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MEMORANDUM

Subject: PP#1F4016 - CYROMAZINE (TRIGARD®) ON LEAFY VEGETABLES (EXCEPT BRASSICA) CROP GROUP.
Review of Residue Data and Analytical Method.
(MRID # 419763-01)[CBTS # 9817]{DP Barcode D177546}

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INTRODUCTION

Ciba-Geigy Corporation, Agricultural Division proposes a crop group tolerance for residues of its insecticide cyromazine, trade named Larvadex® and Trigard® (N-cyclopropyl-1,3,5-triazine-2,4,6-triamine) and its principal metabolite, melamine (1,3,5-triazine-2,4,6-triamine) on the leafy vegetables (except Brassica) crop group at 10 ppm.

Tolerances have been established for combined residues of cyromazine and its metabolite melamine calculated as cyromazine in eggs at 0.25 ppm (see 40 CFR 180.414(a)), in meat, fat, and meat by-products of poultry (from chicken layer hens and chicken breeder hens only) (see 40 CFR 180.414 (b and c) at 0.05 ppm, and at 10 ppm in celery, and 5 ppm in head lettuce (see 40 CFR 180.414(d)).

Cyromazine, per se, tolerances are established in poultry feed at 5 ppm when cyromazine is used as prescribed in 40 CFR

186.1400(a, b, c, and d). Currently there are no cyromazine food additive tolerances.

No Registration Standard for cyromazine has been issued.

No Special Local Need (SLN) registrations have been granted. Recent Emergency Exemptions (Section 18) for use of cyromazine on potatoes (92-Fl-001, October 25, 1991, J. Abbotts; 92-Mi-0003, April 20, 1992, M.J. Nelson; and 91-Fl-0012, February 26, 1991, D. McNeilly) received favorable Chemistry Branch recommendations. For the 1992 Section 18s on potatoes cyromazine residues were not expected to exceed 3 ppm. An Emergency exemption for use of Trigard® (cyromazine) on tomatoes (see 91-Fl-0023, August 21, 1991, J. Abbotts) received favorable recommendation from Chemistry Branch. Cyromazine residues on tomatoes and tomato juice from this Emergency Exemption were not expected to exceed 1 ppm, 2 ppm in wet pomace, 30 ppm in dry tomato pomace, and 4 ppm in catsup. An Emergency Exemption for use of cyromazine on peppers with residues not expected to exceed 3 ppm also received a favorable recommendation from Chemistry Branch (see 91-TX-0026, July 24, 1991, A. Aikens).

CBTS has recommended for several cyromazine and its metabolite melamine tolerances in the following petitions which have not yet been established:

PP# 9E3791, 3 ppm on Chinese mustard,
PP# 9E3752, 3 ppm on Chinese cabbage,
PP# 6F3342, 4 ppm on peppers; and
PP# 5F3177, 10 ppm on mushrooms.

There are also a number of cyromazine petitions currently in reject status for a variety of deficiencies. They are as follows;

PP# 8F3633, 0.2 ppm on swine meat, fat, and meat by-products including kidney, and 0.4 ppm in swine liver,
PP# 6F3333, 1 ppm in tomatoes,
PP# 6F3329, 3 ppm in carrots,
PP# 6F3422, rotational crop tolerances of 0.05 ppm in cabbage, sweet potatoes, sugar beets (roots and tops), wheat grain, barley hay, sorghum forage, 0.5 ppm in wheat forage and straw, 0.2 ppm in wheat hay, 0.1 ppm in barley grain and forage, sorghum grain and fodder, and 1.5 ppm in barley straw, and
PP#5F3332, 0.5 ppm in radishes and 0.5 ppm in sweet corn ears, forage, and fodder, 0.01 ppm in milk, 0.05 ppm in bovine meat, fat, and meat by-products.

There is a co-pending petition, PP# 2F4053, currently under review for a cyromazine tolerance at 2 ppm on the cucurbit vegetable crop group.

The leafy vegetables (except brassica vegetables) crop group is defined in 40 CFR 180.34(f)(9)(iv). The representative

commodities for this crop grouping are lettuce, both leaf and head, celery, and spinach. Some of the other commodities in this crop group are Chinese spinach, celtuce, edible chrysanthemum, upland and garden cress, endive (escarole), purslane, rhubarb, and Swiss chard. Chinese mustard and Chinese cabbage, on which cyromazine tolerances have been recommended, are commodities in the Brassica (cole) vegetables crop group.

EXECUTIVE SUMMARY OF CHEMISTRY DEFICIENCIES

- NEED MULTIRESIDUE METHODS RECOVERY DATA

CONCLUSIONS

1. CBTS Conclusions on Product Chemistry/Chemical Identity

   a. CBTS does not foresee a residue problem in the leafy vegetables (except Brassica) crop group for the impurities identified at or above 0.1% in the TGAI cyromazine when Trigard® is used as directed.

   b. Ciba-Geigy has submitted the results of analysis for nitrosamines in the technical cyromazine. No nitrosamines were detected in cyromazine.

