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

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

04/05/99

MEMORANDUM

Subject: Reassessment of Established Cyromazine Tolerances (40 CFR 180.414) In/On Various Crops. Chemical No. 121301. Barcode DP D254881.

From: Jerry B. Stokes, Chemist
Thurston Morton, Chemist
Chemistry & Exposure Branch 2
Health Effects Division (7509C)

Through: Susan V. Hummel, Branch Senior Scientist
Chemistry & Exposure Branch 2
Health Effects Division (7509C)

To: George Larocca, PM 13
Registration Division (7505C)

The HED Metabolism Assessment Review Committee (MARC) concluded that the cyromazine metabolite melamine should not be included in the cyromazine tolerance expression (40 CFR 180.414). The residue of concern is the parent only in RACs and processed commodities at this time.

According to 40 CFR 180.414 (7-1-98 ed.) the following tolerances are established for the combined residues of cyromazine and metabolite melamine in/on crop groups/commodities as listed :

Table 1. Established Cyromazine Tolerances (Including Melamine)	
Crop	Tolerance
cucurbit vegetables	2.0
leafy vegetables (except Brassica)	10.0
mushrooms	10.0
peppers	4.0
tomato	1.0
cabbage, Chinese	3.0
mustard, Chinese	3.0
celery	10.0
lettuce, head	5.0

Previously, HED has evaluated the proposed tolerances for cyromazine *per se* on the following commodities in pending petitions:

Primary crops: mango (PP5E4450); onion, green and dry bulb (PP5F4576); potato (PP6F4613)
Rotational crops: cottonseed; Corn, sweet (K+CWHR), forage, and fodder; radish, root and tops (PP6F3332). (See memo of 12/11/97, A. Rathman). The following was decided:

Table 2. Proposed Cyromazine Tolerances (Cyromazine *per se*) (Pending Petitions)	
RAC	Tolerance
Mango	0.3 ppm
Onion, green Onion, dry bulb	2.0 ppm 0.1 ppm
Potato	0.8 ppm
Cotton, undelinted seed	0.1 ppm
Corn, sweet (K+CWHR) Corn, sweet, forage Corn, sweet, stover	0.5 ppm 0.5 ppm 0.5 ppm
Radish, root Radish, tops	0.5 ppm 0.5 ppm

In that same memo (12/11/97, A. Rathman), it was stated:

> "5. For eggs and chicken tissue, the currently established tolerances should be revised by removing Section 180.414 (c) which is for residues of melamine in poultry tissue. The tolerances would be 0.25 ppm for eggs and 0.05 ppm for poultry meat, fat, and meat byproducts (from chicken layer hens and chicken breeder hens only)..... .
>
> 6. As a result of the animal feedstuffs potato waste and sweet corn forage being added to the animal diet at this time, the following meat and milk tolerances need to be proposed for residues of cyromazine: 0.05 ppm for milk; 0.05 ppm for meat, fat and meat byproducts of cattle, goats, hogs, horses, and sheep."

Recommendations:

HED has reevaluated the established tolerances listed in 40 CFR 180.414 based on the fact that the MARC has decided that the cyromazine metabolite melamine is no longer of toxicological concern. These tolerances should be adjusted as follows to reflect the expected cyromazine residues if cyromazine formulations are used according to the label directions: head lettuce from 10.0 to 7.0 ppm, cucurbit vegetables from 2.0 to 1.0 ppm, leafy vegetables (except Brassica) from 10.0 to 7.0 ppm, mushroom from 10.0 to 1.0 ppm, pepper from 4.0 to 1.0 ppm, tomato from 1.0 to 0.5 ppm, and celery from 10.0 to 7.0 ppm. The tolerances for Chinese cabbage and celery should remain at 3.0 ppm since an insufficient amount of field trial residue data are available to use as a guide for any tolerance change.

The proposed tolerance adjustments (See comments above from memo of 12/11/97, A. Rathman) for animal commodities remains unchanged.

NOTE to RD: When adjusting these tolerances, the correct crop group/commodity names according to Agency regulations (40 CFR 180.41) should be incorporated, i.e. leafy vegetables (except Brassica vegetables), pepper and mushroom, in the FR notice.

Detailed Considerations

CEB2 has reevaluated the field trial residue data for the crops listed in the following table and recommends the following tolerances for cyromazine only:

Table 3. Reevaluation of Established Cyromazine Tolerances (40 CFR 180.414)

Crop	Existing Tolerance	Existing Field Trial Data	Comments	**Recommended Tolerances**
head lettuce	5.0 ppm (7-day PHI)	Data were collected using 6-9 applications at 0.125lb a.i./A. (MRID#'s 41976301 and 43694401)	Cyromazine residues ranged from <0.05 to 2.5 ppm (7-day PHI) The ratio of cyromazine to melamine in the samples ranged from 0 to 0.84 with a average of 0.36 for 18 samples. Therefore the tolerance could be lowered to 3.0 ppm and adequately cover any cyromazine residues resulting from the maximum label at the 7-day PHI.	3.0 ppm
celery	10.0 ppm (7-day PHI)	Data were collected using 10-15 applications at 0.125lb a.i./A. (MRID#'41976301)	The applied cyromazine ranged from 1.25 to 1.5 lb /A. This is represents 1.7X and 2X rates the present label, respectively. Cyromazine residues ranged from 0.06 to 5.9 ppm (7-day PHI). The cyromazine to melamine ratios varied from 0.4 to 7 for 22 samples. Therefore the tolerance could be lowered to 7.0 ppm and adequately cover any cyromazine residues resulting from the maximum label at the 7-day PHI.	7.0 ppm

Table 3. Reevaluation of Established Cyromazine Tolerances (40 CFR 180.414)				
Crop	Existing Tolerance	Existing Field Trial Data	Comments	**Recommended Tolerances**
leafy vegetables (except Brassica)	10.0 ppm (7-day PHI)	Data were collected using 5 applications at 0.125lb a.i./A. (MRID#'41976301)	This is application rate of the most recently accepted label. Cyromazine residues in leafy lettuce ranged from 0.49 to 7.6 (7-day PHI). The average cyromazine residue for 22 samples was 2.9 ppm. Cyromazine residues in spinach ranged from 0.36 to 7.6 (7-day PHI). The average cyromazine residue for 22 samples was 3.0 ppm. Measurable residues were observed for leafy lettuce at 6.6, 6.8, and 7.6 ppm, and for spinach at 7.6 ppm. All other samples showed residues <5 ppm. However, trials at the 2X rate showed cyromazine residues from 0.65 to 21 ppm with an average of 6.6 ppm. Therefore, the data will support a lowering of the tolerance for leafy vegetables to 7.0 ppm. This level will adequately cover any cyromazine residues resulting from the maximum label rate at the 7-day PHI.	7.0 ppm

Table 3. Reevaluation of Established Cyromazine Tolerances (40 CFR 180.414)				
Crop	Existing Tolerance	Existing Field Trial Data	Comments	**Recommended Tolerances**
cucurbit vegetables	2.0 ppm (0-day PHI)	Application rates varied from 6 at 0.095 lb a.i./A to 8 at 0.125 lb a.i./A. (MRID#42116001)	Cyromazine residues ranged from <0.05 to 0.73 ppm (0-day PHI) in cantaloupe, from 0.11 to 0.24 ppm (0-day PHI) in cucumber, from <0.05 to 0.16 ppm (0-day PHI) in honeydew melon, from 0.06 to 1.1 ppm (0-day PHI) in cucumber, and 0.10 and 0.15 ppm (0-day PHI) in watermelon. In all crops except summer squash, the majority of the combined residue is due to melamine. The 1.1 ppm value was collected in TX after a 1.3 X rate, and this may be due to less rainfall and perhaps fallow watering. Also a 2.6 X rate trial on summer squash in TX gave cyromazine residues of 2.0 ppm. These could be values that could occur in the real world. The residue data will support a lowering from 2.0 to 0.5 for other cucurbit except for summer squash. Therefore 1.0 ppm tolerance would adequately cover cyromazine residues in summer squash and all the other cucurbit.	1.0 ppm

