Adequate enforcement methods for cyromazine and melamine are in PAM II. Two analytical methods were used here for data generation. The first method, an HPLC method designated AG-408, has been published in PAM II for enforcement purposes. The second method, AG-621, was developed to circumvent contamination problems. If the registrant intends this method be used for enforcement purposes, a tolerance method validation (TMV) will be required. No further methodology is necessary for this proposed use.
6. Data have been submitted for the recovery of cyromazine, and its melamine and 1-methyl-cyromazine metabolites by FDA Multiresidue Methods. Cyromazine is recovered by FDA multiresidue methods. Melamine and 1-methyl-cyromazine are not recovered by those methods. No further data are required for this petition.
- 7a. Adequate data have been presented to show that the new use pattern for cyromazine on head lettuce will not produce residues higher than the current established tolerances.
- 7b. There are insufficient residue data to support the proposed rotational crop use. Eleven more rotational crop studies are necessary for alfalfa and eight more each for both cotton and

sudangrass. See the Geographic Representation section of this review for details on suggested trial sites.

7c. The geographic diversity of the studies in this petition is inadequate to represent the major domestic growing regions for cotton, alfalfa, and sudangrass. Although only lettuce is specified as a target crop in this petition, cyromazine is approved for use on other crops. Therefore, it is not appropriate to limit the rotational crop studies to the primary areas of lettuce production (CA, AZ, and TX).

7d. The cotton processing studies are adequate. No further information is necessary for this proposed use. A Section 701 Maximum Residue Limit (MRL) will probably be required for the not ready-to-eat feed cottonseed hulls.

7e. Cotton gin byproducts is a significant feed item. The residues of cyromazine and melamine on that RAC must be determined.

8. There are sufficient storage stability data in EPA files to support the residue data presented with this petition. No further data are necessary for this proposed use.

9. Alfalfa, cotton, and sudangrass, as well as the associated processed commodities of cotton are all significant feed items. Feeding these items containing cyromazine residues to poultry is not expected to be a problem and the established poultry and egg tolerances will remain adequate. However, a dietary burden cannot be determined for beef and dairy cattle without adequate data on cotton gin byproducts.

Recommendations

CBTS recommends against the establishment of the proposed cyromazine tolerances for inadvertent residues for the reasons outlined in conclusions 2, 7b, 7c, 7d, 7e, and 9. Clarification is requested re Conclusion 5 as to whether Method AG-621 is intended for enforcement purposes.

A DRES analysis will be needed, but will not be requested until the deficiencies of this petition are resolved.

Detailed Considerations

Manufacture and Formulation

The product chemistry of cyromazine has been adequately described (PP#9G2230, 11/14/79 and PP#5F3177, 2/13/85). Technical cyromazine (CGA-72662) is 95% pure. CBTS does not foresee a residue problem for the impurities identified at or above 0.1% in

the TGAI cyromazine. No further product chemistry data are required for this proposed use.

Proposed Use

The proposed use directions, Section B, are inadequate. The proposed use directions state that the product, Trigard® (EPA Reg. No. 100-654), a wettable powder containing 75% active ingredient cyromazine, is to be applied at a rate of 0.125 lb ai/A as a foliar spray for leafminer control. For ground applications use 50 gal/A of water and 5 gal/A for air applications. Repeat applications at seven day intervals as necessary. Do not apply within seven days of harvest, 7 day PHI. Do not make more than 6 applications to head lettuce, and 5 applications to leaf lettuce. The maximum number of applications has been reduced from eight to six, on the proposed new federal label. Do not rotate to any other crop except cotton, alfalfa, and sudangrass within 1 month after the last application, and sweet corn and radishes within 3 months after the last application.

All the requirements allowing the rotation to sweetcorn and radishes have not been met. The petition for the rotation to sweetcorn and radishes is currently in reject status awaiting an ILV and a revised Section F (PP#6F3332, 2/13/95). The rotation to sweetcorn and radishes must be deleted from the label. CBTS has no objections to the reduction in the maximum number of applications to lettuce.

Nature of Residue - Plants

The metabolism of cyromazine in plants is adequately understood. The metabolism of cyromazine has been studied in celery, head lettuce, and tomatoes (PP#5G3176, 2/4/85; PP#5F3180, 3/20/85; and PP#6F3329 1/28/87). The residues of concern are cyromazine and its metabolite melamine. Residues are expressed as parent equivalents. No further plant metabolism data are required for this proposed use.