2. CBTS Conclusion on Directions for Use

   a. The petitioner has proposed an adequate set of direction for use of Trigard® containing 75% cyromazine a.i., on the representatives commodities of the leafy vegetables (except Brassica) crop group; ie, head and leaf lettuce, spinach, and celery.

   b. If the petitioner in the future proposes registration on other crops in the leafy vegetables (except Brassica) crop group, the use pattern should be no more liberal than that now being proposed for leaf lettuce and spinach.

3. CBTS Conclusion on the Nature of the Residue - Plants

The primary route for cyromazine metabolism is dealkylation of cyromazine to form melamine and cyclopropane. The nature of the residue in plants is adequately understood. The residues of concern are the parent cyromazine and its metabolite melamine.

4. CBTS Conclusion on the Nature of the Residue - Livestock

   a. Commodities in the leafy vegetables (except Brassica) crop group are not considered to be livestock feed items. Thus, a full discussion on the nature of the livestock residue is not germane to this petition.

b. However, CBTS notes that in non-ruminants; ie, hogs, horses, sheep, and poultry the nature of the cyromazine residue is adequately understood. The metabolic pathway in poultry is the same as in plants. The residues of concern are cyromazine and melamine.

c. CBTS also notes that the nature of the cyromazine residue in ruminants is not adequately understood, but deficiencies noted in previous reviews need not be resolved for this petition.

5. CBTS Conclusion on Residue Analytical Method

a. There are adequate residue analytical methods in FDA's Pesticide Analytical Manual (PAM), Vol-II to gather the crop field trial residue data for cyromazine and its melamine metabolite and to enforce the proposed 10 ppm crop group tolerance.

b. CBTS reiterates that the petitioner needs to submit recovery data for cyromazine and melamine thru the FDA multiresidue methods. We suggest the petitioner provide this data using FDA Pesticide Analytical Manual Vol-I, Appendix II, Protocols A through E.

6. CBTS Conclusion on Storage Stability

Residues of cyromazine and melamine are stable in frozen storage for at least 24 months. There are adequate storage stability data to support the crop field trial residue data in this petition.

7. CBTS Conclusions on Magnitude of the Residue - Crop Filed Trials

a. At the proposed PHI and use rate the maximum total cyromazime residues on head lettuce are 3.6 ppm. Residues of cyromazine plus melamine on head lettuce are not expected to exceed the proposed leafy vegetables (except Brassica) crop group tolerance of 10 ppm when Trigard® is used as directed.

b. At the proposed PHI and with an exaggerated number of applications the maximum total cyromazine residues on celery are 9.0 ppm. With the proposed number of applications on celery reduced from 12 to 6 (to 0.75 lb a.i. cyromazine) we reasonably expect the total cyromazine residues to be less then 9.0 ppm. Residues of cyromazine plus its melamine metabolite on celery are not expected to exceed the proposed 10 ppm tolerance for the leafy vegetables (except Brassica) crop group when Trigard is used as directed.

c. At the proposed PHI and use rate the maximum total cyromazine residues on leaf lettuce are 9.2 ppm.

Residues of cyromazine plus melamine on leaf lettuce are not expected to exceed the proposed leafy vegetable (except Brassica) crop group tolerance of 10 ppm when Trigard® is used as directed.

d. At the proposed PHI and use rates the maximum total cyromazine residues on spinach are 9.3 ppm. Residues of cyromazine plus melamine on spinach are not expected to exceed the proposed leafy vegetables (except Brassica) crop group tolerance of 10 ppm when Trigard® is used as directed.

e. The petitioner has presented an adequate amount of multi-year and geographically representative crop field trials for cyromazine on celery, head and leaf lettuce, and spinach to support a crop group tolerance.

8. **CBTS Conclusion on Magnitude of the Residue - Processed Food/Feed**

There are no processed food or feed commodities associated with the commodities in the leafy vegetables (except Brassica) crop group. Thus, no processing studies are required for cyromazine on the leafy vegetables (except Brassica).

9. **CBTS Conclusion on Magnitude of the Residue - Meat, Milk, Poultry, and Eggs**

Head and leaf lettuce, spinach, celery, and the other commodities in the leafy vegetables (except Brassica) crop group are not considered livestock feed items. There is little likelihood of secondary residues of cyromazine and melamine occurring in meat, milk, poultry, and eggs from the proposed use of Trigard®.

10. **CBTS Conclusion on Harmonization of Tolerances**

a. Compatibility is not a problem with Canadian and Mexican tolerances as these countries have no established cyromazine tolerances for any of the commodities in the leafy vegetables crop group.

b. Codex tolerances for cyromazine, per se, are established at Step 7B on celery and head lettuce at 5 ppm. Compatibility cannot be achieved with the Codex tolerance at this time due to the higher residues detected from the use in USA, and that the metabolite melamine is a significant portion of the total residue.

