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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APR 2 1993

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

Memorandum

Subject: PP#6F3329: Cyromazine on Carrots. Amendment of 2/17/92. CBTS# 9715. MRID# 422243-01 thru -05. DP Barcode# D176914.

and

PP#6F3333/FAP#2H5640: Cyromazine on Tomatoes. Amendment of 2/18/92. CBTS# 9716, 9717. MRID# 422551-01, -02. DP Barcode# D176906, D176909.

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The petitioner, CIBA-GEIGY, has proposed these tolerances for the combined residues of cyromazine (*N*-cyclopropyl-1,3,5-triazine-2,4,6-triamine), its metabolite, melamine (1,3,5-triazine-2,4,6-triamine), and where necessary, its metabolite 1-methylcyromazine, all expressed as cyromazine:

PP#6F3329:
- carrots, 3.0 ppm[1]
- milk, 0.03 ppm[1]
- meat, fat, and meat by-products of cattle, goats, hogs, horses, and sheep, 0.1 ppm[1]
- liver and kidney of cattle, goats, hogs, horses, and sheep, 0.1 ppm[2]

PP#6F3333:
- tomatoes, 0.5 ppm[1]
- processed tomato products excluding juice, 1.2 ppm[1]
- dry tomato pomace, 1.6 ppm[1]

(1 - cyromazine plus melamine; 2 - cyromazine plus melamine plus 1-methylcyromazine)

In addition, the petitioner has proposed the removal of the restriction "from chicken layer hens and chicken breeder hens only" from existing tolerance for cyromazine (§180.414(b)) and melamine (§180.414(c)) on poultry meat, fat, and meat by-products.

(These proposed tolerances reflect revisions in the Sections F for these petitions, and are not necessarily the originally proposed tolerances.) These petitions are being reviewed together because of common concerns over the metabolism of cyromazine in ruminants, and the need for animal feeding studies accounting for exposure from carrots and/or tomatoes. Other deficiencies outlined in the previous reviews of these petitions (PP#6F3329, A. Smith, 1/28/87; PP#6F3333, J. Stokes, 10/6/88, and A. Smith, 2/12/87) have also been addressed. These deficiencies will be reiterated below, followed by the petitioner's responses and our comments.

Executive Summary of Remaining Deficiencies:

Nature of the Residue - Animals (Storage Stability Studies for Liver, Meat, and Milk)
Independent Laboratory Validation for 1-Methylcyromazine (Liver and Kidney)
Milk, Meat, Poultry, and Eggs/Feeding Studies (Storage Stability Studies for Liver, Meat, and Milk)
Revise Section F (Tomatoes)
Revise Section B (Tomaotes)

Conclusions

1. **Proposed Use.** Issues involving directions for aerial application, and specification of the interval bewteen applications, have been resolved. The deficiency listed in Conclusion 3b of PP#6F3329 is satisfied. The deficiencies in Conclusions 4a and 4b of 6F3333 have been satisfied. (However, see Conclusion 4b of this review.)

2a. **Nature of the Residue - Animals.** CBTS is not willing to translate the results of storage stability studies for cyromazine and melamine in eggs to liver, meat, and milk. The petitioner has indicated that storage stability studies are currently underway for cattle meat, liver, and milk (p 18 of MRID# 422243-03). Since samples were stored up to 1 year, CBTS will need to receive the results of that study before concluding its review of ruminant metabolism. The deficiencies listed in Conclusion 1c of PP#6F3329, and Conclusion 3 of PP#6F3333 have not been satisfied.

2b. If the storage stability studies described in Conclusion 2a are acceptable, and indicate that cyromazine and melamine (and 1-methylcyromazine for liver) are stable in liver, meat, and milk, then CBTS can conclude that the metabolism of cyromazine in ruminants has been adequately described. The major residues in milk, meat, and meat by-products (except liver and kidney) would be cyromazine and melamine. The major residues in liver and kidney would be cyromazine, melamine, and 1-methylcyromazine.

3a. **Analytical Methods.** The recovery data, chromatograms, and other data submitted in this report indicate that the proposed method, AG-584A, may be adequate for the

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determination of 1-methylcyromazine in liver and kidney. However, the petitioner has not submitted an independent laboratory validation, as required under PR 88-5. This must be submitted before this method can be sent to EPA's Beltsville laboratories for a petition method validation. CBTS cannot accept this method at this time.

3b. **Multiresidue Methods.** CBTS will forward the submitted report to FDA for their analysis. We note that the methods examined have been superceded by new multiresidue protocols. In our communications with FDA, we will request their opinion regarding the suitability of this submission towards satisfying the multiresidue method requirements. Since newer methods have been in force for a significant period of time, CBTS will not consider this requirement satsified unless FDA is satisfied with this submission. We also note that in our previous reviews, we indicated that the multiresidue study would be necessary for any future tolerance request. (This was not listed as a deficiency.) Therefore, CBTS recommends that this tolerance request not be delayed on this account.

4a. **Residue Data.** The petitioner has submitted an adequate sample handling history and explanation of high residues found in carrot samples from the WA trial. The proposed tolerance of 3.0 ppm adequately covers expected residues of cyromazine and melamine in carrots. The deficiency listed in Conclusion 3a of PP#6F3329 has been satisfied.

4b. CBTS concludes that the tomato field trial and prrocessing studies were carried out adequately. However, the residue data suggest that 7- and 14-day PHIs have little effect on overall residue levels. Therefore, new tolerances based on 0-day PHI data must be proposed. The petitioner should submit a revised Section F with the following tolerances proposed for the combined residues of cyromazine and melamine:

Tomatoes	1.0 ppm
Tomato pomace, wet and dried	2.5 ppm
Processed tomato products (except juice)	2.5 ppm.

In addition, the petitioner must submit a revised Section B removing the 7-day PHI restriction and explicitly stating that there is no pre-harvest interval associated with this use.

5a. **Meat, Milk, Poultry, and Eggs.** The petitioner has proposed revised tolerances for poultry commodities, as suggested by CB. The deficiencies outlined in Conclusion 4a of PP#6F3329 and Conclusion 6a of PP#6F3333 have been resolved.

5b. The petitioner has not adequately demonstrated the long-term stability of cyromazine and its metabolites in frozen animal matrices; however, in the submitted animal feeding study, samples were stored for up to 18 months. CBTS awaits the results of an appropriate storage stability study before concluding on the adequacy of this feeding study and the proposed animal tolerances. The deficiencies outlined in Conclusions 4b and 4c of PP#6F3329, and Conclusions 6b and 6c of PP#6F3333, have not been satisfied.

5c. If the requested storage stability studies are acceptable, and indicate that cyromazine and

its metabolites are stable in animal matrices, CBTS will conclude that the feeding study is acceptable. However, CBTS calculates the dietary burden to be higher than the petitioner has estimated. Based on these exposure levels, the petitioner should propose revised tolerances, as follows:

Amend §180.414(b) [residues of cyromazine alone] to include...