Table 3. Reevaluation of Established Cyromazine Tolerances (40 CFR 180.414)				
Crop	Existing Tolerance	Existing Field Trial Data	Comments	**Recommended Tolerances**
tomato	1.0 ppm (0-day PHI)	The number of applications and rates from earlier field trials (8) varied from 11 to 19 applications and 0.125 to 0.5 lb a.i./A. (ACC#260565). Later trials (14) were run according to the label, 6 applications at 0.125 lb a.i./A. (MRID#42255101)	In both sets of field trials residue data at the label PHI of 0-day show similar amounts of cyromazine and melamine residues (ca. 50% of combined residue is melamine). Thus the data will support the lowering of the 1.0 ppm tolerance to 0.5 ppm. The processing studies showed average concentration factors for puree and paste at 0.6X and 1.0X, respectively. Thus the 0.5 ppm tolerance for tomato would still cover the these processed commodities.	0.5 ppm
mushroom	10.0 ppm (ca. 4 weeks PHI)	A variety of treatments involving preplant compost incorporation and or drenching, at a resulting rate of 5 and/or 10 ppm.	Majority (90%) of combined residue is melamine from either a 5.0 ppm or 10 ppm compost treatment prior to mushroom spawning.	1.0 ppm
pepper	4.0 ppm (7-day PHI)	12 applications at 0.125 lb a.i./A were applied to bell, chili and tabasco peppers. The most recent label only allows 6 applications maximum at 0.125 lb a.i./A. Thus the field trial data reflect a 2X application	Based on the 2X residue data the tolerance may have been established too high. The tolerance could have been established at 2.0 ppm and still provided adequate coverage of combined residues of cyromazine and melamine. Approximately 50% of the combined residue is melamine. Thus, in consideration of these facts, the tolerance for peppers could be lowered..	1.0 ppm
Chinese mustard	3.0 ppm (7-day PHI)	7 applications at 0.125 lb a.i./A or 0.25 lb a.i./A. Label allows 6 applications at 0.125 lb a.i./A.	Submitted data showed <20% melamine: >80% cyromazine for both 1X and 2X trials. However, the data do not support a lowering of the established tolerance.	3.0 ppm

Table 3. Reevaluation of Established Cyromazine Tolerances (40 CFR 180.414)				
Crop	Existing Tolerance	Existing Field Trial Data	Comments	**Recommended Tolerances**
Chinese cabbage	3.0 ppm (7-day PHI)	7 applications at 0.125 lb a.i./A or 0.25 lb a.i./A. Label allows 6 applications at 0.125 lb a.i./A.	Submitted data showed <20% melamine: >80% cyromazine for both 1X and 2X trials. However, the data do not support a lowering of the established tolerance.	3.0 ppm

Animals:

Since there are not any feedstuffs for the above crops that have been reevaluated, an adjustment different from that previously discussed (See memo of 12/11/97, A. Rathman) to the proposed tolerances for animal commodities, will not be necessary.

cc: PP6F4613; J. Stokes (CEB2), W. Wassell (TOX2) , cyromazine SF, RF
RDI: SHummel: 04/05/99
7509C:CM2:Rm816D:305-7561:JStokes:js:04/05/99

End of Document

11 5[illegible]

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

12 | 301

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

11 Mar 1998

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Subject: Cyromazine - 121301: Health Effects Division Risk Characterization for Use of the Chemical Cyromazine in/on Mangoes (5E4450), Crop Group 3: Bulb Vegetables (5F4576), Potatoes (6F4613), Cottonseed (5F4546), Sweet corn and Radishes (6F3332). Barcode: D242798, D242799, D242801, D242802

From: Andrew R. Rathman
Albin Kocialski Ph. D.
Jeff Evans
Registration Action Branch I
Health Effects Division (7509C)

Through: Melba Morrow, D.V.M., Senior Scientist
Registration Action Branch I
Health Effects Division (7509C)

To: George Larocca, PM 13
Registration Division (7505C)

The Health Effects Division (HED) of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The Registration division (RD) of OPP has requested that HED evaluate the toxicology and residue chemistry data and conduct dietary and worker risk assessments to estimate the risk to human health that will result from the use of cyromazine on mangoes, onions, green and dry bulb, potatoes and from inadvertent residues on cottonseed, sweet corn and radishes.

Novartis Crop Protection, Inc. has petitioned for permanent tolerances for residues of the insecticide/larvicide cyromazine (N-cyclopropyl-1,3,5-triazine-2,4,6-triamine) as follows:

Mangos	0.3 ppm
Onion, green	2.0 ppm
Onions, dry bulb	0.1 ppm
Potatoes	0.8 ppm

Additionally, tolerances are being requested for indirect or inadvertent as follows:

Cotton, undelinted seed	0.1 ppm
Corn, sweet, (K+CWHR)	0.5 ppm
Corn, sweet, forage	0.5 ppm
Corn, sweet, stover	0.5 ppm
Radishes, root	0.5 ppm
Radishes, tops	0.5 ppm

Meat and milk tolerances for residues of cyromazine are also being requested as follows:

Milk	0.05 ppm
Meat, Fat and Meat by-products*	0.05 ppm

*of beef, goat, hogs, horses and sheep

A summary of the findings and an assessment of human risk resulting from the proposed uses are provided in this document. The hazard assessment was provided by Albin Kocialski, of RAB1 Steve Dapson of TOX2; the residue chemistry data review by Jerry Stokes, of CEB2, Joel Garbus of CEB2, William Cutchin, of RAB2 and Andrew Rathman. of RAB1; the dietary risk assessment by Andrew Rathman, RAB1; the drinking water exposure assessment by James K. Wolf, Ph.D, of EFED; the occupational exposure assessment by Jeff Evans, of RAB1.

I. EXECUTIVE SUMMARY

HED has reviewed toxicology and residue chemistry data submitted by Novartis Crop Protection, Inc. (formerly Ciba-Geigy Corp.) in accordance with the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and 40 CFR §158, to support pending registrations containing the active ingredient (ai) cyromazine as a technical product for use as an insecticide on mangoes, onions, potatoes and for inadvertent residues on cottonseed, sweet corn and radishes.

The HED Toxicological Endpoint Selection Committee (revised document dated 1/10/97) considered the No Observed Effect Level (NOEL) in the 6-month dog feeding study (MRID 00103193) of 0.75 mg/kg/day to be the appropriate end-point for establishing the reference dose (RfD) for cyromazine. An uncertainty factor (UF) of 100 was applied to account for interspecies extrapolation and intraspecies variability. FFDCA §408 provides that EPA shall apply an additional 10-fold margin of exposure (safety) for infants and children in the case of threshold effects to account for pre- and post-natal toxicity and the completeness of the data base unless EPA determines that a different margin of safety will be safe for infants and children. The Hazard Identification Assessment Review Committee recommended (see 11/4/97 memo) that the 10 X factor to account for enhanced sensitivity of infants and children be removed. For chronic dietary risk assessment, an uncertainty factor of 100 is adequate because of the following:

(I) Developmental toxicity studies showed no increases sensitivity in fetuses as compared to maternal animals following *in utero* exposures in rats and rabbits.

(ii) A two generation reproduction toxicity study in rats showed no increased sensitivity in pups when compared to adults.

(iii) The toxicology data base is complete and there are no data gaps.

On this basis the RfD was calculated to be 0.0075 mg/kg/day utilizing the 100-fold uncertainty factor. The Committee recommended that a developmental neurotoxicity study in rats **not** be required.

The cancer classification for cyromazine is E (evidence of non-carcinogenicity for humans).

Toxicological endpoints of concern have been identified for chronic dietary exposure and short-term, intermediate-term and chronic (other than cancer) occupational or residential exposure. HED recommends the following endpoint be used for risk assessment purposes: The NOEL from the 6-month dog study (MRID 00103193) of 0.75 mg/kg/day for chronic dietary risk assessments, as well as for short-term, intermediate-term, and chronic (other than cancer) occupational and residential risk assessments. Since the endpoint for occupational and residential risk assessment is from an oral study , for dermal exposure scenarios a dermal absorption factor of 8% should be used. No acute dietary risk assessment is necessary because there were no toxicological effects attributable to a single exposure (dose) observed in oral toxicity studies including the developmental toxicity studies in rats or rabbits.

Anticipated residue values of 0.01 ppm for milk and meat, fat, and meat byproducts (except kidney) of cattle, goats, hogs, horses and sheep; and 0.04 ppm for kidney of cattle, goats, hogs, horses and sheep were used for the chronic dietary risk assessment. For crops tolerance level residues (except for cabbage at 0.05 ppm) were used. Percent crop treated values were used for a few crops.