RECOMMENDATION

CBTS cannot, at this time, recommend for the requested cyromazine plus melamine tolerance on the leafy vegetables (except Brassica) crop group for the reason cited in the Executive Summary and further described in Conclusion 5b.

For further consideration the petitioner should be advised to resolve the deficiency noted above.

DETAILED CONSIDERATIONS

PRODUCT CHEMISTRY/CHEMICAL IDENTITY

All product chemistry data for cyromazine has been previously submitted and adequately reviewed (see memoranda in PP# 9G2230 by A. Rathman dated November 14, 1979; and in PP# 5F3177 by E. Haeberer dated February 13, 1985). The description of the starting materials, manufacturing process, formation of impurities, both actual and theoretical, and analysis of various batches of the technical material have been presented and reviewed. Technical cyromazine (CGA-72662) is 95% pure. CBTS does not foresee a residue problem in the crop group leafy vegetables (except Brassica) for the impurities identified at or above 0.1% in the TGAI cyromazine when the formulation Trigard® is used as directed.

Ciba-Geigy has submitted the results of analysis for nitrosamines in the technical cyromazine. No nitrosamines were detected in cyromazine. CBTS (aka DEB) accepted the results of the study (see memorandum by K. Doctor dated January 27, 1989).

DIRECTIONS FOR USE

The petitioner proposes use of Trigard® (EPA Reg. No. 100-654), a wetable powder containing 75% active ingredient cyromazine to control leafminers in the leafy vegetables (except Brassica) crop group. Trigard® is packaged in 2 pound bags only with the inner bag being a water soluble bag. The entire bag is mixed with water and applied at a rate of 1/6 lb. Trigard® (0.125 lb a.i. cyromazine) per acre per application in 50 gallons water spray solution by ground equipment, or 5 gallons spray solution by aerial application. The initial Trigard® application is made when the leafminers first appear. The repeat application interval is 7 days and the PHI is 7 days.

Rotational crop restrictions are do not rotate to any crops other then the leafy vegetables crop group, except corn and radishes, and then plant these 3 months after the last Trigard® application.

At present Trigard® is registered for use on celery at a maximum of 12 applications (1.5 lbs a.i. cyromazine) per crop growing season and on head lettuce at a maximum of 8 applications (1.0 lb a.i. cyromazine) per crop growing season. For the proposed use on the leafy vegetables (except Brassica) crop group the petitioner proposes a lower total application rate for celery and head lettuce at a maximum of 6 application (0.75 lb a.i.

cyromazine) per crop growing season. CBTS has no objections to the proposed lower total application rate for celery and head lettuce as this lower application rate is not expected to have an adverse impact on the existing and proposed cyromazine tolerances. On leaf lettuce and on spinach the proposed total application are 5 for a maximum of 0.625 lb. cyromazine per crop growing season.

The petitioner has proposed an adequate set of direction for use of Trigard® containing 75% cyromazine a.i., on the representatives commodities of the leafy vegetables (except Brassica) crop group; ie, head and leaf lettuce, spinach, and celery.

If the petitioner in the future proposes registration on other crops in this crop grouping, the use pattern should be no more liberal than that now being proposed for leaf lettuce and spinach.

NATURE OF THE RESIDUE - PLANTS

No new plant metabolism studies were submitted in this petition. [^{14}C-(U)-triazine]-cyromazine metabolism studies in the representative commodities celery and lettuce were presented and have been reviewed. A cyromazine metabolism study in tomatoes was also presented and reviewed (see memoranda in PP# 5G3176 by E. Haeberer dated February 4, 1985; in PP# 5F3180 by C. Deyrup dated February 8 and March 20, 1985; and PP# 6F3329 by A. Smith dated January 28, 1987). These studies are summarized as follows:

CELERY

Celery was treated at a rate of 0.25 lb (2X maximum proposed use rate) with ^{14}C-cyromazine 6 times (maximum application was 1.5 lbs a.i. cyromazine). Mature celery had total ^{14}C-cyromazine equivalent residues of 1.55 ppm at 14 days PHI. Cyromazine, per se, was 48.2% of the total radioactivity (0.744 ppm) and the metabolite melamine was 25.45% (0.388 ppm) of the residue.

In another study celery was grown to maturity in soil treated with ^{14}C-cyromazine at a rate 0.9 lb a.i. per acre. After 6 weeks of growth the celery stalks had 0.75 ppm of ^{14}C-cyromazine equivalents and at maturity the ^{14}C-cyromazine equivalents were 0.34 ppm. At 6 weeks cyromazine, per se, was 60.3% (0.45 ppm) and melamine was 10.7% (0.08 ppm) of the residue. In the mature celery cyromazine, per se, was 43% (0.146 ppm) and melamine was 30% (0.10 ppm) of the radioactive residue.