Nature of Residue - Animals

The metabolism of cyromazine in animals is adequately understood. The residues of concern in meat, milk, and meat byproducts (except liver and kidney) are cyromazine and melamine. The residues of concern in liver and kidney is cyromazine and melamine, and 1-methyl-cyromazine (PP#6F3329, 4/2/93). The residues of concern in poultry and eggs are cyromazine and melamine (1F4016, 12/8/92). No further animal metabolism data are required for this proposed use.

Analytical Methods- Enforcement

Adequate methodology exists for the determination of the residues of cyromazine and its metabolite melamine in plants. Ciba-Geigy Method AG-408, has been validated as an enforcement method and has been published in PAM II June 1986. Samples are extracted by refluxing with aqueous methanol. An aliquot of the extract is evaporated until only water remains. The sample is diluted in 0.1 N HCl and partitioned with CH₂Cl₂ and hexane. The sample is cleaned by cation exchange chromatography followed by an amino exchange cartridge. Both analytes are quantitated by HPLC with a two column switching system and UV detector.

A method for the determination of cyromazine residues in animal tissues, designated Method AG-548A, has been submitted but has yet to undergo an adequate independent laboratory validation (ILV). This must be completed before the method is sent for tolerance method validation (PP#6F3333/FAP#2H5640, 2/13/95).

The contract laboratory for the submitted field trial studies, ADPEN Laboratories, encountered problems with contaminated control samples. A new plant method designated AG-621 was developed to circumvent the difficulties. The method substitutes gas chromatography with a nitrogen/phosphorus detector in place of the HPLC. A solid phase silica gel column is also used when additional clean-up is required and 20 ml of water is added to the dry substrates to hydrate them prior to extraction. Control samples of the various substrates were fortified with cyromazine from 0.05 to 5 ppm. Recoveries for both the 0.05 ppm and for all the cyromazine fortification levels were 92% (stdev=20). Control samples of the various substrates were fortified with melamine from 0.04 to 5 ppm. Recoveries for both the 0.04 ppm and all the melamine fortification levels were 91% (stdev=20). The performing laboratory provided sample calibration curves, and chromatograms with the petition. If the registrant intends this new method for enforcement purposes, a TMV will be required. Clarification by the petitioner is needed.

Analytical Methods- Multiresidue

Multiresidue methods data indicate the recovery of cyromazine via FDA Multiresidue Protocol III, while no recovery of melamine or 1-methyl-cyromazine via any of the multiresidue methods was accomplished. The information has been forwarded to FDA for evaluation (PP#1F4016 & 2F4053, 7/16/93). No further testing is necessary for this proposed use.

Magnitude of Residue: MRID#:436944-01

There are sufficient data to show that the new use pattern will not produce residues of cyromazine and melamine in excess of the established tolerances on head lettuce. Data from six field

studies conducted in 1991 in California (2), Texas (1), Florida (1), and Arizona (2) were presented with the petition. In each test, the maximum use rate of 0.125 lb ai/A was sprayed on head lettuce 6 times at 7 day intervals over the growing season for the maximum seasonal total of 0.75 lb ai/A/season. In addition, studies 02-IR-009-91 in CA and 0W-IR-505-91 in AZ included two additional plots each which were sprayed at 3x and 5x the maximum use rate. Head lettuce samples from all these plots were taken after the last application, 0-day PHI, and at seven days, 7-day PHI. Lettuce samples from the exaggerated use plots were not analyzed. The analysis of the 1x head lettuce samples indicate that the new use pattern will not produce residues higher than the current established tolerance, 5 ppm.

The performing laboratory, ADPEN Laboratories, provided sample calibration curves, and chromatograms with the petition.

Table 1: Maximum Cyromazine Residues in/on Head Lettuce Using New Application Pattern.

Sample	Cyromazine ppm	Melamine ppm	Combined* ppm
Heads, 0-day (untrimmed)	3.8	0.8	4.4
Heads, 7-day (untrimmed)	2.5	1.1	3.2
Heads, 7-day (trimmed)	0.6	0.3	0.8
Trimmings, 7- day	6.2	2.0	8.1

* Maximum combined residue found on an individual sample.