A partially refined chronic dietary exposure analysis was performed. Because cyromazine has no residential uses, the aggregate exposure risk assessment is limited to food plus water. The chronic analysis showed that exposure from the tolerances proposed in the current actions under consideration plus the established tolerances for children (1-6 years old) (the subgroup with the highest exposure) would be 82% of the RfD, while the exposure for the general U.S. population would be 48% of the RfD. Based on the chronic dietary (food) exposures and using default body weights and water consumption figures, chronic drinking water levels of concern (DWLOC) for drinking water were calculated. For chronic exposure, based on an adult body weight of 70 kg and 2 L consumption of water per day, HED's level of concern from chronic exposure in drinking water is 136 μg/L. For children (10 kg and consuming 1L water/day), our level of concern for drinking water is 13.3 μg/L. Because the estimated chronic drinking water exposure for cyromazine is 9.63 μg/L, which is one-third (1/3) of the value of the 56-day concentration

estimated with the EFED screening model GENEEC. EFED and HED management determined that this better reflects results of monitoring data. Thus the potential residues in drinking water are not greater than HED's level of concern. **Therefore, the combined exposure of chronic dietary and drinking water exposure to cyromazine would be no greater than 100% of the RfD for children or the general U.S. population.**

The drinking water values were developed for use in eco-risk assessment and represent a reasonable upper-bound estimate for eco-risk assessment. It is expected they represent an even more substantial overestimate for human health chronic risk assessments. The chronic dietary analysis is also an overestimate of dietary exposure as 100 percent of most commodities were assumed to be treated with cyromazine. Therefore, even without further refinements, HED does not consider the combined aggregate chronic dietary/drinking water risk to exceed the level of concern.

Since there is no concern with acute risk, no Margin of Exposure (MOE) was calculated for acute exposure.

Occupational exposure risk estimates do not exceed HED's level of concern. MOE's for mixer/loaders are 375 for aerial application and 1500 for ground boom. MOE's for applicators are 1500 for aerial application and 1900 for ground boom. The MOE for flaggers is 500.

To provide for the periodic evaluation of the anticipated residues and percent crop treated, the Agency will require under Section 408 (b) (2) (E) new information on those crops for which percent crop treated was used every five years as long as the proposed tolerances remain in force. Additional residue data for meat and milk will not be required since the tolerances are based on the methods limit of quantitation and not on the actual residues present which were used in the anticipated residue calculations.

The residue and toxicological data bases are adequate to support the tolerance under consideration here for mango in terms of human health risk. The data bases are adequate to support conditional registration and time-limited tolerances for onion, green and bulb; and potato, tuber in terms of human health risk. The data bases are also adequate to support tolerances for items for which registration is not required, these include secondary residues in meat and milk, as well as indirect or inadvertent residues in cotton, undelinted seed; corn, sweet (K+CWHR); corn, sweet, forage; corn, sweet, stover and radishes, roots and tops. In the case of cottonseed, additional data are required and a time-limited tolerance should be established for this commodity. Novartis Crop Protection, Inc. has committed to obtain additional data for cottonseed and cotton gin byproducts that have been requested.

The registrant must also submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate issues related to whether cyromazine shares a common mechanism of toxicity with any other substance

and, if so, whether any tolerances for cyromazine need to be modified or revoked.

II. BACKGROUND

Cyromazine is a member of the triazine class of chemicals. Most of the chemicals of this class of chemicals are herbicides. Cyromazine is an insecticide/larvicide and therefore use of the chemical is different than most of the other triazines. For crops, use is generally throughout the season as a foliar spray. For onions, it is used as a seed treatment and for poultry, it is used as a feed through for fecal breeding flies. The two formulations under consideration here include Trigard a 75% wettable powder in water-soluble packets and Trigard OMC also a 75% wettable powder. Trigard OMC is not in water soluble packets and is intended for the seed treatment use of onions only.

III. SCIENCE ASSESSMENT

A. Identification of Active Ingredient

Chemical Name: N-cyclopropyl-1,3,5-triazine-2,4,6-triamine

Common Name: Cyromazine

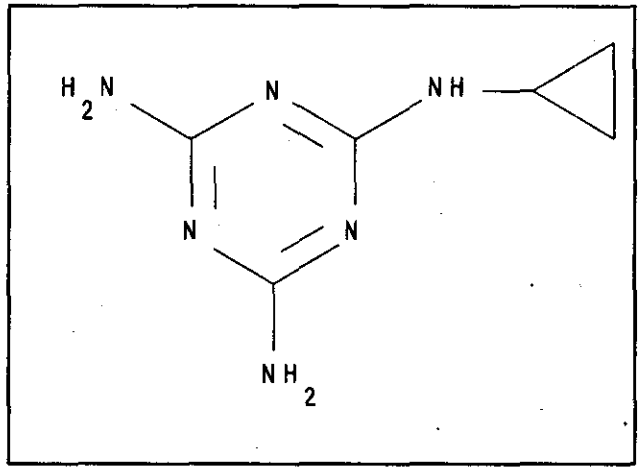
PC Code Number: 121301

CAS Registry No.: 66215-27-8

Empirical Formula: $C_6H_{10}N_6$

Molecular Weight: 166.18

Structural Formula:



B. Human Risk Assessment

1. Hazard Assessment

Acute Toxicity for Cyromazine

Guideline/Study	Results	Tox. Cat.
§81-1 Acute Oral Toxicity - Rat	LD_{50} = 3387 mg/kg	III
§81-2 Acute Dermal Toxicity - Rabbit	LD_{50} > 3100 mg/kg	III
§81-3 Acute Inhalation Toxicity - Rat	LC_{50} >2.9 mg/kg	IV
§81-4 Primary Eye Irritation - Rabbit	Non-irritant	IV
§81-5 Primary Dermal Irritation - Rabbit	Mild irritant	IV
§81-6 Dermal Sensitization - Guinea Pig	Non-sensitizer	

Chronic Toxicity for Cyromazine

Guideline/Study	NOEL	LOEL
§83-1 6-Month chronic feeding - Dog	30.0 ppm (0.75 mg/kg)	300.0 ppm (7.5 mg/kg) based on decreased hematocrit and decreased hemoglobin
§83-1 2 Year oncogenicity feeding - Mouse	50.0 ppm (7.5 mg/kg)	1000.0 ppm (150.0 mg/kg) based on decreased body weight Negative for oncogenicity in mouse at 3000.0 ppm (450.0 mg/km)
§83-3 Developmental - Rat	100.0 mg/kg (maternal) 300.0 mg/kg (developmental)	300.0 mg/kg (maternal) based on decreased body weight gain and clinical observations 600.0 mg/kg based on an increase of minor skeletal variations

Guideline/Study	NOEL	LOEL
§83-3 Developmental - Rabbit	10.0 mg/kg (maternal) ≥ 60.0 mg/kg (developmental) HDT	30.0 mg/kg (maternal) based on decreased body weight gain and food consumption ≥ 60.0 mg/kg (developmental) HDT (highest dose tested)
§83-4 2 Generation reproduction - Rat	30.0 ppm (1.5 mg/kg) systemic 1000.0 ppm (50.0 mg/kg) reproductive effects	1000.0 ppm (50.0 mg/kg) systemic based on decreased body weights associated with decreased food efficiency 3000.0 ppm (150.0 mg/kg) reproductive effects based on decreased body weights at birth thru weaning
§83-5 2 Year chronic feeding - Rat	30.0 ppm (1.50 mg/kg)	300.0 ppm (15.0 mg/kg) based on decreased body weights
§83-5 2 Year oncogenicity feeding - Rat	> 3000.0 ppm (150.0 mg/kg) Highest dose tested (HDT) - negative for oncogenicity at 3000.0 ppm (150.0 mg/kg)	

2. Dose Response Assessment

a. Special Sensitivity to Infants and Children

FFDCA Section 408 provides that EPA shall apply an additional 10-fold margin of safety for infants and children in the case of threshold effects to account for pre- and post-natal toxicity and the completeness of the data base unless EPA determines that a different margin of safety will be safe for infants and children. Margins of safety are incorporated into EPA risk assessment either directly through use of a margin of exposure analysis or through using uncertainty (safety) factors in calculating a dose level that poses no appreciable risk to humans. In either case, EPA generally defines the level of appreciable risk as exposure that is greater than 1/100 of the no observed effect level in the animal study appropriate to the particular risk assessment. This 100-fold uncertainty (safety) factor/margin of exposure (safety) is designed to account for inter-species extrapolation and intra-species variability. HED believes that reliable data support using the 100-fold margin/factor, rather than the 1000-fold margin/factor, when EPA has a complete

data base under existing guidelines, and when the severity of the effect in infants or children, the potency or unusual toxic properties of a compound, or the quality of the data do not raise concerns regarding the adequacy of the standard margin/factor.

The HED Hazard Identification Assessment Review Committee met on October 28, 1997 to evaluate the toxicological data base of cyromazine with special reference to the reproductive, developmental and neurotoxicity data. These data were re-reviewed specifically to address the sensitivity of infants and children from exposure to cyromazine as required by the Food Quality Protection Act (FQPA) In addition, the Committee also reassessed the doses and endpoints selected for acute dietary, chronic dietary (RfD) as well as occupational and residential risk assessments. The findings of this meeting are reported in a memorandum dated Nov. 4, 1997.