LETTUCE

Lettuce was treated with ^{14}C-cyromazine at a rate of 0.25 lb a.i. (2X the proposed application rate) 4 times for a total amount of 1 lb a.i. cyromazine. Total ^{14}C-cyromazine equivalent residues in mature head lettuce at 7 days PHI were 3.69 ppm. In

the lettuce cyromazine, per se, was 74% (2.72 ppm) and melamine was 10.9% (0.41 ppm).

TOMATO

In the ^{14}C-cyromazine in tomato metabolism study tomatoes were treated with ^{14}C-cyromazine at a rate of 0.25 lb. (2X proposed use rate) 6 applications for a total amount of 1.5 lbs a.i. cyromazine. Total ^{14}C-cyromazine equivalent residues in tomatoes at 0 day PHI were 0.19 ppm, at 7 days PHI were 0.08 ppm ,and 0.12 ppm at 14 day PHI. The formation of melamine is rapid as at 0 day PHI melamine was 11% (0.021 ppm) while cyromazine was 76% (0.15 ppm) of the residue. At day 7 cyromazine dropped to 41% (0.032 ppm) and melamine increased to 22% (0.018 ppm) of the radioactive residue. The residue profile changed only slightly at 14 days PHI as cyromazine was 39% (0.048 ppm) of the residue, and melamine increased slightly to 26% (0.03 ppm) of the residue. By 6 weeks the cyromazine portion of the total residue dropped to 37% (0.137 ppm) while melamine increased to 44% (0.163 ppm).

ROTATIONAL CROP ^{14}C-CYROMAZINE STUDIES

Various rotational crop ^{14}C-cyromazine studies have been reported and reviewed (see memorandum PP# 6F3422 by A. Smith dated January 28, 1987). In one study ^{14}C-cyromazine was applied to soil at a rate of 0.05 lb a.i. per acre and aged 30 days before wheat, sugar beets, and lettuce were planted. Mature lettuce, sugar beet tops and roots, and wheat grain each contained less then 0.009 ppm ^{14}C-cyromazine equivalents.

SUMMARY

The primary route for cyromazine plant metabolism is dealkylation of cyromazine to form melamine and cyclopropane. Small amounts of several more polar metabolites form as plants approach maturity. The nature of the residue in plants is adequately understood. The residues of concern are the parent cyromazine and its metabolite melamine.

NATURE OF THE RESIDUE - LIVESTOCK

No new livestock cyromazine metabolism studies were submitted in this petition. Commodities in the leafy vegetables (except Brassica) crop group are not considered to be livestock feed items. Thus, a full discussion on the nature of the livestock residue is not germane to this petition.

Animal cyromazine metabolism studies have been presented in other petitions and adequately reviewed. We note that in ruminants the nature of the cyromazine residue is not adequately understood. A significant portion of the residue in milk; ie, 34%, has not been identified and a major component in liver needs verification. One metabolic pathway identified is the same as in plants which is dealkylation of cyromazine to form melamine and

cyclopropane. Another metabolite reported, but not confirmed in ruminants is 1-methylcyromazine.

In non-ruminants; ie, hogs, horses, sheep, and poultry the nature of the cyromazine residue is adequately understood. The ^{14}C-cyromazine study in poultry had laying hens fed 5 ppm of ^{14}C-cyromazine for 7 days. The egg whites had 0.09 ppm to 0.22 ppm of ^{14}C-cyromazine equivalents and the egg yolks had 0.08 ppm to 0.15 ppm of ^{14}C-cyromazine equivalents. Poultry tissues had <0.002 ppm to 0.003 ppm cyromazine equivalents. Cyromazine and melamine accounted for 77% to 85% of the residue in poultry. The cyromazine metabolic pathway in poultry is the same as in plants. The residues of concern are cyromazine and melamine.

RESIDUE ANALYTICAL METHODS

The primary residue analytical method used to gather the residue data on the representative commodities is titled "High Pressure Liquid Chromatographic Determination of Residues of Cyromazine and Melamine in Crops" dated July 15, 1983, and coded AG-408. Some of the crop field trial residue data was gathered using method AG-402, which is an earlier version of this procedure that uses GPC clean-up while AG-408 uses an anion exchange column clean-up. The methods have been previously submitted and reviewed (see memorandum in PP# 5F3180 by C. Deyrup dated February 8, 1985).