Rotational Crops: MRID#:436944-01

There are insufficient data presented with this petition to support inadvertent residue (rotational crop) tolerances on cotton, alfalfa, and sudangrass. Thirty days after the last application of cyromazine to head lettuce, the test plots in California (2) and Arizona (2) were replanted with stands of cotton, alfalfa, and sudangrass. The Texas study was replanted only with cotton. The Florida study was not replanted. Samples of the rotated crops were harvested at the appropriate time, normal harvest, for these crops. The samples were stored frozen until analysis. Cotton and alfalfa planted following the head lettuce which received exaggerated application rates were harvested and sent for simulated commercial processing.

The maximum combined residue of cyromazine and melamine found in

cotton grown in soil from the 1x rate plots was 0.18 ppm. The maximum combined residues found on alfalfa commodities found in the 1x rate plots was in alfalfa hay at 1.4 ppm. The highest combined residue found in sudangrass grown in the 1x rate plots was in hay at 1.4 ppm.

Table 2: Maximum Cyromazine Residues Found in Rotational Crops After 30 Day Plant Back Interval.

Substrate	Cyromazine ppm	Melamine ppm	Combined* ppm
Cotton	<0.05	0.18	0.18
Alfalfa			
Forage			
early bloom 87-108 days	0.19	0.75	0.85
mature 99-151 days	0.32	0.76	0.85
Hay 99-151 days	0.51	1.20	1.40
Seed 202-212 days	<0.05	0.12	0.12
Sudangrass			
Forage 15-30"	0.46	0.25	0.67
mature	0.17	0.12	0.26
Hay	0.10	1.30	1.40

* Maximum combined residue found on an individual sample.

There are two cotton raw agricultural commodities (RAC) of regulatory concern: undelinted cotton seed and cotton gin byproducts. While some data for cottonseed has been submitted, data for the residues of cyromazine on cotton gin byproducts (commonly called gin trash) are also required. Cotton gin byproducts, plant residues from ginning cotton, consist of burrs, leaves, stems, lint, immature seeds, and sand and/or dirt. Cotton must be harvested by commercial equipment (stripper and mechanical picker) to provide an adequate representation of plant residue for the ginning process. At least three field trials for

each type of harvesting are needed for a total of 6 trials. These can be conducted with the additional cotton residue studies.

There are insufficient rotational crop studies to support the proposed inadvertent residue tolerances. The rotational field studies data above show that detectable residues will occur at the 30 day plant back interval requested, which indicates that rotational crop tolerances will be required. The number of trials required is the same as that to establish primary tolerances on all crops. Twelve rotational crop studies for each of the RACs must be performed with the correct geographic diversity to establish the tolerances. Eleven more studies on alfalfa and eight more on each of cotton and sudangrass are required (EPA Pesticide Reregistration Rejection Rate Analysis Residue Chemistry, EPA 738-K-001, 6/94). Cotton gin byproducts data must also be collected.

Chromatograms from control, samples, and fortifications, as well as standard curves were provided with the petition by the performing laboratory, ADPEN Laboratories.

Processing Studies: MRID#:436944-01

The data from the processing studies on cotton and alfalfa are adequate.

The alfalfa processing studies indicate that 0.6 to 1.7x, average 1x, concentration of cyromazine residues occur in the processed commodities. No further processing data for inadvertent cyromazine residues in alfalfa are necessary. In fact, no processing studies are required at all for alfalfa per Table II (9/95) of the Residue Chemistry Guidelines.

Table 3: Alfalfa Processing Study Following Inadvertent Cyromazine Exposure.

Alfalfa Commodity	Cyromazine Equivalents ppm			Concentration Factor			
	1x	3x	5x	1x	3x	5x	AVG
Study 02-IR-009-91							
Hay	1.4	2.3	5.0	-	-	-	-
Meal	1.4	2.4	4.0	1	1	0.8	1
Pellets	1.2	2.8	4.6	0.9	1.2	0.9	1

Study OW-IR-505-91							
Hay	1.2	7.4	12	-	-	-	-
Meal	1.0	6.6	20	0.8	0.9	1.7	1.1
Pellets	0.7	7.1	16	0.6	1	1.3	1

The data from the cotton processing studies show that cyromazine combined residues concentrate 0.9 to 2.7x (avg. 1.5x) on cottonseed hulls and 0.6 to 1.5x (avg. 1.1x) in cottonseed meal. No residues were found in oils or soapstock even at the 5x rate. No further processing data for inadvertent cyromazine residues in cotton are necessary. The concentration of residues in meal is not significant. A Section 701 MRL will probably be required for the not ready-to-eat animal feed cottonseed hulls.

Table 4: Cotton Processing Study Following Inadvertent Cyromazine Exposure.