Meat, fat, and meat by-products of cattle, goats, hogs, horses, and sheep	0.05 ppm
Milk	0.05 ppm

Amend §180.414(c) [residues of melamine alone] to include...

Meat, fat, and meat by-products of cattle, goats, hogs, horses, and sheep	0.05 ppm
Milk	0.05 ppm

Create §180.414(e), for tolerances of 1-methylcyromazine (1-methyl-N-cyclopropyl-1,3,5-triazine-2,4,6-triamine), calculated as cyromazine, in

Liver and kidney of cattle, goats, hogs, horses, and sheep	0.05 ppm

Recommendations

CBTS recommends against the proposed tolerances for cyromazine and its metabolites in/on carrots and the milk, meat, fat, and meat by-products of cattle, goats, hogs, horses, and sheep (6F3329), and against the proposed tolerances for residues of cyromazine and its metabolites in/on tomatoes, processed tomato products (excluding juice), and dry tomato pomace (6F3333) for the reasons outlined in Conclusions 2a, 3a, 4b, and 5b.

Detailed Considerations

- **Deficiency: Proposed Use**

◇ **PP#6F3329: (3b).** There are no residue data which reflect the proposed aerial applications. Because of the variation possible in residue levels between ground and aerial applications, residue data are needed which reflect aerial applications on carrots. Alternatively, the use directions may be revised to restrict treatments to ground applications only.

◇ **PP#6F3333: (4a).** Section B should be revised to limit aerial applications in a minimum of 10 gallons to reflect the residue data.

◇ (4b). To avoid the possibility of an over tolerance due to repeated applications at less than 7-day intervals, the petitioner should submit a revised Section B changing "Repeat application at 7-day intervals or as necessary to maintain control" to "Repeat application at a minimum of 7-day intervals when necessary to maintain control."

CIBA-GEIGY's response to the deficiency of PP#6F3329 is as follows: "EPA letter of December 6, 1991, from Robert S. Quick to Richard F. Holt, Chairman, NACA Registration Committee, states the following: 'Provided that the pesticide product label specifies that aerial applications are to be made in a minimum of 2 gallons water per acre (or 10 gallons per acre in the case of tree crops), crop field trials reflecting aerial applications will no longer be required in those cases where adequate data are available from the use of ground equipment reflecting the same application rate, number of applications, and preharvest interval.' The data originally provided in [the residue data] cover these provisions, and data from aerial trials are no longer necessary."

For PP#6F3333, CIBA-GEIGY has submitted a revised Section B reflecting changes in the proposed use rate arising from new residue field trial data submitted in support of this petition (see below). The new Section B proposes a 7-day PHI and a total of 6 applications at 1/6 lb Trigard per acre (0.125 lb ai/A); the former rate had no PHI and a maximum of 12 applications at 0.125 lb ai/A.

CBTS Comment: The Section B for PP#6F3329 limits aerial application to a minimum of 5 gallons of water per acre. The deficiency listed in Conclusion 3b is satisfied. For PP#6F3333, the requirement listed in Conclusion 4a is superceded by the aerial/ground application equivalence described above. The proposed Section B is appropriate for the residue data submitted. It also includes references to the existing label for Trigard for use on head lettuce and celery, which specifies a minimum dilution of 5 gallons of water per acre for aerial application. The change requested in Conclusion 4b has also been incorporated. The deficiencies in Conclusions 4a and 4b have been satisfied.

- **Deficiency: Nature of the Residue - Animals**

◇ **PP#6F3329: (1c).** The nature of the residues in ruminants (cows, goats, horses, and sheep) is not adequately understood. Unidentified components make up significant portions of the residues in milk and tissues. These components must be identified, and the study which characterizes the residue components must be submitted.

◇ **PP#6F3333: (3; 2/12/87).** The nature of the residues in ruminants is not adequately understood. Ingested cyromazine is metabolized and excreted with some deposition in milk and meat. In ruminants (cows, goats, sheep), the metabolite 1-methylcyromazine is reported to comprise a significant portion of the residues, and an unidentified component is about one-third of milk residue. The petitioner has been requested (PP#6F3329) to submit the characterization study for 1-methylcyromazine and to identify the unidentified component in milk.

CIBA-GEIGY has submitted a new animal metabolism study. "Metabolism of [Triazine -^{14}C]-Cyromazine in Lactating Goats", by Nicholas J. Tortora, 12/3/91, Lab. Proj. ID No. F-00105, MRID# 422243-02. A GLP compliance statement was signed and included with the report. Two lactating goats were fed one daily dose (gelatin capsule) of 150mg of uniformly triazine ring-labeled ^{14}C cyromazine (specific activity, 42.9 μCi/mg) for four days. Goats were fed ad libitum; feed consumption was monitored. Goat #1 (referred to as Goat #86 in the study) received 107 ppm; Goat #2 (Goat #85) received 75 ppm. Milk was collected twice daily (PM

and AM), excreta once daily, and tissues 6 hours after the last dose was administered. The following samples were collected and analyzed: feces, urine, whole blood, plasma, and packed cells, milk, liver, kidney, heart, bile, tenderloin, leg muscle, perirenal fat and omental fat. The in-life portions of the study (biological and analytical phases) were conducted from 7/18/90 - 8/24/90. Characterization took place between 9/18/90 and 10/29/91. Samples were stored frozen during this time period. (It has been previously concluded (A. Smith, PP#6F3329, 1/28/87) that cyromazine is stable in frozen eggs for a 23-month period.)

Total radioactivity levels were determined as follows: for tissues, blood, and feces, samples were homogenized, and triplicate subsamples of each were combusted, with determination by liquid scintillation counting of trapped CO_2. Triplicate subsamples of milk and urine were analyzed by direct aliquoting. Distribution of the activity into these various tissues is presented in Table 1. Activity was characterized for these samples: milk, liver, kidney, tenderloin, omental fat, and bile. Extraction procedures and analysis results are presented below. Typical chromatograms for all tissue samples are shown in Figure 1. Identification of the various

Table 1. Distribution of Radioactivity in Goats After Treatment with ^{14}C-Cyromazine.

	% Total Dose		
Tissue	**Goat 1**	**Goat 2**	**Avg. ppm**
Milk (PM)[1]	0.577	0.317	1.170
Milk (AM)[1]	0.109	0.077	0.187
Liver	0.429	0.366	2.703
Kidney	0.108	0.083	4.588
Tenderloin	3.142	2.178	0.866
Omental Fat	0.017	0.040	0.102
Heart	0.033	0.030	0.893
Whole Blood	0.734	0.482	1.080
Bile	0.008	0.004	3.155
Urine[1]	61.695	57.192	147.640
GI Contents	6.664	8.234	6.444
Feces[1]	1.524	3.804	4.788
TOTAL	76.04	72.81	---

1 - Average of daily samples.

metabolites was made by TLC, with MS confirmation.