The Committee determined that a UF of 100 is adequate because

(i) Developmental toxicity studies showed no increased sensitivity in fetuses as compared to maternal animals following *in utero* exposures in rats and rabbits.

(ii) A two generation reproduction toxicity study in rats showed no increased sensitivity in pups when compared to adults.

(iii) The toxicology data base is complete and there are no data gaps.

Based upon a review of the currently available data base for Cyromazine, a developmental neurotoxicity study in rats was not recommended by the Committee. This determination was based upon the following evidence:

- The chemical class (triazine) does not generally target the central or peripheral nervous system.
- No indication of abnormalities in the development of the fetal nervous system, was observed in the prenatal developmental toxicity studies in either rats or rabbits, at maternally toxic oral doses up to 600 or 60 mg/kg/day, respectively.
- Clinical observations of inactivity and hyperactivity were noted in the prenatal developmental toxicity study in rats which was dosed by gavage, and an absolute brain weight decrease (not related to histopathology) was noted in the 2-year chronic study in rats. However, no other neurotoxic effects were observed in the clinical observation data, brain weights, or histopathology (nonperfused) of the nervous system in the subchronic and chronic toxicity studies with Cyromazine in several species.

3. Toxicological Endpoints

Based upon a review of the toxicology database for cyromazine, by the Toxicology Endpoint Selection (TES) Committee on November 7, 1995 and the Hazard Identification Assessment Review Committee on October 28, 1997, toxicology endpoints and dose levels of concern have been identified for use in risk assessments corresponding to the categories below.

a. Acute Dietary (One Day)

There were no toxicological effects attributable to a single exposure (dose) observed in oral toxicity studies including the developmental toxicity studies in rats or rabbits. Therefore, a dose and an endpoint was not selected for this risk assessment.

b. Chronic Dietary [Reference Dose (RfD)]

The study selected for the RfD was a 6-month toxicity (dog) (guideline §82-1b), MRID No. 00103193. Groups of male and female beagle dogs (4/sex/dose) were fed diets containing cyromazine at 0, 30, 300 or 3000 ppm (0, 0.75, 7.5 or 75 mg/kg/day, respectively) for 6 months. No treatment-related effects were observed in survival, clinical signs or body weight parameters. Pronounced effects on hematological parameters, were manifested as decreases in hematocrit and hemoglobin levels at 300 and 3000 ppm. The NOEL was 30 ppm (0.75 mg/kg/day) and the LOEL was 300 ppm (7.5 mg/kg/day) based on pronounced alterations in hematological parameters. The RfD was calculated to be 0.0075 mg/kg/day using an UF of 100. A 100 UF is adequate because; 1) the developmental toxicity studies showed no increased sensitivity in fetuses and compared to maternal animals following *in utero* exposures in rats and rabbits, 2) a two generation reproduction toxicity study in rats showed no increased sensitivity in pups when compared to adults, and 3) the toxicology data base is complete and there are no data gaps.

c. Short Term, Intermediate Term and Chronic (Non-Cancer) Occupational and (dermal and inhalation)

Short term (1-7 days), intermediate term (7 days to several months) and chronic endpoints of concern were identified. The NOEL of 0.75 mg/kg/day from the 6 month feeding study in beagle dogs (MRID 00103193) was selected as the endpoint to be used for all exposure periods. This is based treatment related decreases in hematocrit and hemoglobin at the 7.5 mg/kg/day dose. Toxicity endpoints are established for the active ingredient for short-term, intermediate-term, and chronic occupational or residential exposure. A no observed effect level (NOEL) of 0.75 was selected from a six month dog feeding study in which pronounced hematological parameters were manifested as decreases in hematocrit and hemoglobin levels. These effects were observed during the first week of the study and were maintained throughout the study. An UF/MF of 100 is considered appropriate for this chemical. The UF is based on 100 to account for interspecies extrapolation and intraspecies variability. The factor of 100 (margin of exposure for occupational/residential exposures) is adequate because; 1) the developmental toxicity studies

showed no increased sensitivity in fetuses and compared to maternal animals following *in utero* exposures in rats and rabbits, 2) a two generation reproduction toxicity study in rats showed no increased sensitivity in pups when compared to adults, and 3) the toxicology data base is complete and there are no data gaps. Since an oral NOEL was selected, a dermal absorption factor of 8%, should be used in risk assessments. This dermal absorption factor was obtained from a 7.75% dermal absorption observed at 10 hours post treatment in a dermal absorption study. The dose identified for inhalation risk assessment from an oral study. Therefore; 1) the inhalation exposure component (i.e., mg/L) using a 100% absorption rate (default value) should be converted to a dose (mg/kg/day), 2) the dermal exposure component (i.e. mg/kg/day) using 8% dermal absorption may be combined with this converted dose (mg/kg/day), 3) this dose should then be compared to the oral NOEL of 0.75 mg/kg/day to calculate the Margin of Exposure.

d. Cancer Classification

Cyromazine has been classified a Group E (evidence of non-carcinogenicity for humans) chemical by the Cancer Peer Review Committee.

Summary of Toxicological Endpoints for Cyromazine

Exposure Duration	Exposure Route	Endpoint and Toxicological Effect
Acute	Dietary	No effects attributable to a single dose. Therefore, no dose and endpoint were selected for risk assessment.
Short-Term (1-7 days) Occupational/Residential	Dermal/Inhalation[1]	NOEL: 0.75 mg/kg/day (decreases in hematocrit and hemoglobin levels at the 7.5 and 75 mg/kg/day dose levels in the 6-month dog study)
Intermediate-Term (one week to several months) Occupational/Residential	Dermal/Inhalation[1]	NOEL: 0.75 mg/kg/day (decreases in hematocrit and hemoglobin levels at the 7.5 and 75 mg/kg/day dose levels in the 6-month dog study)

Exposure Duration	Exposure Route	Endpoint and Toxicological Effect
Chronic-Term (greater than several months) Occupational/Residential	Dermal/Inhalation[1]	NOEL: 0.75 mg/kg/day (decreases in hematocrit and hemoglobin levels at the 7.5 and 75 mg/kg/day dose levels in the 6-month dog study)
Cancer	Dietary/Dermal/Inhalation[1]	Classified as E (evidence of non-carcinogenicity for humans)
Chronic (non-cancer)	Dietary	NOEL: 0.75 mg/kg/day (decreases in hematocrit and hemoglobin levels at the 7.5 and 75 mg/kg/day dose levels in the 6-month dog study)

[1]The NOEL selected is from an oral study and therefore conversion to equivalent dermal and inhalation doses using appropriate absorption rates for there routs (i.e., 8% absorption for dermal and 100% for inhalation) was performed.

4. Dietary Exposure and Risk Assessment/Characterization

a. Dietary Exposure (Food sources)

i. Directions for Use

For potatoes, cyromazine is formulated as Trigard, a 75% WP, containing 75% cyromazine and is packaged as water-soluble packets. The product can be used for treatment of Colorado Potato Beetle or Leafminers. For Colorado Potato Beetle, Trigard is an insect growth regulator and is most effective for control of first and second instar larvae. Trigard does not control the adult beetles. Trigard is to be applied at 1/6 lb. (2.66 oz.) to 1/3 lb. (5.3 oz.) per acre as a foliar spray at beginning of egg hatch, using the higher rate for heavier infestations. If necessary, a second application may be made 10 to 14 days later. The product is to be applied is sufficient water for full coverage of the foliage by ground equipment and a minimum of 5 gallons of water per acre when applying by air. For Leafminers, Trigard is to be applied at the rate of 1/6 lb. (2.66 oz) per acre as a foliar spray. Use sufficient water to obtain full coverage by ground equipment and a minimum of 5 gallons of water per acre by air. Applications may be repeated at 7-day intervals or as necessary to maintain good control. A maximum of 2/3 lb. (0.5 lb. active ingredient) may be applied per acre per year. There is a 7-day PHI.

For onions, green and dry, cyromazine is formulated as Trigard OMC, as 75% WP, containing

75% cyromazine. The product is for control of onion maggots. The product is to be applied to the seed at the rate of 6.6 lbs. of product per 100 lbs. seed (4.95 lbs. active ingredient per 100 lbs. of seed). There is a PHI of 60-days.