Cotton Commodity	Cyromazine Equivalents ppm			Concentration Factor				
	Appl Rate	1x	3x	5x	1x	3x	5x	AVG
Study 02-IR-009-91								
Cottonseed		0.09	0.28	0.12	-	-	-	-
Hulls		0.16	0.26	0.32	1.8	0.9	2.7	1.8
Meal		<0.10	0.18	0.18	<1.1	0.6	1.5	1.1
Oil, crude		<0.10	<0.10	<0.10	<1.1	<0.4	<0.8	<0.8
Oil, refined		<0.10	<0.10	<0.10	<1.1	<0.4	<0.8	<0.8
Soapstock		<0.10	<0.10	<0.10	<1.1	<0.4	<0.8	<0.8
Study OW-IR-505-91								
Cottonseed		0.08	0.30	0.75	-	-	-	-
Hulls		<0.10	0.34	0.75	<1.3	1.1	1.0	1.1
Meal		0.08	0.43	0.82	1.0	1.4	1.1	1.2
Oil, crude		<0.10	<0.10	<0.10	<1.3	<0.3	<0.1	<0.6
Oil, refined		<0.10	<0.10	<0.10	<1.3	<0.3	<0.1	<0.6
Soapstock		<0.10	<0.10	<0.10	<1.3	<0.3	<0.1	<0.6

The petitioner did not include the RAC cotton gin byproducts in the field portion of the submitted studies. Because cotton gin byproducts is up to 20% of the diets of beef and dairy cattle (Table 2, 9/95), cotton field trials must include cotton gin byproducts.

Geographic Representation

Although only lettuce is specified as a target crop in this petition, cyromazine is approved for use on other crops. Therefore, it is not appropriate to limit the rotational crop studies to the primary areas of lettuce production (CA, AZ, and TX). In order to establish the requested inadvertent residue tolerances on alfalfa, cotton, and sudangrass, twelve studies must be conducted for each commodity (the same number required to establish a primary tolerance). Therefore, the following requirements apply, for alfalfa, 11 additional studies with the following geographic distribution are necessary: one study in each of Regions 1, 2, 9, and 11, and six studies in Region 5. For cotton, eight additional studies with the following geographic distribution are necessary: one in each of Regions 2 and 6, three in Region 4, and four in Region 8. For sudangrass, eight additional studies spread throughout the U.S. at the petitioner's discretion (EPA Pesticide Reregistration Rejection Rate Analysis Residue Chemistry, EPA 738-K-001, 6/94).

Storage Stability

Head lettuce, leaf lettuce, celery, mushrooms, and tomatoes containing cyromazine and melamine residues were analyzed and frozen at -15°C for periods from 9 to 24 months. Samples were removed from storage and reanalyzed; there were no significant changes in the level of the residues. Residues of cyromazine and melamine were stable in/on those crops in frozen storage for at least 24 months (PP#6F3329, 1/28/87).

The longest harvest-to-analysis time for commodities in the present submission was for lettuce samples, which were stored for 6-25 months. Sudangrass matrices were stored for 15-24 months, cottonseed and processed fractions for 9-20 months, and alfalfa matrices for 11-22 months. The storage stability data in EPA files are sufficient to support the residue data. No further storage stability data are necessary for this proposed use.

Meat, Milk, Poultry, and Eggs

Cottonseed and alfalfa meal are significant poultry feed items. The dietary burden of inadvertent cyromazine residues for poultry based on the proposed tolerances would be 0.27 ppm as a result of feeding residue containing cottonseed meal (0.2 ppm tolerance x 20% of diet/ 89% dry matter = 0.045 ppm) and alfalfa meal (2 ppm tolerance x 10% of diet/ 89% dry matter = 0.225 ppm). Cyromazine is registered as a feed-through larvicide at 5 ppm in the poultry diet. The addition of cyromazine residues in cottonseed and alfalfa meal would not result in significant tissue or egg residues. The established poultry and egg tolerances of 40 CFR §180.414 remain adequate.

Cottonseed, cotton meal, cotton hulls, cotton gin byproducts, alfalfa forage, alfalfa hay, alfalfa meal, grass forage, and

grass hay are significant feed items for beef and dairy cattle. The dietary burden for beef and dairy cattle cannot be determined without the appropriate data for cotton gin byproducts. The petitioner must provide the data for cotton gin byproducts. This is a deficiency for this petition.

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2/20/96

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