Milk samples from both goats were extracted by addition of acetonitrile to the sample, followed by mixing and centrifugation. The first precipitate was separated by decanting the supernatant,

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which was then lyophilized. The dried residue was dissolved in methanol. These residues were analyzed by HPLC/LSC. Milk solids containing residues which were not released by the methanol were dissolved in water; however, these residues were not characterized due to low concentration levels of radioactivity.

Residue levels in daily milk samples (sampled in the evening and morning) are shown in Table 2. It can be seen that during the 4-day period, levels did not vary significantly from day to day. Evening samples (immediately after the sample was administered) showed much higher residue levels than morning samples, indicating that the goats quickly eliminated the residues.

Table 2. ^{14}C Cyromazine Residues in Goats Milk.

	Goat 1				Goat 2			
	PM		AM		PM		AM	
Day	ppm	% Dose	ppm	%Dose	ppm	%Dose	ppm	%Dose
1	1.094	0.138	0.194	0.042	1.059	0.077	0.257	0.029
2	1.168	0.157	0.157	0.033	1.191	0.083	0.171	0.023
3	1.197	0.159	0.165	0.034	1.091	0.083	0.175	0.025
4	1.325	0.123	No sample[1]		1.234	0.074	No sample	

[1] Goats were sacrificed 6 hours after the last dose.

Liver samples from both goats were extracted four times with 90/10 acetonitrile/water. The extractions were combined, concentrated under reduced pressure, and filtered, and then analyzed by HPLC/LSC. Most of the residues were released in this initial extraction. Bound components were reextracted with a second 90/10 ACN/H_2O solution, and then sequentially with acetone, water, and methanol, before a final combustion analysis of the remaining residue. Activity from the second ACN/H_2O and water extractions was also characterized. Too little activity was recovered from the acetone and methanol extractions (<0.5%) to permit characterization.

Kidney and tenderloin samples were extracted in the same way as liver samples, with the exception that the bound residues were not reextracted. Omental fat samples were extracted initially in hexane, but only 0.85% of the activity was extracted. Samples were then extracted with ACN, which released 97% of the activity. For kidney, muscle, and fat, only samples from goat #1 were analyzed. The similarity of the residue profiles from the liver and milk samples suggest that the residues in the goat #2 would be similar.

Characterization and analysis results are presented in Table 3.

CBTS Comments. In several cases (notably milk and fat samples) there were large portions of the extracted activity that were not characterized or identified. However, examination of the

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Table 3. Characterization of Metabolites in Goats Fed ^{14}C-Cyromazine. (MRID# 422243-02)

Commodity/ Extract	Cyromazine	Melamine	1-Methyl-cyromazine	Hydroxy-cyromazine	Extr., Not ID	Non-Extr.
Milk						
Goat 1, Day 1	46.4%				26.2%	10.8%[C]
Goat 1, Day 4	63.2%	2.3%[A]	BDL[B]	ND[B]	22.4%	10.6%
Goat 2, Day 4	53.4%				21.6%	12.4%
(avg. ppm)	(0.66)	(0.03)				
Liver (Goat 1)[D]						
ACN - 1	32.2%	7.35%	41.8%	ND	13.7%	27.8%
ACN - 2	ND	ND	0.85%	0.59%	2.64%	---
H_2O	ND	ND	0.26%	0.18%	1.16%	---
combustion	---	---	---	---	---	8.2%
Liver (Goat 2)						
ACN - 1	32.9%	4.02%	39.4%	ND	22.7%	14.4%
ACN - 2	ND	ND	1.82%	ND	1.52%	---
H_2O	ND	ND	0.58%	0.23%	2.65%	---
combustion	---	---	---	---	---	3.1%
(avg. ppm)	(0.93)	(0.16)	(1.16)			
Kidney[E]	82.5%	27.0%	6.9%	ND	1.13%	0.36%
(avg. ppm)	(3.78)	(1.24)	(0.31)			
Tenderloin[F]	85.4%	3.4%	3.9%	ND	14.3%	4.58%
(avg. ppm)	(0.79)	(0.03)	(0.03)			
Omental Fat[G]	48.9%	ND	ND	ND	48.1%	N/A
(avg. ppm)	(0.11)					

[A]- Melamine level reported is the average of the three samples. [B]- BDL: Below detection limit (0.02 ppm); ND: Not Detected. [C]- Milk solids were subjected to further extraction; however, recovered activity was too low for characterization. [D]- Acetone extraction after 2nd ACN extraction, and methanol extraction after water extraction, each yielded <0.5% of activity, and were not characterized. [E]- Overall recovery was hgher than recovery from combustion analysis. [F]- Petitioner reports, "HPLC column recovery was somewhat high at 126.8%." Confirmation of melamine and 1-methylcyromazine was not possible due to low levels of activity. Assignment based on retention times of HPLC peaks. [G]- Several minor peaks were not identified, due to low levels of activity.

chromatograms shows that there are no unidentified peaks at levels exceeding the trigger values (10% TRR/0.05 ppm). Also, greater than 10% of the TRR was found in bound residues in both milk and liver samples. Bound residues in milk were released by dissolving the solids in water; bound residues in liver were released by the sequential use of ACN, acetone, water, and methanol. Adequate steps were taken to release these residues.

CBTS is not willing to translate the results of storage stability studies for cyromazine and melamine in eggs to liver, meat, and milk. The petitioner has indicated that storage stability studies are currently underway for cattle meat, liver, and milk (p 18 of MRID# 422243-03). Since samples were stored up to 1 year, CBTS will need to receive the results of that study before concluding its review of ruminant metabolism. However, if the storage stability studies

indicate that cyromazine and melamine (and 1-methylcyromazine for liver) are stable, then CBTS can conclude that the metabolism of cyromazine in ruminants has been adequately described. The major residues in milk, meat, and meat by-products (except liver and kidney) would be cyromazine and melamine. The major residues in liver and kidney would be cyromazine, melamine, and 1-methylcyromazine.

- **Deficiency: Analytical Methods**

◇ **PP#6F3329: (2c).** Adequate analytical methods are available for enforcement of the proposed tolerances in carrots as well as suggested tolerances in meat, fat, and meat byproducts of livestock.

◇ **PP#6F3333: (3b).** A residue method is available for the metabolite 1-methylcyromazine in tissues. When the presence of this component has been verified through an RCB review of the requested study [confirming the identity of 1-methylcyromazine in animal matrices], a method trial will be performed by EPA to determine the adequacy of the method for enforcement purposes.

CIBA-GEIGY: "With the identification of 1-methylcyromazine as a major metabolite in liver and kidney of cattle and goats, a new analytical method, AG-584A, was developed to determine this metabolite in meat, milk, and blood."

This method is contained in the report "Cyromazine: Analytical Method for the Determination of 1-Methylcyromazine in Meat, Milk, and Blood by High Performance Liquid Chromatography, Including Validation Data", by Robert A. Yokley, August 22, 1991, Lab. Proj. ID No. AG-584A, MRID# 422243-04. A GLP compliance statement has been signed and included with the document. This method is nearly identical to method AG-398, which has been previously determined to be adequate for the determination of 1-methylcyromazine in milk and tissues (see PP#6F3329, A. Smith review of 1/28/87).