For mangoes, English translation of the Mexican label was provided. The proposed use directions state that the product is to be applied to mangoes starting when the fruits are 1 inch long. The product is applied at a rate of 20-25 g (15-18.75 g active ingredient)/100 L at a volume of 500 l/ha. Including a feed attractant, hydrolyzed protein, in the spray is recommended to encourage consumption of the product by larvae. The product may be applied up to a maximum of 5 times per season at 15 day intervals with a 15 day PHI.

ii. Nature of the Residue - Plants

Studies for [^{14}C-(U)-triazine]-cyromazine metabolism in celery, lettuce, and tomato have been reviewed. These studies are summarized below. Identification of isolated residues in all studies was accomplished by thin layer chromatography (TLC) using co-chromatography techniques with 14C reference compounds of parent cyromazine and metabolite melamine. Additional reference compounds were not tested.

Celery

Celery crops were treated either by multiple foliar sprays or grown in soil amended with [U-ring-^{14}C]-cyromazine. Celery was harvested at maturity. In the study with the treated soil celery, the treatment rate of 0.9 lb a.i./A reflects the maximum expected runoff from celery spray treated 12 times at the use rate of 0.125 lb a.i/A.

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 was 60% (0.45 ppm) and melamine was 11% (0.08 ppm) of the residue. In the mature celery cyromazine was 43% (0.15 ppm) and melamine was 30% (0.10 ppm) of the radioactive residue.

Head Lettuce

Head lettuce crops were treated by multiple foliar sprays [U-ring-^{14}C]-cyromazine. Crops were harvested at maturity. Lettuce was treated at either 0.375 lb. a.i./A or at 1 lb. a.i./A. There was a 7-day PHI after the last treatment. From the 0.375 lb. rate cyromazine was 56% (1.43 ppm) and melamine was 16% (0.41 ppm) of the residue. From the 1 lb. rate cyromazine was 74% (2.72 ppm) and melamine was 11% (0.41 ppm) of the residue.

Tomato

Tomato crops were treated with [U-ring-^{14}C]-cyromazine. The formation of melamine is rapid as at the 0-day PHI some 11% of the residue is malamine, but cyromazine is the dominant residue.

At day 7 cyromazine residue had decreased and melamine residue increased. The residue profile changed only slightly at 14 days PHI. By 6 weeks the cyromazine portion of the total residue had dropped and melamine residue continued to increase. Residues of cyromazine ranged from a maximum of 76% of the residue to a low of 37% of the residue with residues of melamine ranging from 11-44% of the residue.

The HED Metabolism Committee met to discuss cyromazine on 11/4/97. The conclusion of the committee was that only residues of cyromazine need to be regulated and used for risk assessment at this time.

iii. Nature of the Residue - Livestock

Ruminants

CIBA-GEIGY has submitted an animal metabolism study entitled, "Metabolism of [Triazine-14C]-Cyromazine in Lactating Goats", by Nicholas J. Tortora, 12/3/91, MRID# 422243-02.

Two lactating goats were dosed once daily with 150 mg of uniformly triazine ring-labeled 14C cyromazine, 42.9 μCi/mg) for four days. Goat #1 received 107 ppm; Goat #2 (Goat #85) received 75 ppm. Identification of the various metabolites was made by TLC, with MS confirmation. Residues in milk samples 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.

Liver samples from both goats were analyzed by HPLC/LSC. Most of the residues were released in this initial extraction. Bound components were reextracted before a final combustion analysis of the remaining residue. Kidney and tenderloin samples were extracted in the same as the 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 acetonitrile, which released 97% of the activity.

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 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 acetonitrile, acetone, water, and methanol. Adequate steps were taken to release these residues.

The major residues in milk, meat, and meat by-products (except liver and kidney) are cyromazine and melamine. The major residues in liver and kidney are cyromazine, melamine, and 1-methylcyromazine.

Poultry

A 14C-cyromazine study in poultry had laying hens fed 5 ppm of 14C-cyromazine for 7 days. The egg whites had 0.09 ppm to 0.22 ppm of 14C-cyromazine equivalents and the egg yolks had 0.08 ppm to 0.15 ppm of 14C-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 egg white contained 25% melamine and 58% cyromazine. The egg yolk contained 5% melamine and 69% cyromazine. The cyromazine metabolic pathway in poultry is the same as in plants. The major residues are cyromazine and melamine. The study was not analyzed for 1-methyl cyromazine. However, HED does not expect this residue in poultry. HED concludes that it is a metabolite with ruminants only.

The HED metabolism Committee met to discuss cyromazine on 11/4/97. The conclusion of the committee was that only residues of cyromazine need to be regulated and used for risk assessment at this time.

iv. Residue Analytical Methods

Methods AG-408 and AG-417A are the tolerance enforcement methods as published in PAM, Vol II. These methods combined, and with minor modifications is Method AG-621. The residue data on the treated crops was analyzed by these methods. The crop matrix is extracted at reflux in methanol:water, acidified after cooling with dilute acid, partitioned with organic solvents, and then the water solubles are passed through an ion exchange column and a silica gel column for final cleanup before GLC analysis. The limit of quantitation is 0.05 ppm for cyromazine and 0.05 ppm for melamine expressed as cyromazine equivalents. These extraction and cleanup procedures are similar to the Methods AG-408 and AG-417, but AG-621 uses a gas chromatography for analysis, while the other methods use high pressure liquid chromatography for determination of cyromazine and melamine levels in the crop matrix.

Methods AG-408 and AG-417 as listed in FDA's Pesticide Analytical Manual (PAM), Vol-II are adequate to enforce the proposed tolerance. AG-621 is acceptable to support the crop field trial residue data for cyromazine and its melamine metabolite on RAC's.

Secondary residues of cyromazine, melamine, and 1-methylcyromazine could occur in animal commodities from the feeding of potato culls, potato processed waste, sweet corn forage and stover.

The petitioner has used method AG-403 to analyze residues in meat and milk. EPA has validated this method in the Agency laboratory for chicken meat and eggs. This method is very similar to the Method I in PAM II referenced in the petitioner submissions as AG-417 or AG-417A. The only major difference between the two methods is the use of a gel permeation chromatography (AG-403) vs. ion exchange chromatography (AG-417) for additional sample cleanup after the first ion exchange chromatographic sample cleanup common to both methods.

Method AG-403 has been radiovalidated for milk from a 14C goat metabolism. Method AG-403 is referenced as MRID#00128232 in the Agency files. The method AG-403 allows detection of cyromazine and melamine residues in milk at 0.01 ppm.

The PAM II enforcement method for the determination of cyromazine and melamine residues limit of quantitation (LOQ) is 0.05 ppm for each compound in meat, fat, and meat byproducts. Based on the estimation of expected cyromazine residues in animal commodities (See discussion Meat, Milk, Poultry, and Eggs, this memo), residues would be below the LOQ.

v. Multiresidue Methods

Data for cyromazine and its metabolites melamine and 1-methylcyromazine through the FDA multiresidue methods have been previously submitted for the FDA Pesticide Analytical Manual. Melamine and 1-methylcyromazine are not recovered by these methods. Cyromazine gives marginal recovery using Protocol D.

vi. Storage Stability Data

Storage stability data have been previously submitted for other crops and reviewed (See memo 01/28/87, A. Smith). 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. Samples removed from storage and reanalyzed reflected no significant changes in the residues. Residues of cyromazine and melamine are stable in frozen storage for at least 24 months. The treated potato field trial samples in this petition were stored from 5.5 to 12 months. The existing storage stability data for the listed crops are adequate to support the proposed use.

vii. Crop Field Trials

Mangoes (MRID# 4344703-01-08)

Data from six field trials conducted in Mexico showed residues of cyromazine ranging from 0.04 (below the limit of quantitation) to 0.25 ppm on day 0 and from <0.03 (non-detectable) to 0.10 ppm on day 28. No melamine residues were found in any sample. These results are contained in the data review of W. Cutchin (PP# 5E4450, 5/3/95). Therefore, the proposed tolerance level of 0.3 ppm is adequate.

Onions (MRID# 437631-01)

Data for onions (green and dry bulb) were submitted in connection with PP# 5F4576 and discussed in detail in the J. Stokes review dated 7/9/96. A total of eleven trials at the 1 and 2X application rate were submitted. Maximum cyromazine residues on green onions from the 1X

rate were 1.7 ppm and from the 2X rate were 2.0 ppm. Cyromazine residues in dry bulb onions were a maximum of 0.06 ppm at the 1 rate and <0.05 ppm at the 2X rate. From these data we conclude that the proposed tolerance levels for onion, green at 2.0 ppm and for onion, bulb at 0.1 ppm are adequate.

Potatoes (MRID#'s 438262-02 and 438262-03)

Data for potatoes were reviewed in the J. Stokes memo of 9/12/96 in connection with PP# 6F4613. Residue levels in samples from field trials using the proposed 0.75 lb a.i./A (1X) rate show average cyromazine residues of 0.23 ppm. The maximum value detected in the 1X samples was 0.75 ppm. Samples from the other application rates (0.75X-5X) show a fairly linear relationship with estimated (calculated) values of cyromazine residues all falling below 0.8 ppm. As a result, we conclude that the proposed tolerance of 0.8 ppm for potato, tuber is adequate.