In summary, for method AG-408 25 grams of crop are refluxed in 250 ml CH_3OH-H_2O (9+1) for 2 hours. A 5 gram aliquot of the extract is evaporated on a rotary evaporator at 40°C to the aqueous solution, diluted with 100 ml 0.1 N HCl, and cleaned-up first by partitioning 2 X 50 ml CH_2Cl_2 followed by 50 ml hexane, then the acidic solution is further cleaned-up on a cation exchange column of Dowex 50W-4. Cyromazine and melamine are eluted off the Dowex 50W-4 column in 20 ml of NH_4OH-CH_3OH (1+19). Additional clean-up, if necessary, is through an anion exchange column of Dowex 1-X8 with cyromazine and melamine being eluted off in 30 ml of NH_4OH-CH_3OH (1+3). Determination is by HPLC using a Waters 6000A pump, a 25 cm X 4 mm (id) column packed with LiChrosorb-NH_2, 10um particle size. The mobile phase solvent is isocratic ACN-H_2O (9+1) at a flow rate of 0.5 ml per minute and at ambient temperature. Detection is by UV at 214 nm. Under these conditions cyromazine elutes off at about 9.5 minutes and melamine elutes off about 13 minutes.

A Petition Method Validation (PMV) was requested for method AG-408 for cyromazine and melamine on lettuce (see memorandum in PP# 5F3180 by C. Deyrup dated March 13, 1985). Lettuce was to be spiked with cyromazine at 4 and 8 ppm and with melamine at 1 and 2 ppm. EPA recoveries through the first ion exchange clean-up column ranged from 81% to 95% for cyromazine and ranged from 80% to 106% for melamine. EPA recoveries through the complete method for cyromazine ranged from 68% to 93% and for melamine recoveries ranged from 77% to 96%. The control samples used in the PMV

showed 0.17 ppm cyromazine equivalents and 0.07 ppm melamine equivalent when the samples were analyzed after the first ion exchange cleanup, but neither cyromazine nor melamine were detected in control samples taken through the entire method (see memorandum in PP# 5F3180 by M.Law of ABC/BEAD dated May 8, 1985). EPA's limit of detection for cyromazine in the PMV was 0.05 ppm using both clean-up steps. CBTS (aka RCB) concluded the method was suitable to enforce the 5 ppm cyromazine tolerance in lettuce and the 10 ppm tolerance in celery. The methods were forwarded to FDA's Technical Editing Group and published in the Pesticide Analytical Manual, Vol-II as of June 1986.

Samples of head lettuce were fortified with cyromazine and melamine at levels of 0.05 ppm, 0.2 ppm, 0.5 ppm, and 1.0 ppm Cyromazine recoveries from head lettuce ranged from 62% to 145% ($X = 85\% \pm 25\%$, $n = 9$). Melamine recoveries from head lettuce ranged from 67% to 130% ($X = 86\% \pm 20\%$, $n = 9$).

Samples of celery were fortified with melamine and cyromazine at levels of 0.05 ppm, 0.1 ppm, 0.2 ppm, and 1.0 ppm. Cyromazine recoveries ranged from 62% to 131% ($X = 92\% \pm 19\%$, $n = 17$). Melamine recoveries from celery ranged from 60% to 162% ($X = 92\% \pm 23\%$, $n = 18$).

Samples of leaf lettuce were fortified with cyromazine and melamine at levels of 0.05 ppm, 0.2 ppm, 0.4 ppm, 0.5 ppm, 1 ppm, 2 ppm, 4 ppm, and 5 ppm. Cyromazine recoveries ranged from 68% to 135% ($X = 93\% \pm 16\%$, $n= 21$). Melamine recoveries from leaf lettuce ranged from 71% to 139% ($X = 99\% \pm 17\%$, $n = 21$).

Samples of spinach were fortified with cyromazine and melamine at levels of 0.05 ppm, 0.1 ppm, 0.2 ppm, 0.5 ppm, 1 ppm, 2 ppm, and 5 ppm. Cyromazine recoveries ranged from 65% to 107% ($X = 83\% \pm 10\%$, $n = 21$). Melamine recoveries from spinach ranged from 68% to 131% ($X = 89\% \pm 15\%$, $n = 22$).

The petitioner presented photocopies of 9 chromatograms for cyromazine and melamine standards at 0.1 ng, 1 ng, 2 ng, 2.5 ng, 4 ng, and 5ng. These standards were used to prepared the cyromazine and melamine standard curves. The petitioner presented a chromatogram for one control sample each of head lettuce, leaf lettuce, celery, and spinach. There were no unidentified analytical responses (UARs) in leaf lettuce, spinach ,and celery that could interfere with the determination of either cyromazine or melamine. We noted a elevated base line in the control head lettuce; however this should not interfere with the quantitation of cyromazine and melamine. The petitioner presented copies of chromatograms showing the 1 ppm spike in head lettuce, 0.1 ppm spike in celery, 2 ppm spike in leaf lettuce, and the 0.5 ppm spike in spinach. We agree the limit of quantitation (LOQ) is in the 0.05 ppm range for both cyromazine and melamine. One chromatogram each for leaf lettuce, head lettuce, spinach, and celery showing field incurred residues was presented. The petitioner has presented adequate supporting chromatographic data.