Residues of 1-methylcyromazine in tissues are extracted by homogenizing samples in 90/10 ACN/water. Milk and blood samples are extracted by shaking in 90/10 ACN/water for twenty minutes. For all samples, an aliquot is then cleaned up on a cation-exchange column. After the sample is loaded, the column is washed with 10 ml of water, 10 ml of methanol, and 10 ml of 15/85 NH_4OH/H_2O; the washes are then discarded. Then 40 ml of 90/10 NH_4OH/H_2O are run though the column and collected in two scintillation vials. The eluate is then transferred to a 250-mL round-bottom flask for rotary evaporation. The vials are each rinsed with 15 mL of methanol; the methanol is also transferred to the round bottom flask. The contents are reduced to dryness. Contents are prepared for analysis by LC by dissolving them in 1 mL of the appropriate mobile phase - 80/20 (meat, fat, and milk) or 90/10 (liver, kidney, and blood) ACN/H_2O, adjusted to pH 4.0 $\pm$ 0.1 with acetic acid/ammonium acetate buffer.

The report states that the extraction and cleanup of 5 samples can be completed in 8 hours, and that LC analysis can be performed overnight if automatic injection is available. Also, "Interferences are possible for liver and kidney substrates if the '90%' mobile phase is not prepared as directed." Note that reagent blanks for perirenal fat, liver, and milk showed no

peaks near the retention time of the analyte.

Recovery data are presented for a number of different substrates, as shown in Table 4. Also, the petitioner has compared recovery of ^{14}C-1-methylcyromazine to liquid scintillation counts for samples obtained from the animal metabolism study reviewed above. Recoveries from three samples containing ~1.15 ppm averaged 109%. The demonstrated level of detection is 0.05 ppm for tissues and blood, and 0.10 ppm for milk (cyromazine equivalents).

Table 4. Percent Recovery of 1-Methylcyromazine from Cattle Matrices[1]

	Fortification Level (ppm)		
Matrix	0.05[2]	0.50	1.00
Tenderloin	89, 74	89	95
Round	93, 93	95	94
Perirenal Fat	115, 106	107	105
Omental Fat	100, 94	106	95
Kidney	88, 88	90	94
Liver	114, 96	128	86
Blood	76, 84	90	88
Milk	90, 98	92	95

1 - MRID# 422243-4. Recoveries expressed as cyromazine equivalents.
2 - 0.01 ppm for milk.

CBTS Comments. The recovery data, chromatograms, and other data submitted in this report indicate that the proposed method, AG-584A, may be adequate for the determination of 1-methylcyromazine in liver and kidney. However, the petitioner has not submitted an independent laboratory validation, as required under PR 88-5. This must be submitted before this method can be sent to EPA's Beltsville laboratories for a petition method validation. This deficiency is not satisifed.

◇ **PP#6F3329/PP#6F3333: (Note to PM).** Residues of cyromazine and its metabolites must be subjected to analysis by the FDA multiresidue protocols in any future tolerance request.

CIBA-GEIGY. A study has been submitted, entitled "Determination of Cyromazine and its Major Metabolites by U.S. Food and Drug Administration (FDA) Multiresidue Protocols I, II, III, and IV," by R.K. Williams, 3/1/90, Lab. Proj. No. ABR-88136, MRID# 422243-05. The following results were found. "Cyromazine and its metabolites (cyromazine, melamine, or 1-methylcyromazine) were analyzed by HPLC (Protocol IV) using fluorescence detection. None of the compounds gave a measurable response. Protocol IV procedures cannot successfully

determine these compounds. None of the test compounds were profiled on the Florisil column described in Protocol I, either because of lack of sensitivity or the non-detectability of the compounds by EC detection. Cyromazine and melamine were determinable on the four GC columns specified for N/P detection in Protocols II and III. 1-Methylcyromazine was only determinable on the 3% OV-17 column. The charcoal cleanup column of Protocol II was evaluated for use in determining these compounds in crop and animal tissues. None of these compounds were detected baove the required 30% recovery limit on the charcoal cleanup column. Cyromazine, 1-methylcyromazine and melamine were fortified on tomatoes, lettuce, poultry lean meat, and beef liver and analyzed by Protocol III to determine if the test compounds were quantifiable by this method. The findings of this study indicate that only two of the substrates, tomatoes and lettuce, can be marginally screened by Protocol II procedures for residues of cyromazine on the 2% DEGS column at 1.0 ppm or higher. The procedures of Protocol III lack the sensitivity to accurately detect melamine and 1-methylcyromazine."

CBTS Comments. CBTS will forward this study to FDA for their analysis. We note that the methods investigated in this study have been superceded by new multiresidue protocols. In our communications with FDA, we will request their opinion regarding the suitability of this submission towards satisfying the multiresidue method requirements. Since newer methods have been in force for a significant period of time, CBTS will not consider this requirement satsified unless FDA is satisfied with this submission. We also note that in our previous reviews, we indicated that the multiresidue study would be necessary for any future tolerance request. Therefore, CBTS recommends that this tolerance request not be delayed on this account.

- **Deficiencies - Residue and Processing Data**

◇ **PP#6F3329: (3a).** RCB is not able to conclude if residues from the proposed use [on carrots] will exceed the proposed tolerance (3.0 ppm). A detailed history of the samples from the State of Washington is needed (from field collection to analysis) in order to adequately evaluate the residue picture. [Residues from that sample exceeded the proposed tolerance on first analysis. On second analysis, the residues were below the tolerance.]

CIBA-GEIGY has resubmitted analysis reports for the first and second analyses of the Washington sample. The reports were initially available in the original submission (Acc# 260634) and do not present any new information. Samples were harvested on 10/17/83. The original sample prep was performed on 11/1/83, with extraction and analysis on several dates in 6/84 and 7/84. When not being prepared, samples were stored frozen. The second analysis was done on different carrots from the same trial (as opposed to a reanalysis of the extract from the first analysis.) The complete reanalysis, including prep, was done on 12/4-6/84. (Residues of cyromazine and its metabolites have been shown to be stable in plant matrices for up to 2 years. Thus, storage stability is not a concern in this case.)

In addition, the petitioner has submitted a written explanation of the unusual results. They emphasize several times that the carrot samples were "very small", implying that the carrots

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were abnormal. There is no indication of severe weather conditions or other reasons explaining why the carrots were so small, nor is there any suggestion that carrots that small would be held out of commerce solely because of their size. The petitioner also notes a difference in preparation of the samples between the two analyses. In the first, the attached dirt was "brushed off"; in the second, the carrots were "rinsed briskly with cold water", and the samples were described as "very sandy".