Cottonseed (MRID# 436944-01)

The tolerance request for cottonseed is for inadvertent residues when cotton is planted as a rotational crop. A detailed review of the data is contained in the W. Cutchin memo of 2/15/96 of PP# 5F4546. Data are available from five studies conducted in CA(2), AZ(2) and TX. These studies show no detectable residues of cyromazine (<0.05 ppm) from a 1X application. These data were found deficient in that there were an inadequate number of studies and there were no data available for cotton gin byproducts (commonly called cotton gin trash). In a more recent review of this petition request (A. Rathman, 12/11/97), we had no objections to a time-limited rotational crop tolerance for residues of cyromazine 0.1 ppm noting the need for additional residue data and data for cotton gin byproducts for a permanent tolerance. The proposed time-limited rotational tolerance of 0.1 ppm is adequate. The company has committed to conduct the additional residue trials and obtain data for cotton gin byproducts requested in previous reviews.

Sweet Corn and Radishes

The data for sweet corn and radishes were originally reviewed in 1987 by A. Smith. Data of the level of parent vs. the metabolite melamine are not available in the branch files at this time. Therefore, we will use the levels found acceptable in the J. Garbus review of PP# 6F3332, 8/26/96 for the DRES calculations; these levels are also acceptable for tolerance setting purposes. These levels are the following:

Corn, sweet (K+CWHR)	0.50 ppm
Corn, sweet, forage	0.50 ppm
Corn, sweet, stover	0.50 ppm
Radishes, root	0.50 ppm
Radishes, tops	0.50 ppm

viii. Processed Food/Feed

Processing studies were conducted where potatoes were processed into wet and dry peel, potato chips and potato granules. Average concentration factors for the various processed products were calculated to be the following: Wet peel - 0.4; dry peel - 3; potato chips - 1.7; potato granules - 2.4. Since the concentration factors for potato chips and potato granules were greater than 1, we used the highest average residue in the field trials (HAFTA = 0.48) to multiply by the mean concentration factors for these processed commodities to determine the highest expected residue in the processed items.

Potato chips	0.48 ppm x 1.7X = 0.8 ppm
Potato granules	0.48 ppm x 2.4X = 1.15 ppm

Since the maximum expected residue in potato chips is the same as the tolerance level required, no tolerances is needed for this processed commodity. For potato granules the concentration factor is below the 1.5X value that is generally used for setting tolerances for processed commodities.

ix. Meat, Milk, Poultry, Eggs

Meat and Milk

The only significant animal feed items from either published or proposed tolerances are potato culls, processed potato waste and sweet corn forage and stover. Since none of these items are fed to poultry, the established poultry tolerances need only be reevaluated on the basis of the established feed through use of Larvadex. Secondary residues could occur in meat, fat and meat byproducts of animals and in milk. Animal diets and the dietary burden to animals was discussed in detail in the J. Stokes review of PP# 6F4613, 9/12/96. At that time alfalfa was also a significant feed item, but has been removed from consideration (A. Rathman review dated 11/13/97). We have reexamined the animal diets considering only potato culls and sweet corn forage since this results in the highest dietary burden and find that maximum dietary burden for diary cattle would be 2.4 ppm and for beef cattle the maximum level would be 3.4 ppm; see the following table:

COMMODITY	PERCENT DM	PERCENT IN DIET	LEVEL IN COMMODITY, ppm	DAILY DIETARY BURDEN
BEEF CATTLE				
Potato culls	20	75	0.8	3.0

Sweet corn forage (rotational)	30	25	0.5	0.4
			Total	3.4
DAIRY CATTLE				
Potato culls	20	40	0.8	1.6
Sweet corn forage (rotational)	30	50	0.5	0.8
			Total	2.4

A ruminant feeding study has been reviewed (R. Lascola, 4/2/93). In this study residues in milk appeared to plateau by day seven. Residue analyses were conducted for parent and the metabolites melamine and 1-methylcyromazine. Since the metabolism committee has determined that only residues of cyromazine need be considered in animal commodities unless the dietary burden to animals increases significantly, we have calculated the levels of cyromazine that might be present in milk, meat, liver and kidney. Very little residues were detected in fat, regardless of feeding level. Residue levels increase with increasing feeding levels and appear to be linear for milk and tissues (except fat). The table below shows the feeding levels and the amount of cyromazine detected along with calculations on the level of cyromazine to be expected for milk, meat, liver and kidney from the maximum dietary burdens from the table above.

MEASURED RESIDUES FROM 10, 50, AND 100 PPM FEEDING LEVELS VS. CALCULATED VALUES		
Feeding level, ppm	Cyromazine residues detected	Calculated levels from 2.4 ppm dairy diet and 3.4 ppm beef cattle diet
Milk (Day 7)		
10	<0.04	<0.02
50	0.20	0.01
100	0.50	0.01
Meat (Day 28)		
10	<0.05	<0.02
50	0.12	0.01
100	0.25	0.01
Liver (Day 28)		
10	<0.05	<0.02

MEASURED RESIDUES FROM 10, 50, AND 100 PPM FEEDING LEVELS VS. CALCULATED VALUES		
Feeding level, ppm	Cyromazine residues detected	Calculated levels from 2.4 ppm dairy diet and 3.4 ppm beef cattle diet
50	0.12	0.01
100	0.21	0.01
Kidney (Day 28)		
10	0.09	0.03
50	0.66	0.04
100	0.80	0.03

The following proposed tolerance levels for residues of cyromazine are adequate: 0.05 ppm for milk; 0.05 ppm for meat, fat and meat byproducts of cattle, goats, hogs, horses, and sheep. These levels are based on the limit of quantitation of the analytical method and overstate the actual maximum residues likely to be present in milk and animal tissues. As a result, the following anticipated residues should be used for chronic risk assessment: 0.01 ppm for milk; 0.01 ppm for meat, fat and meat byproducts (other than kidney) of cattle, goats, hogs, horses and sheep. With a level of 0.04 ppm in the kidney of cattle, goats, hogs, horses, and sheep.

Poultry

For eggs and chicken tissue, the currently established tolerances should be revised by removing Section 180.414 (c) which is for residues of melamine in poultry tissue. The tolerances would be 0.25 ppm for eggs and 0.05 ppm for poultry meat, fat, and meat byproducts (from chicken layer hens and chicken breeder hens only). There are no poultry feed items that would require the poultry and egg tolerances to be raised. These tolerances are based on the feed through use of Larvadex.

x. Water, Fish, and Irrigated Crops - Not applicable

xi. Food Handling - Not applicable

xii. Confined Accumulation in Rotational Crops

Cyromazine is persistent in soils and residues will be present in many crops that are rotated to treated crops. Field studies have been submitted for a number of crops and tolerances are being proposed. For those crops with no tolerances established, a one year plant back interval is specified on the label.

xiii. Field Accumulation in Rotational Crops

Rotational crop tolerances are being requested for cottonseed, sweet corn (K+CWHR), sweet corn forage and stover as well as radish, roots and tops (leaves). For a discussion of the data see under the Crop Field Trials section of this review.

xiv. Tolerance Reassessment Table

Since the metabolite melamine is being removed from the tolerance expression, all established tolerances will need to be reevaluated at reregistration. We have commented only on the poultry tolerances in this review since residues of the parent and metabolite are in different subsections of the regulation.

xv. Anticipated Residues

Meat and Milk: Tolerance levels are being set on the basis of the limit of quantitation of the analytical method. Even using maximum diets, residues in milk and animal tissues will not exceed 0.01 ppm (except for kidney). For kidney a value of 0.04 ppm is appropriate
Percent crop treated values for sweet peppers (6%), tomatoes (28%), celery (27%), leaf lettuce (1%), lettuce unspecified (4%), and head lettuce (3%) were used in the DRES analysis.
Tolerance levels were used for all crops except for cabbage at 0.05 ppm.

b. Dietary Exposure (Drinking Water Sources)

i. Ground Water

Based on review of environmental fate data (requirements listed under 40 CFR §158.290) by EPA's Environmental Fate and Effects division (EFED), cyromazine is somewhat mobile. Ground water estimates were made by James K. Wolf, Ph. D. of the Environmental risk Branch III using the SCI-GROW model.. The assumption of 6 applications of 0.125 lbs ai/A resulted in a calculated value of 1.6 μg/L.

ii. Surface Water

Surface water estimates were also made by James K. Wolf, Ph. D. using the EFED GENEEC model. The assumptions of 6 applications of 0.125 lbs ai/A and three soil aerobic half-lives resulted in a calculated value of 28.9 μg/L. EFED and HED management have determined that this value devided by 3, better represents monitoring data. Thus 9.6 μg/L was used in HED's dringing water assessment. Three aerobic soil metabolism half-life values; 150, 300 and 450 days were used in the calculations. Since little difference in estimated concentrations were obtained, HED used the 450 day half-life, since it is the most conservative. Only a single soil aerobic metabolism half-life value of 150 days was actually available. When a single value is available EFED multiplies the single value times 3 (450 days) to consider uncertainty. The 300

days was considered to show that modle was generally insensitive to these long half-lives (≥ 150 days). No data were available for aquatic degradation, so it was not considered. Aquatic degradation would further reduce cyromazine concentrations in surface water.

c. Dietary Risk Assessment and Characterization

i. Chronic Risk

A chronic dietary risk assessment is required for cyromazine. The RfD used for the chronic dietary analysis is 0.0075 mg/kg bwt/day.