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With the EPA PMV recovery data and the recovery data presented in this petition CBTS concludes that the petitioner has adequately validated residue method AG-408 to gather the magnitude of the cyromazine and melamine residues from the limit of quantitation of 0.05 ppm to above 8 ppm in the leafy vegetables (except Brassica) crop group. This method has passed an EPA PMV and is in PAM-II as Method II as of June 1986. AG-408 is suitable to enforce the proposed 10 ppm crop group tolerance.

CBTS reiterates that the petitioner needs to submit recovery data for cyromazine and melamine thru the FDA multiresidue methods. We suggest the petitioner provide this data using FDA Pesticide Analytical Manual Vol-I, Appendix II, Protocols A through E.

STORAGE STABILITY

No new storage stability data were submitted with this petition. Storage stability data have been previously submitted and adequately reviewed (see memorandum in PP# 6F3329 by A. Smith dated January 28, 1987). In summary, field trial samples of head lettuce, leaf lettuce, celery, mushrooms, and tomatoes containing residues were analyzed and frozen at -15°C for periods from 9 to 24 months. When samples were removed from storage and reanalyzed there were no significant changes in the residues. CBTS reiterates that residues of cyromazine and melamine are stable in frozen storage for at least 24 months. There are adequate storage stability data to support the crop field trial residue data in this petition. Field trial samples in this petition were stored from 3 to 16 months.

MAGNITUDE OF THE RESIDUE - CROP FIELD TRIALS

HEAD LETTUCE

No new crop field trial residue data were presented for cyromazine residues on head lettuce. These data have been previously presented and reviewed (see memorandum in PP# 5F3180 by C. Deyrup dated February 8, 1985). In summary, cyromazine residue data were presented on head lettuce for the 1982 and 1983 crop years from 6 field trials in Florida (2), New York, California, Wisconsin, and Texas. Head lettuce was treated with Trigard® at the proposed use rate of 0.125 lb a.i. cyromazine per acre per application 7 to 9 times with a repeat application interval of 7 days. The maximum total cyromazine application was 1.125 lbs. Three trials were also treated with an exaggerated application Trigard® at a rate of 0.25 lb (2X) a.i. cyromazine per acre per application 7 or 8 times with a repeat application interval of 7 days. In all trials a control plot that received no cyromazine applications was grown and harvested. Samples from the treated plots were grown to maturity and harvested at 0 day PHI, 7 days PHI, and 14 days PHI. Samples were frozen, then shipped with dry ice to the laboratory, and were stored in a

freezer until sample preparation and analysis. Sample preparation followed the guidance in FDA's PAM-I, Section 141.

Cyromazine residue results in head lettuce are as follows:

TABLE 1

Residue	PHI		
	0 Day	7 Day	14 Day
Cyromazine			
1X	0.13 - 8.8 ppm	<0.05 - 2.3 ppm	0.05 - 1.2 ppm
2X	0.57 - 16 ppm	<0.05 - 0.06 ppm	0.05 - 0.07 ppm
Melamine			
1X	0.09 - 0.5 ppm	<0.05 - 1.3 ppm	0.05 - 1.1 ppm
2X	0.15 - 0.45 ppm	<0.05 ppm	0.05 ppm

At the proposed PHI and use rate the maximum total cyromazime residues on head lettuce are 3.6 ppm. Residues of cyromazine plus melamine on head lettuce are not expected to exceed the proposed leafy vegetables (except Brassica) crop group tolerance of 10 ppm when Trigard® is used as directed.

CELERY

No new crop field trial residue data for cyromazine on celery were presented in this petition. These crop field trial data have been previously presented and reviewed (ibid). In summary, the petitioner has celery crop field trial data from the 1982 and 1983 crop years for 11 trials in Florida (5), California (3), Texas, New York, and Michigan. Residue data from these states represent celery production on 37,360 acres out of a national celery production on 37,660 acres. (see Agricultural Statistics, 1991). The petitioner has presented an adequate amount of multi-year and geographically representative crop field trials for cyromazine on celery to support a crop group tolerance.

Celery was treated with Trigard® at the proposed use rate of 0.125 lb a.i. cyromazine 12 to 15 times with a 7 day repeat application interval. In 3 of the trials a separate plot was treated with Trigard® at an exaggerated rate of 0.25 lb. (2X) a.i. cyromazine 12 or 15 times with a repeat application interval of 7 days. The maximum total cyromazine application was 1.5 to 1.875 lbs. A separate celery control plot at each trial site was grown to maturity without cyromazine treatments, and sampled. Celery samples were harvested at 0 days, 7 and 14 days after the last Trigard® application. Samples were frozen after harvest, then shipped with dry ice to the laboratory, and were stored in a freezer until sample preparation and analysis. Sample preparation followed the guidance in FDA's PAM-I, Section 141.