CBTS Comments. The most important information in this section is the indication that the samples included a large amount of soil. It is possible that the majority of the residues found in the analyses of the WA carrots resided in the soil. This is supported by two facts: the residues decreased sharply when the second set of carrots were washed, rather than brushed clean, and the carrots were small, which would cause a larger surface/volume ratio and increase the effects of any surface contaminants. Also, the wide range of residues observed in the first analysis (1.55 to 7.5 ppm) is consistent with soil contamination, if the soil is not uniformly cleaned off the samples. The more consistent results of the second analysis (2.1 to 2.22 ppm) support this view. Given these facts, CBTS concludes that the second set of analyses of the WA samples is probably more indicative of the true level of residues in the samples. The entirety of the residue data support the proposed tolerance of 3.0 ppm in/on carrots. This deficiency is resolved.

◇ **PP#6F3333: (5c) (2/12/87).** Residue data are needed to show the level of residues expected in the tomato byproducts catsup, puree, and paste. If residues in these items exceed the level in the RAC tomatoes, then a food additive tolerance will be needed to cover such residues.

CIBA-GEIGY has responded by submitting the study, "Magnitude of Residues of Cyromazine and Melamine in Tomatoes and Tomato Processed Fractions Resulting from Foliar Applications of Trigard", by M.C. Grunenwald, 1/8/91, Lab. Proj. ID No. ABR-91045, MRID# 422551-01. A GLP compliance statement is included.

Twelve field trials were conducted in eight states - CA(4), FL(2), TX, SC, MI, OH, NJ, and PA - in which **Trigard 75W** was applied six times, at 7 day intervals, at a rate of 0.125 lb ai/A/application, for a total application of 0.75 lb ai/A. In addition, six trials were conducted in four states - CA(3), FL, TN, SC - at exaggerated rates of 0.25 lb ai/A/application (i.e. 2X) (0.313 lb ai/A for TN) (other application parameters were identical). All applications were postemergence, foliar applications with spray volumes ranging from 40-66 GPA. Samples were collected at random within the plots, frozen and shipped to CIBA-GEIGY labs in NC, where the samples were maintained frozen (-20°C) until analysis. Maximum storage time was (13) months. Storage stability studies have shown that cyromazine residues are stable in frozen tomatoes for up to 24 months (A. Smith, 2/12/87).

Samples from two CA sites were also selected for processing studies. These samples were treated at identical rates as the samples described above. Processing was conducted in CA; samples were shipped fresh from the field site to the factory. Samples were processed into whole canned tomatoes, wet pomace, dry pomace, canned tomato juice, puree, paste, and catsup. Processing procedures simulated normal commercial processing conditions as closely as possible. After processing, fractions were frozen and shipped in dry ice to NC, where they

were stored frozen until analysis.

Subsamples were weighed and extracted within eight hours after removal from the freezer and analyzed for cyromazine plus melamine residues. Analytical methods AG-408 (primarily) and AG-417A were used in the analyses. These methods have been validated and considered acceptable for enforcement and data collection purposes (A. Smith, 2/12/87). Procedural percent recoveries of cyromazine and melamine, respectively, in each fraction were as follows: fresh tomatoes, 90±13/93±15 (n=44); unwashed tomatoes, 83±4/80±3 (n=3); washed tomatoes 92/95 (n=1); whole canned tomatoes, 67/78 (n=1); wet pomace, 67±0/67±11 (n=2); dry pomace, 61±11/53±14 (n=4); canned tomato juice, 77±17/103±8 (n=2); tomato puree, 87±4/93±12 (n=2); tomato paste, 81/83 (n=1); and catsup, 72±2/90±12 (n=2).

(In addition, selected tomato samples were analyzed for the cyromazine metabolite 1-methylcyromazine, in order to confirm that it is not a plant metabolite. (1-Methylcyromazine has been identified as a metabolite in liver and kidney, see above.) Method AG-584A, which has been used for identification of this metabolite in animal commodities, was used to analyze fresh tomato samples. Procedural recoveries of 1-methylcyromazine from fortified tomatoes were 78 ± 4% (n=2). No residues (<0.05 ppm) were found in any analyzed samples, including 1X and 2X treatment rates, and 0- and 7-day PHIs.)

Results of the analysis are reported in Table 5. No apparent residues were found in any controls, except for the NJ trials, for which melamine residues of 0.06 and 0.07 ppm were found in the 7-day PHI samples, and melamine residues of 0.05 ppm were found in the 14-day PHI samples. Maximum combined residues (cyromazine plus melamine, expressed as cyromazine) found in the samples representing the proposed rate (7-day PHI, 6 applications of 0.125 lbs ai/A) were 0.36 ppm (CA).

Results of the analysis of processed products are reported in Table 6. No residues were found in any controls. The following average concentrations are observed: wet pomace, 0.7X; dry pomace, 2.4X; canned juice, 0.8X; puree, 1.2X; paste, 2.2X; and catsup, 0.75X.

Table 5. Residues of Cyromazine and Melamine in Tomatoes. MRID# 422551-01.

Location	Rate[1]	PHI (days)	Cyromazine (ppm)	Melamine[2] (ppm)	Combined (ppm)
CA_1	[redacted]	0	0.07, 0.14	<0.05, 0.06	0.07, 0.20
		[redacted]	[redacted]	[redacted]	[redacted]
		14	0.06, 0.07	0.06, 0.08	0.12, 0.15
	2X	0	0.08	<0.05	0.08
		7	0.13	<0.05	0.13
		14	0.08	0.06	0.14

Table 5. Residues of Cyromazine and Melamine in Tomatoes. MRID# 422551-01.

Location	Rate[1]	PHI (days)	Cyromazine (ppm)	Melamine[2] (ppm)	Combined (ppm)
CA_2	[redacted]	0	0.25, 0.27	0.27, 0.24	0.52, 0.51
		[redacted]	[redacted]	[redacted]	[redacted]
		14	0.08, 0.09	0.19, 0.20	0.27, 0.29
	2X	0	0.45	0.50	0.95
		6	0.27, 0.15	0.53, 0.23	0.80, 0.38
		14	0.28	0.39	0.67
CA_3	[redacted]	0	0.11, 0.13	0.06, 0.07	0.17, 0.20
		[redacted]	[redacted]	[redacted]	[redacted]
		14	<0.05, <0.05	<0.05, <0.05	<0.10, <0.10
FL_1	[redacted]	0	0.23, 0.20	0.07, 0.09	0.30, 0.29
		[redacted]	[redacted]	[redacted]	[redacted]
		14	0.11, 0.12	0.15, 0.11	0.26, 0.23
	2X	0	0.39	0.11	0.50
		7	0.40	0.20	0.60
		14	0.32	0.20	0.52
FL_2	[redacted]	0	0.24, 0.17	0.10, 0.07	0.34, 0.21
		[redacted]	[redacted]	[redacted]	[redacted]
		14	0.18, 0.13	0.12, 0.09	0.30, 0.22
TN	[redacted]	0	0.26, 0.34	0.08, 0.10	0.34, 0.44
		[redacted]	[redacted]	[redacted]	[redacted]
		14	0.08, 0.07	0.05, <0.05	0.13, 0.07
TX	[redacted]	0	0.13, 0.06	<0.05, <0.05	0.13, 0.06
		[redacted]	[redacted]	[redacted]	[redacted]
		14	0.07, 0.06	<0.05, <0.05	0.07, 0.06
SC	[redacted]	0	0.11, 0.06	<0.05, <0.05	0.11, 0.06
		[redacted]	[redacted]	[redacted]	[redacted]
		14	0.06, 0.06	<0.05, <0.05	0.06, 0.06
	2X	0	0.16	<0.05	0.16
		7	0.11	<0.05	0.11
		14	0.12	<0.05	0.12
CA_4	[redacted]	0	0.21, 0.34	0.23, 0.39	0.44, 0.73
		[redacted]	[redacted]	[redacted]	[redacted]
		14	0.05, 0.11	0.12, 0.12	0.17, 0.23
	2X	0	0.74	0.64	1.38
		7	0.49, 0.57, 0.41	0.83, 0.97, 0.63	1.32, 1.54, 1.04
		14	0.16	0.23	0.39
MI	[redacted]	0	0.09, 0.18	0.06, 0.05	0.15, 0.23
		[redacted]	[redacted]	[redacted]	[redacted]
		14	0.07, 0.06	0.15, 0.13	0.22, 0.19