Anticipated residue values for cyromazine of 0.01 ppm in milk and meat (other than kidney) and 0.04 ppm in kidney were used for this dietary risk assessment.

Chronic dietary exposure estimates (DRES) for cyromazine are summarize in Attachment I (run dated //). The DRES analysis utilized the anticipated residues calculated from field trial data for potatoes and animal commodities. The analysis also used percent crop treated for sweet peppers (6%), tomatoes (28%), celery (27%), leaf lettuce (1%), lettuce unspecified (4%), and head lettuce (3%). For all other crops, the value of 100% crop treated was used. The proposed and established cyromazine tolerances result in an Anticipated Residue Contribution (ARC) that is equivalent to the following percents of the RfD:

U.S. Population	47%
Hispanics	42%
Non-Hispanics Others	60%
Non-Nursing Infants (<1 year old)	76%
Females (13+ years, nursing)	48%
Children (1-6 years old)	81%
Children (7-12 years old)	65%

The subgroups listed above are: (1) the U.S. population (48 states); (2) infants and children; and, (3) other subgroups for which the percentage of the RfD occupied is equal to, or greater than, that occupied by the subgroup U.S. population (48 states).

This chronic analysis for cyromazine is an over-estimate of dietary exposure with 100 percent of most of the commodities treated with cyromazine. Additionally, most of the residue values for crops include the metabolite melamine which is no longer of toxicological concern. This also results in an over-estimate of the risk. HED does not consider the chronic dietary risk to exceed the level of concern.

ii. Carcinogenic Risk

In accordance with the EPA proposed Guidelines for Carcinogenic Risk Assessment (April 10,

1996), cyromazine was characterized as "evidence of non-carcinogenicity for humans".

iii. Acute Dietary Risk

There were no toxicological effects attributale to a single exposure (dose) observed in oral toxicity studies including the developmental toxicity studies in rats or rabbits. Therefore, a dose and an endpoint was not selected for this risk assessment.

iv. Drinking Water Risk (Chronic)

OPP has calculated drinking water levels of concern (DWLOCs) for chronic (non-cancer) exposure to cyromazine in surface and ground water, the drinking water levels of concern are 136, 153, 13, and 146 ppb for the U.S. Population, Females, Children, and Males, respectively. To calculate the DWLOC for chronic (non-cancer) exposure relative to a chronic toxicity endpoint, the chronic dietary food exposure (from DRES) was subtracted from the RfD to obtain the acceptable chronic (non-cancer) exposure to cyromazine in drinking water. DWLOCs were then calculated using default body weights and drinking water consumption figures. Cyromazine has no residential uses; therefore, aggregate exposure is limited ot food plus water.

Estimated maximum concentrations of cyromazine in surface and ground water are 10 and 1.6 ppb, respectively. Estimated average concentrations of cyromazine in surface and ground water are 9.6 and 1.6 ppb, respectively. [Note: For the purposes of the screening-level assessment, the maximum and average concentrations in ground water are not believed to vary significantly.] The estimated average concentrations of cyromazine in surface and ground water are less than OPP's levels of concern for cyromazine in drinking water as a contribution to chronic aggregate exposure. Therefore, taking into account the present uses and uses proposed in this action, OPP concludes with reasonable certainty that residues of cyromazine in drinking water (when considered along with other sources of exposure for which OPP has reliable data) would not result in unacceptable levels of aggregate human health risk at this time.

OPP bases this determination on a comparison of estimated concentrations of cyromazine in surface waters and ground waters to back-calculated "levels of concern" for cyromazine in drinking water. These levels of concern in drinking water were determined after OPP has considered all other non-occupational human exposures for which it has reliable data, including all current uses, and uses considered in this action. The estimates of cyromazine in surface and ground waters are derived from water quality models that use conservative assumptions (health-protective) regarding the pesticide transport from the point of application to surface and ground water. Because OPP considers the aggregate risk resulting from multiple exposure pathways associated with a pesticide's uses, levels of concern in drinking water may vary as those uses change. If new uses (including crop or residential) are added in the future, OPP will reassess the potential impacts of cyromazine on drinking water as a part of the aggregate risk assessment process.

d. Statement of the adequacy of the dietary exposure data base to assess infants' and children's exposure

The dietary (food and water) exposure data base for cyromazine is adequate to assess infants' and children's exposure.

5. Occupational and Residential Exposure Risk

a. Occupational and Residential Exposure

i. Summary of Use Patterns and Formulations: Occupational and Residential

The information in two tables below is taken from Trigard 75% WP (enclosed in water soluble packets) and other sources as cited.

Registration Request for Use of Trigard in/on potatoes.

Factors	Comments
Crop to be treated	potato
Pests	Colorado potato beetle
Application methods	Foliar applications using aerial and groundboom equipment. Aerial applications are suggested when ground conditions prohibit application by ground equipment.
Application rate	For leafminers and at the beginning of egg hatch for Colorado potato beetle - 0.125 lb ai per acre and 0.25 lb ai per acre for heavy infestations of Colorado potato beetle.
Maximum number of applications	Not more than 0.5 lb ai/A/year.
Percent Absorption	8 percent [MRID 40168601]
Estimated Acreage of Application per Day	**Aerial** - 350, and **Ground boom** - 80 acres[1]
Manufacturer	Novartis Crop Protection, Inc.

[1] The estimate of acreage used in this assessment of worker exposure are standard defaults representing acreage for aerial and ground boom applications to large scale production areas for potato production.

Registration Request for Use of Trigard in/on onions.

Factors	Comments
Crop to be treated	onions (use site also includes garlic, great-headed garlic, leeks, Welch onions and shallots)
Pests	Used for onion maggots in soils having organic matter greater than 10%.
Application methods	Commercial seed treatment.
Maximum application rate	4.95 lb ai/100 pounds of seed.
Maximum number of treatments	not known
Percent Absorption	8 percent [MRID 40168601]
Average pounds of seed treated per day	not known
Manufacturer	Novartis Crop Protection, Inc.

Toxicity endpoints are established for the active ingredient for short-term, intermediate-term, and chronic occupational or residential exposure. A no observed effect level (NOEL) of 0.75 was selected from a six month dog feeding study in which pronounced hematological parameters were manifested as decreases in hematocrit and hemoglobin levels. These effects were observed during the first week of the study and were maintained throughout the study. A dermal absorption rate of 8 percent was identified to be used in conjunction with this oral dose. This endpoint was also selected by the Hazard Identification Assessment Review Committee for use in inhalation exposure assessments.

Risk assessments are required for short-term, intermediate-term, and chronic exposure, where appropriate. Short and intermediate term exposures are expected for the use of cyromazine on potatoes. Information regarding the frequency and duration the seed treatment use is not known. However, the endpoint is the same for all exposure durations.

TYPE OF TOXICITY	TOXICITY CATEGORY Active ingredient
Acute Oral	III
Acute Dermal	III
Acute Inhalation	IV
Primary Eye	IV
Primary Dermal	IV
Dermal Sensitization	non-sensitizer

ii. Handler Exposures and Assumptions

HED's exposure assessment is based on the assumptions in the following table.