Cyromazine residue results on celery are as follows:

TABLE 2

Residue	PHI		
	0 Days	7 Days	14 Days
Cyromazine			
1X	0.05 -19 ppm	0.06 - 5.9 ppm	0.05 - 4.3 ppm
2X	0.08 - 26 ppm	0.05 - 13 ppm	0.07 - 3.6 ppm
Melamine			
1X	0.1 -1.9 ppm	0.12 - 4.3 ppm	0.05 - 3.9 ppm
2X	0.06 - 2 ppm	0.1 - 4.4 ppm	0.22 - 2.2 ppm

At the proposed PHI and with an exaggerated number of applications the maximum total cyromazine residues on celery are 9.0 ppm. With the proposed number of applications on celery reduced from 12 to 6 (to 0.75 lb a.i. cyromazine) we reasonably expect the total cyromazine residues to be less then 9.0 ppm. Residues of cyromazine plus its melamine metabolite on celery are not expected to exceed the proposed 10 ppm tolerance for the leafy vegetables (except Brassica) crop group when Trigard® is used as directed.

LEAF LETTUCE (MRID # 419763-01)

The petitioner presented magnitude of the residue data for cyromazine and its melamine metabolite on leaf lettuce in a study titled "CYROMAZINE - LEAFY VEGETABLES CROP GROUP RESIDUE SUMMARY" by M.W. Cheung, dated February 7, 1991, and coded ABR-89103.

Magnitude of the residue data for cyromazine and its melamine metabolite were presented on leaf lettuce for the crop years 1986 and 1987 from 9 trials in Arizona (2), California (2), New York, Colorado, Texas, and Florida (2). The crop field trials for both leaf and head lettuce represent lettuce production on 224,900 acres out of a national lettuce production on 231,300 acres (see Agricultural Statistics, 1991). CBTS concludes the petitioner has presented an adequate amount of multi-year and geographically representative lettuce (leaf and head) crop field trials to support a crop group tolerance.

Leaf lettuce was treated with Trigard®at the proposed use rate of 1/6 lb (0.125 lb a.i. cyromazine) 5 times with a repeat application interval of 7 days and a PHI of 7 days. The maximum total cyromazine applied was 0.625 lb. In 7 of the trials a separate plot was treated with Trigard® at an exaggerated rate of 0.25 lb. (2X) a.i. cyromazine 5 times. At each trial site a separate control leaf lettuce plot was planted, grown to maturity without cyromazine treatment, and harvested. Samples were harvested after the last Trigard® application at 0, 7, 14, and 21-22 days. Samples were frozen after harvest, shipped on dry ice to the laboratory, and stored frozen until sample preparation and analysis. Sample preparation followed the guidance in FDA's PAM-I, Section 141.

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Cyromazine residue results in leaf lettuce are as follows:

TABLE 3

Residue	PHI			
	0 Day	7 Day	14 Day	21-22 Day
Cyromazine				
1X	4.7 - 16 ppm	0.49- 7.6 ppm	0.12- 2.0 ppm	<0.05-1.2 ppm
2X	11 - 26 ppm	0.87- 8.5 ppm	0.26- 4.2 ppm	0.05 -2.4 ppm
Melamine				
1X	0.53 - 3 ppm	0.16- 2.7 ppm	0.1 - 1.9 ppm	<0.05-0.68 ppm
2X	0.8 - 5.9 ppm	0.4 - 5.4 ppm	0.17- 2.1 ppm	<0.05-0.83 ppm

At the proposed PHI and use rate the maximum total cyromazine residues on leaf lettuce are 9.2 ppm. Residues of cyromazine plus melamine on leaf lettuce are not expected to exceed the proposed leafy vegetable (except Brassica) crop group tolerance of 10 ppm when Trigard® is used as directed.

SPINACH (MRID# 419763-01)

The petitioner presented magnitude of the residue data for cyromazine and its melamine metabolite on spinach in a study titled "CYROMAZINE - LEAFY VEGETABLES CROP RESIDUE SUMMARY" by M.W. Cheung, dated February 7,1991, and coded ABR-89103.

Magnitude of the residue data for cyromazine and its melamine metabolite were presented on spinach for the crop years 1986 and 1987 from 9 trials in New York (2), California (2), Texas, Florida, Mississippi, Nebraska, and North Carolina. The crop field trials for spinach represent production for both fresh market and processed on 20,150 acres out of a national spinach (fresh market and processed) production on 37,490 acres (see Agricultural Statistics, 1981). CBTS concludes the petitioner has presented an adequate amount of multi-year and geographically representative spinach crop field trials to support a crop group tolerance.