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Table 5. Residues of Cyromazine and Melamine in Tomatoes. MRID# 422551-01.

Location	Rate[1]	PHI (days)	Cyromazine (ppm)	Melamine[2] (ppm)	Combined (ppm)
OH	[illegible]	0	0.19, 0.23	<0.05, 0.16	0.19, 0.39
		[illegible]	[illegible]	[illegible]	[illegible]
		14	0.07, 0.06	0.10, 0.18	0.17, 0.24
NJ	[illegible]	0	0.22, 0.13	0.10, 0.11	0.32, 0.24
		[illegible]	[illegible]	[illegible]	[illegible]
		14	0.11, 0.16	0.11, 0.14	0.22, 0.30
PA	[illegible]	0	0.10, 0.16	<0.05, <0.05	0.10, 0.16
		[illegible]	[illegible]	[illegible]	[illegible]
		14	0.08, 0.06	0.05, <0.05	0.13, 0.11

1 - 1X Rate = 6 applications at 0.125 lbs ai/A. 2X = 6 x 0.25 lbs ai/A.
2 - Melamine residues reported as cyromazine equivalents.
3 - TN "2X" rate results not reported; Trigard was applied at 0.313 lbs ai/A/app.

Table 6. Concentration of Cyromazine and Melamine Residues in Processed Tomato Products. MRID# 422551-01.

Substrate	Rate[1]	Cyromazine (ppm)[2]	Melamine (ppm)[2]	Combined (ppm)[2]	Concentration[2]
Fruit, unwashed	1X	0.06, 0.10	0.09, 0.13	0.15, 0.23	—
	2X	0.20, 0.18	0.15, 0.23	0.35, 0.41	—
Fruit, washed	1X	<0.05	<0.05	<0.10	
	2X	0.15	0.07	0.22	
Fruit, can. whole	1X	<0.05	0.11	0.11	
	2X	0.08	0.10	0.18	
Pomace, wet	1X	0.09, 0.08	0.07, <0.05	0.16, 0.08	1.1X, 0.3X
	2X	0.18, 0.19	0.11, 0.09	0.29, 0.28	0.8X, 0.7X
Pomace, dry	1X	0.16, 0.27	0.11, 0.34	0.27, 0.61	1.8X, 2.6X
	2X	0.48, 0.62	0.21, 0.68	0.69, 1.3	2.0X, 3.2X
Juice, canned	1X	0.06	0.08	0.14	0.9X
	2X	0.14	0.12	0.26	0.7X
Puree	1X	0.11	0.12	0.23	1.5X
	2X	0.19	0.14	0.33	0.9X
Paste	1X	0.16	0.18	0.34	2.2X
	2X	0.40	0.32	0.72	2.1X
Catsup	1X	0.10	0.07	0.17	1.1X
	2X	0.08	0.07	0.15	0.4X

1 - 1X Rate = 6 applications @ 0.125 lbs ai/A. 2X = 6 X 0.25 lbs ai/A.
2 - Residue values are from field trial CA_1. Duplicate values are from CA_2.

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CBTS Comments. CBTS concludes that the field and processing trials were carried out adequately. Geographical representation is appropriate; the states included represent 90.8% of 1987 US production for fresh market and 88.2% of 1987 production for processing (1988 Agricultural Statistics). The highest combined (cyromazine plus melamine) residues found in fresh tomatoes treated at the proposed treatment rate was 0.36 ppm (CA_4 trial). However, we note that there is only a small residue level decrease at 7- and 14-day PHI intervals, compared to 0-day PHI samples. (Average residue level decreases are 20% for 7 days and 25% for 14 days.) Since we can therefore expect minimal residue depletion with a 7 or 14 day PHI, we must consider the 0-day PHI data in our assessment of the tolerance. The highest combined residues (cyromazine plus melamine) observed, therefore, are 0.73 ppm (CA_4 trial). The petitioner should submit a revised Section F, proposing tolerances for the combined residues of cyromazine and melamine on tomatoes at 1.0 ppm. The petitioner should also revise Section B, removing the 7-day PHI restriction and explicitly stating that there is no preharvest interval associated with this use.

Processing trials were conducted in accordance with commercial procedures. The only significant concentrations found in processed commodities were in dry pomace (worst case, 3.2X; average, 2.4X) and paste (2.2X). Because many tomatoes are pooled together during processing, CBTS recommends that the food and feed additive tolerances be base upon the average, rather than the worst-case, concentration factors. Considering the revised tolerance suggested above for fresh tomatoes, CBTS recommends that the petitioner submit a revised Section F proposing tolerances for the combined residues of cyromazine and melamine of 2.5 ppm in wet and dried tomato pomace and in processed tomato products (except juice). [The feed additive tolerance should be in terms of wet and dry tomato pomace, in order to avoid questions of dry matter content during enforcement of the tolerance. However, for estimating the residue levels in the livestock diet from wet pomace, the tolerance for the raw commodity should be used (see below), since no concentration was observed in wet pomace per se.]

- **Deficiency: Milk, Meat, Poultry, and Eggs / Feeding Studies**

◇ **PP#6F3329: (4a).** Residues are likely to occur in eggs and meat of poultry due to the use of the feed item wet tomato pulp (PP#6F3333) [§180.6(a)(1)]. However, such residues would be adequately covered be existing tolerances [§180.414(b) and (c)]. However, these sections should be amended to include poultry in general by deleting the phrase "from chicken layer hens only." A tolerance level of 0.05 ppm is appropriate and should be proposed for poultry.

◇ **PP#6F3333: (6a).** Combined residues of cyromazine and its metabolite melamine could occur in eggs and meat of poultry, hogs, and horses. However, residues in eggs and pooultry would be adequately covered by the level of the existing tolerances for layer hens (0.05 ppm). The established tolerance should be revised to reflect poultry, in general. As a result, revised tolerance proposals are needed and should be submitted.

CIBA-GEIGY has submitted a revised Section F containing the proposed changes, and also a summary of a study entitled, "Residues of Cyromazine and Melamine in Chicken Eggs Resulting from the Feeding of Cyromazine in the Diet - A California Study", by M.W. Cheung, Ph.D., CIBA-GEIGY, Greensboro, NC, 12/12/86, Lab. Proj. ID No. ABR-86104, MRID# 422551-02.

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This study was originally submitted to California as part of the residue and efficacy requirements for registration in that state. Note that this study predates GLP requirements. This report is a summary; no chromatograms or raw data have been included. In the study, White Leghorn hens were divided into three groups: a group fed cyromazine at 5 ppm continuously for 12 weeks, a group fed cyromazine at 5 ppm on an alternating schedule (7 days on followed by 7 days off) for 12 weeks, and a control group. Each treatment group contained 24 birds. Ten eggs were taken from each treatment group at weekly intervals. Samples were packed in dry ice and shipped to the NC laboratory, where they were stored at -14°C (length of storage not indicated). Samples were analyzed for cyromazine and melamine using method AG-417A. The limits of detection are 0.05 ppm for both cyromazine and melamine. Results showed maximum residues of cyromazine of 0.13 ppm in eggs. No melamine residues were observed. Residues plateaued within 7 days of the first treatment. Residues were also depleted to below detection limits within 7 days after the cessation of treatment.

In addition, based on recommendations from the Agency in our last review, the petitioner has proposed revised tolerances for poultry commodities, removing previous restrictions from chicken layer hens and chicken breeder hens only:

0.05 ppm - residues of cyromazine in or on poultry fat, meat, and meat by-products
0.05 ppm - residues of melamine in or on poultry fat, meat, and meat by-products.

CBTS Comments: The submitted study is not necessary to support the proposed poultry tolerances. It will be maintained in our files as supplementary information. The submitted Section F is adequate; these deficiencies are satisfied.

◇ **PP#6F3329: (4b).** Residues could occur in milk, meat, fat, and meat byproducts of cattle, goats, hogs, horses, and sheep [§180.6(a)(1)] due to the feed use of sweet corn ears, forage, fodder, and cannery waste {PP#6F3332), tomato pulp (PP#6F3333), and carrots. The following levels are sufficient to cover expected residues:

0.50 ppm - Meat and meat byproducts of cattle, goats, hogs, horses, and sheep.
0.05 ppm - Fat of cattle, goats, hogs, horses, and sheep.

The identification study for 1-methylcyromazine has been requested [see Conclusion 1c]. When the study is received, revised tolerance proposals for ruminants may be needed. If the study verifies the presence of the metabolite 1-methylcyromazine, then tolerance levels for ruminants should include this metabolite.

◇ **(4c).** No estimates of residues in milk can be made until the information requested under Conclusion 1c above is submitted and reviewed.

◇ **PP#6F3333: (6b).** [Conclusion 6b identifies the same deficiencies as Conclusion 4b in PP#6F3329.]

◇ **(6c).** [Conclusion 6c identifies the same deficiencies as Conclusion 4c of PP#6F3329.]

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CIBA-GEIGY has responded to these deficiencies by submitting a study describing residues of cyromazine in the milk, blood, and tissues of dairy cows. They have also submitted revised Sections F for tolerances on animal commodities, reflecting the results of these studies. (The proposed levels are somewhat different from the levels suggested in EPA's last review of these petitions.)

The petitioner has submitted a study entitled, "Residues of Cyromazine, Melamine, and 1-Methylcyromazine in Milk, Blood, and Tissues of Dairy Cows Receiving Cyromazine in Their Diet", by John N. Darnow, Ph.D., CIBA-GEIGY, Greensboro, NC, 1/31/92. Lab. Proj. ID# ABR-91080, MRID# 422243-03. A GLP statement has been signed. There were three groups of cows; each group was fed cyromazine for 28 days at a different rate - 10, 50, or 100 ppm. Each group contained three Holstein cows weighing between 470 and 634 kg, producing between 10.1 to 20.6 kg milk/day. Two control cows were also included in the study. Milk samples were collected before dosing and on Days 1, 4, 7, 12, 19, and 26. One cow from each group was sacrificed on days 14, 21, and 28 (within 20-24 hours of the final dose), and the following samples were collected: blood, liver, kidney, perirenal fat, omental fat, round meat, and tenderloin. Samples were shipped in dry ice and frozen for up to 18 months at -20°C until analysis.

Cyromazine and melamine residues in milk were analyzed using analytical method AG-403, and in other matrices using AG-417A. These methods have been previously reviewed and deemed acceptable by the Agency (see PP#2F2707). Briefly, the two methods are very similar. Samples are mixed or extracted with 90/10 ACN/water, cleaned up on a C-18 column (AG-403 only) and run through a cation exchange column. (For AG-417A, the eluant was further subjected to an anion-exchange/cation-exchange tandem.) Final determination of cyromazine and melamine was made on an aminopropyl HPLC column with ~95/5 ACN/water as the mobile phase and UV detection at 214 nm. Melamine residues are detected as cyromazine. 1-Methylcyromazine residues were analyzed in all commodities using AG-584A (reviewed above). 1-Methylcyromazine residues are detected as cyromazine. Procedural recoveries, as reported elsewhere, range from 84-90% for all three analytes in all tissue and liquid samples. The limits of detection for each of the three analytes are 0.01 ppm in milk and 0.05 ppm in tissues. Adequate and sufficient chromatographic evidence is presented in the report.

Detected residues in milk and tissues are shown in Tables 6 and 7, respectively. To summarize, residues in milk seemed to plateau by Day 7. Maximum combined residues observed (cyromazine plus melamine plus 1-methylcyromazine, all expressed as cyromazine) were as follows: 10 ppm feeding level, 0.09 ppm; 50 ppm feeding level, 0.38 ppm; 100 ppm feeding level, 0.69 ppm. No residues of 1-methylcyromazine were found in milk. In tissues, no residues were found at levels greater than 0.15 ppm, the combined detection limit for the three analytes, for the 10 ppm feeding level group. Residues of 1-methylcyromazine were found only in liver and kidney, and only at the higher feeding levels. Residue levels generally increase with increasing feeding level. This increase is roughly proportional for milk, and is somewhat less than linear for organ and muscle tissues. Very little residues were detected in fat, regardless of feeding level.

Based on the results of these studies, CIBA-GEIGY has proposed a revised Section F proposing tolerances on animal commodities. The animal feed commodities under consideration for

Page ___ is not included in this copy.