Spinach in 8 trials was treated with Trigard® at the proposed use rate of 1/6 lb (0.125 lb a.i. cyromazine) per application 5 times for a total cyromazine application of 0.625 lb per crop growing season. The repeat application interval was 7 days and the PHI was 7 days. In 6 trials a separate plot was treated with at an exaggerated rate of 1/3 lb Trigard® (2X or 0.25 lb a.i. cyromazine) per application 5 times with a repeat application interval and PHI of 7 days. A separate spinach control plot was planted at each trial site, grown to maturity without cyromazine treatment, and harvested. One field trial received 8 applications at the proposed use rate of 1/6 lb Trigard® per acre per application and a separate plot received the exaggerated application rate of 1/3 lb (2X) Trigard® per acre per application. Spinach samples were harvested at 0, 7, 14, and 21-22 days

after the last Trigard® application. Samples were frozen after harvest, then shipped on dry ice to the laboratory, and stored frozen until sample preparation and analysis. Sample preparation followed the guidance in FDA's PAM-I, Section 141.

Cyromazine residue results on spinach are as follows:

TABLE 4

Residue	PHI			
	0 Day	7 Day	14-15 Day	21-22 Day
Cyromazine				
1X	1.3 - 21 ppm	0.36 - 7.6 ppm	0.09 - 3.7 ppm	<0.05- 2.6 ppm
2X	2.9 - 36 ppm	0.65 - 21 ppm	0.09 - 9.2 ppm	0.05 - 4 ppm
Melamine				
1X	0.19 - 11 ppm	0.15 - 3.3 ppm	0.07 - 2.5 ppm	<0.05- 1.7 ppm
2X	0.29 - 17 ppm	0.26 - 5.0 ppm	0.11 - 5 ppm	<0.05- 2.5 ppm

At the proposed PHI and use rates the maximum total cyromazine residues on spinach are 9.3 ppm. Residues of cyromazine plus melamine on spinach are not expected to exceed the proposed leafy vegetables (except Brassica) crop group tolerance of 10 ppm when Trigard® is used as directed.

MAGNITUDE OF THE RESIDUE - PROCESSED FOOD/FEED

There are no processed food or feed commodities associated with the commodities in the leafy vegetables (except Brassica) crop group. Thus, no processing studies are required for cyromazine on the leafy vegetables (except Brassica).

MAGNITUDE OF THE RESIDUE - MEAT, MILK, POULTRY, AND EGGS

Head and leaf Lettuce, spinach, celery, and the other commodities in the leafy vegetables (except Brassica) crop group are not considered livestock feed items. There is little likelihood of secondary residues of cyromazine and melamine occurring in meat, milk, poultry, and eggs from the proposed use of Trigard®.

While poultry and ruminant cyromazine feeding studies are not needed from the proposed use of cyromazine we note that these studies have been previously submitted and reviewed (see memorandum in PP# 6F3422 by A. Smith dated October 5, 1987).

HARMONIZATION OF TOLERANCES

An International Residue Limit Status Sheet (IRL) is attached to this review.

Compatibility is not a problem with Canadian and Mexican tolerances as these countries have no establishes cyromazine tolerances for any of the commodities in the leafy vegetables crop group.

Codex tolerances for cyromazine, per se, are established at Step 7B on celery and head lettuce at 5 ppm. Compatibility cannot be achieved with the Codex tolerance at this time due to the higher residues detected from the use in USA, and that the metabolite melamine is a significant portion of the total residue.

ATTACHMENT: International Residue Limit Status Sheet

cc: R.F.,Circ,Reviewer(FDG),PP# 1F4016.
H-7509C:CBTS:Reviewer(FDG):CM#2:Rm804Q:305-5826:fdg:12/3/92:edit:fdg:12//92.
RDI:SecHd:RSQuick:12/8/92:BrSrSci:RALoranger:12/8/92.

INTERNATIONAL RESIDUE LIMIT STATUS

CHEMICAL Cyromazine (Trigard®)

CODEX NO. 169

CODEX STATUS:

☐ No Codex Proposal Step 6 or above

Residue(if Step 8): _____

Cyromazine

Step 7B

Crop(s)	Limit (mg/kg)
Celery	5
Lettuce (Head)	5

PROPOSED U.S. TOLERANCES:

Petition No. 1F4016

RCB Reviewer F.D. Griffith, Jr. 3 Dec. 92

Residue: For 40 CFR 180.414(d)
Cyromazine * and its metabolite Melamine

Crop(s)	Limit (mg/kg)
Leafy Vegetables (except Brassica) Crop Group	10

CANADIAN LIMITS:

☑ No Canadian limit

Residue: _____

Crop(s)	Limit (mg/kg)

MEXICAN LIMITS:

☑ No Mexican limit

Residue: _____

Crop(s)	Limit (mg/kg)

NOTES:

* N-cyclopropyl-1,3,5-triazine-2,4,6-triamine

R1

13544

R060348

Chemical:	**Cyromazine**
PC Code:	**121301**
HED File Code	**11000 Chemistry Reviews**
Memo Date:	**12/09/92 12:00:00 AM**
File ID:	**DPD177546**
Accession Number:	**412-04-0141**

HED Records Reference Center
04/22/2004