Page 20 through 22 are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

✓ FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

cyromazine are sweet corn forage and cannery waste (PP#6F3332), wet and dry tomato pomace, and carrots. (There are other tolerances pending for wheat, barley, and sorghum commodities in PP#6F3422; the potential exposure from those uses will be accounted for in the review of that petition.) The petitioner has calculated a worst-case dietary burden for beef and dairy cattle, using percentages from Table II of the Pesticide Assessment Guidelines, Subdivision O. The estimates are as follows:

	Proposed Tolerance	Beef Cattle		Dairy Cattle	
Crop	(ppm)	% of Diet	Burden (ppm)	% of Diet	Burden (ppm)
Sweet corn forage	0.5	25	0.125	10	0.05
Tomato dry pomace	1.6	25	0.4	25	0.4
Carrot roots	3.0	30	0.9	20	0.6
Total			1.425 ppm		1.05 ppm

The calculated dietary burdens are below the feeding levels used in the submitted study. Based on these calculations, CIBA-GEIGY has proposed the following tolerances:

0.03 ppm - combined residues of cyromazine and melamine, expressed as cyromazine, in milk of dairy cattle

0.1 ppm - combined residues of cyromazine and melamine, expressed as cyromazine, in meat, fat, and meat byproducts (except liver and kidney) of cattle, goats, hogs, horses, and sheep

0.1 ppm - combined residues of cyromazine, melamine, and 1-methylcyromazine, expressed as cyromazine, in liver and kidney of cattle, goats, hogs, horses, and sheep.

CBTS Response: As noted in our review of the animal metabolism study, the petitioner has not adequately demonstrated the long-term stability of cyromazine and its metabolites in frozen animal matrices. Samples were stored for up to 18 months. CBTS awaits the results of an appropriate storage stability study before concluding on the adequacy of this feeding study and the proposed animal tolerances. These deficiencies are not resolved.

[If the storage stability studies are acceptable, and indicate that cyromazine and its metabolites are stable in animal matrices, CBTS will conclude that the feeding study is acceptable. However, CBTS does not agree with the petitioner's calculation of the dietary burden to animals. The petitioner has not accounted for the amount of moisture in the proposed feed items. Since the feed percentages are on a dry-matter basis, but the tolerances are on an "as-fed" basis, the moisture must be accounted for. Also taking into account the need for the animal to have a balanced diet, CBTS calculates the following reasonable worst-case scenarios:

Table 8. Calculated Dietary Burdens for Beef and Dairy Cattle.

Crop	Feed	Feed %DM	Feed Consumption Percent	Tolerance (ppm)	Dietary Burden (ppm)
Corn, Field	Grain	88%	45.0%	0.000	0.000
Corn, Sweet	Forage	25%	25%	0.500	0.500
Carrot	Culls	12%	30.0%	3.000	7.500
Beef Cattle	**Total:**		**100.0%**	**Total:**	**8.000**
Corn, Sweet	Forage	25%	50%	0.500	1.000
Tomato	Pomace, Wet	15%	10%	1.000	0.667
Carrot	Culls	12%	25%	3.000	6.250
Sunflower	Meal	92%	15%	0.000	0.000
Dairy Cattle	**Total:**		**100.0%**	**Total:**	**7.917**

(These diets meet or exceed protein and energy requirements for beef and dairy cattle, as determined using the SPARTAN program.) The calculated burden is higher than the petitioner has calculated; however, the predicted levels are easily covered by the feeding levels in the above feeding study. Based on these exposure levels, the petitioner should propose revised tolerances. The tolerance expression should also be changed to mimic the expression for poultry commodities, i.e. separate tolerances for cyromazine and melamine. This form of the tolerance expression will allow the Agency to more accurately track melamine residues when calculating its risk assessment. Assuming that acceptable storage stability studies indicate the stability of cyromazine and its metabolites, new tolerances should thus be proposed as follows:

Amend §180.414(b) [residues of cyromazine alone] to include...

Meat, fat, and meat by-products of cattle, goats, hogs, horses, and sheep	0.05 ppm
Milk	0.05 ppm

Amend §180.414(c) [residues of melamine alone] to include...

Meat, fat, and meat by-products of cattle, goats, hogs, horses, and sheep	0.05 ppm
Milk	0.05 ppm

Create §180.414(e), for tolerances of 1-methylcyromazine (1-methyl-N-cyclopropyl-1,3,5-triazine-2,4,6-triamine), calculated as cyromazine, in

Liver and kidney of cattle, goats, hogs, horses, and sheep	0.05 ppm]

cc: R. Lascola, RF, Circulation, D. Edwards, PP#6F3329, PP#6F3333, J. Fleuchaus (LB-132P)
H7509C:CBTS:RLascola/rjl:CM#2:Rm805B:305-7478: 3/18/93 (Rev. 3/29/93)
RDI: P.V.Errico:3/30/93; R.Loranger:3/30/93
[redacted]:Disk\3329&33A.TXT

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CBTS ACTION STUDY ACCEPTABILITY

Reviewer: ROBERT LASCOLA	**Petition No.:** 6F3329 // 6F3333
Barcode No.: D176914 // D176906 D176909	**CBTS No.:** 9715 // 9716, 9717
Chemical: CYROMAZINE	**Chemical Code:** 121301

INSTRUCTIONS:
Please enter the MRID [illegible] guideline number. (A [illegible] to fulfill requirements. [illegible] upgradeable.)

MRID No.	Guideline No.	Acceptable	Upgradeable (Additional Info.)	Unacceptable
Product Chemistry				
Nature of the Residue				
422243-02	171-4 b		✓	
Analytical				
422243-04	171-4 d	✓		
*422243-05	*			

MRID No.	Guideline No.	Acceptable	Upgradeable (Additional Info.)	Unacceptable
Storage Stability				
Magnitude of Residue (Plant and Animal Processing)				
422551-01	k, l	✓		
422551-02	j			✓
422243-03	j		✓	
Reviewed				

cc: COllinger, reviewer, file

* Multi-residue method; sent to FDA for evaluation

Note: MRID # 422243-01 is not a study per se.

CSTS ACTION STUDY ACCEPTABILITY

Reviewer: ROBERT LASCOLA	**Petition No.:** 6F3329 // 6F3333
Barcode No.: D176914 // D176906 D176909	**CSTS No.:** 9715 // 9716, 9717
Chemical: CYROMAZINE	**Chemical Code:** 121301

INSTRUCTIONS: [redacted]

MRID No.	Guideline No.	Acceptable	Upgradeable (Additional info.)	Unacceptable
Product Chemistry				
Nature of the Residue				
422243-02	171-4		✓	
[redacted]				
422243-04	171-4d	✓		
422243-05	*			

MRID No.	Guideline No.	Acceptable	Upgradeable (Additional info.)	Unacceptable
Storage Stability				
Magnitude of Residue (Plant and Animal Processing) 171-4				
422551-01	k, l	✓		
422551-02	j			✓
422243-03	j		✓	
[redacted]				

cc: COllinger, reviewer, file

* Multi-residue method; sent to FDA for evaluation

Note: MRID # 422243-01 is not a study per se.

13544

R060353

Chemical:	**Cyromazine**
PC Code:	**121301**
HED File Code	**11000 Chemistry Reviews**
Memo Date:	**04/02/93 12:00:00 AM**
File ID:	**DPD176906; DPD176914; DPD176909**
Accession Number:	**412-04-0141**

HED Records Reference Center
04/22/2004