Assumptions for Worker Exposure Assessments

Factors	Quantities/Units
Mixer/Loader and Applicator body weight	70 kg
Flagger body weight	70 kg
Application rate (Seed Treatment Aerial and Groundboom)	0.125 - 0.25 lb ai/A
Acres treated per day (Aerial) Acres treated per day (Groundboom)	350 acres 80 acres[1]
Applicator unit exposure from Pesticide Handlers Exposure Database (PHED); (Aerial application; liquid; closed cab; with long-pants, long-sleeved shirt, and no gloves).	Dermal - 5.0 µg/lb ai handled[2] Inhalation - 0.1 µg/lb ai handled[2]
Applicator unit exposure from PHED; (Ground boom application; liquid; open cab; with long-pants and long-sleeved shirt. No gloves). Inhalation exposure does not assume the use of a respirator.	14 µg/lb ai handled[2] Inhalation - 0.7 µg/lb ai handled[2]
Mixer/loader unit exposure from PHED, (In support of Aerial and Ground applications; use of wettable powder enclosed in water soluble packets; wearing long pants and long-sleeved shirt. No gloves). Inhalation exposure does not assume the use a respirator.	Dermal - 21 µg/lb ai handled[2] Inhalation - 0.1 µg/lb ai handled[2]

Factors	Quantities/Units
Airblast Applicator unit exposure from PHED; open cab; wearing long pants and long-sleeved shirt. No gloves). Inhalation exposure does not assume the use of a respirator.	Dermal - 390 µg/lb ai handled[2] Inhalation - 4.5 µg/lb ai handled[2]
Flagger unit exposure from PHED; liquid applications by aircraft; Wearing long-sleeved shirt and long pants. No gloves. Inhalation exposure does not assume the use of a respirator.	Dermal - 11 µg/lb ai handled[2] Inhalation - 0.35 µg/lb ai handled[2]
Personal protective equipment (PPE), per label.[3]	**For all labels:** long-sleeved shirt and long pants; chemical-resistant gloves.

[1] Standard assumptions of the acreage treated per day given the crop.
[2] Source: Pesticide Handlers Exposure Database (PHED) V1.1, Surrogate Exposure Guide (May 97).
[3]Although handeler MOE's are acceptable for this use based on surrogate data without the use of gloves. Reduced PPE are not recommended at this time.

iii. Post-Application Exposures & Assumptions - Occupational and Residential

Post application exposure is expected for workers involved in handset irrigation equipment in potato fields as well as for crop advisors scouting potato fields. Potatoes are harvested mechanically, however individuals sorting vines and other trash from potatoes may result in lower exposures than those involved in the activites mentioned above. There is a high potential for postapplication exposure for workers harvesting mangos. Post application exposure is unlikely for the seed treatment as the pesticide treated seed will be situated below the soil surface.

iv. Handler Exposure Assessment (includes mixer/loaders, applicators and other handlers)

The table below, summarizes the HED/RAB1 estimates for total handler exposure for mixer/loaders, applicators and flaggers in the proposed use of cyromazine on potatoes. Usage data and surrogate data are not available to assess exposure for the use of cyromazine to treat onion seed. These handler estimates are based on the assumptions outlined in the following table.

Handler Exposure to Trigard WP Insecticide

Job Function	Average Dermal Daily Dose for Trigard WP mg ai/kg bw/day	Dermal Short & Intermediate-Term MOE
Mixer/loaders	Aerial - 0.002 Ground boom - 0.0005	Aerial - 375 Ground boom - 1,500
Applicators	Aerial - 0.0005 Groundboom -0.0004	Aerial - 1,500 Groundboom - 1,900
Flaggers	0.0015	500

MOE = NOEL/ADD (where NOEL = 0.75 mg/kg/day)

The exposure estimates in the above table are based on treatment of 350 acres per day by aerial and 80 acres per day by ground boom.

The following calculations were used to determine the expected worker exposures resulting from the handling and application of cyromazine (Trigard WP) to potatoes.

Example calculation (Dermal exposure for mixer/loaders supporting aerial applications).

$$0.25\ lbs.\ ai\ applied/acre \times 350\ of\ acres\ treated/day = 87.5\ lbs\ ai/day$$

$$5.0\ \mu g/lb\ ai\ handled\ (PHED,\ Version\ 1.1) \times 87.5\ lbs\ ai/day = 437.5\ \mu g\ ai/day$$

$$\frac{437.5\ \mu g\ ai/day}{70\ kg\ bw} = 6.25\ \mu g\ ai/kg\ bw/day$$

$$\frac{6.25\ \mu g\ ai/kg\ bw/day}{1000\ \mu g/mg} = 0.00625\ mg\ ai/kg\ bw/day$$

$$0.00625 \times 8\% = 0.0005\ mg\ ai/kg\ bw/day$$

v. Post-Application Exposure Assessment

The petitioner did not provide post-application exposure sampling data. This should be considered a data gap.

b. Occupational and Residential Risk Assessment/Characterization

i. Risk from Dermal and Inhalation Exposures

The Agency does not generally have an occupational or residential concern unless MOEs are below 100 when the NOEL is based upon data generated in animal studies. The 100 accounts for interspecies extrapolation and intraspecies variability. FFDCA section 408 provides that EPA shall apply an additional 10-fold margin of safety for infants and children in the case of threshold effects to account for pre-and post-natal toxicity and the completeness of the data base unless EPA determines that a different margin of safety will be safe for infants and children. The additional 10X is not necessary for cyromazine (per Hazard I.D. Comm.) due to no increased sensitivity to fetuses (rats and rabbits) and pups (rats); therefore, HED's level of concern for cyromazine are for MOEs that are below 100. There are no residential uses registered for cyromazine.

ii. Risk From Post-Application Exposures

The interim WPS, REI is 12 hours. Registration for potatoes and onions should be considered conditional until post application reentry exposure data are required consisting of Dislodgeable Foliar Residue data (132-1a) and Dermal and Inhalation exposure data (133-3 and 133-4 respectively). Because there are other uses of cyromazine that result in post-application exposure, the registrant should consider a reentry study design addressing all post-application exposures to cyromazine.

iii. Restricted Entry Interval

See ii, above.

Other data gaps include the generation of mixer/loader/applicator data addressing the seed treatment use of cyromazine. These guidelines are dermal exposure at an indoor site (233) and inhalation exposure at an indoor site (234). This registration should be considered conditional pending the submission of these data as well as the reentry data for potatoes.

6. Aggregate Exposure and Risk Assessment/Characterization

a. Acute Aggregate Exposure and Risk

There were no toxicological effects attributale to a single exposure (dose) observed in oral toxicity studies including the developmental toxicity studies in rats or rabbits. Therefore, a dose and an endpoint was not selected for this risk assessment.

b. Short- and Intermediate-term Aggregate Exposure and Risk

Since there are no residential uses of cyromazine, no short- and intermediate-term aggregate risk

exists for cyromazine.

c. Chronic Aggregate Exposure and Risk

For the U.S. Population, 48% of the RfD is occupied by dietary (food) exposure. As noted above, potential chronic exposure from drinking water is at a level below OPP's level of concern.

7. Other Food Quality Protection Act (FQPA) Considerations

a. Cumulative Risk

Section 408 of FQPA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency considers "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." While the Agency has some information in its files that may be helpful in determining whether a pesticide shares a common mechanism of toxicity with any other substances, EPA does not at this time have the methodology to resolve the scientific issues concerning common mechanism of toxicity in a meaningful way. EPA has begun a pilot process to study this issue further through the examination of particular classes of pesticides. The Agency hopes that the results of this pilot process will enable it to develop and apply policies for evaluating the cumulative effects of chemicals having a common mechanism of toxicity. At present, however, the Agency does not know how to apply the information in its files concerning common mechanism issues to most risk assessments.

In the case of cyromazine, HED has not yet determined whether or how to include this chemical in a cumulative risk assessment. These tolerance determinations therefore does not take into account common mechanism issues. After EPA develops a methodology for applying common mechanism of toxicity issues to risk assessments, the Agency will develop a process (either as part of the periodic review of pesticides or otherwise) to reexamine those tolerance decisions made earlier.

On this basis, the registrant must submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate issues related to whether cyromazine share(s) a common mechanism of toxicity with any other substance and, if so, whether any tolerances for cyromazine need to be modified or revoked.

b. Endocrine Disruption

EPA is required to develop a screening program to determine whether certain substances (including all pesticides and inerts) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect...". The Agency is currently working with interested stakeholders, including other government agencies, public

interest groups, industry and research scientists in developing a screening and testing program and a priority setting scheme to implement this program. Congress has allowed 3 years from the passage of FQPA (August 3, 1999) to implement this program. At that time, EPA may require further testing of this active ingredient and end use products for endocrine disrupter effects.

c. Determination of Safety (U.S. Population, Infants, and Children)

Using the exposure assumptions described above, HED has concluded that the percentage of the RfD that will be utilized by chronic dietary (food only) exposure to residues of cyromazine ranges from 17 percent for nursing infants less than one year old, up to 82 percent for children 1-6 years old. Despite the potential for exposure to cyromazine in drinking water, HED does not expect the chronic aggregate exposure to exceed 100% of the RfD. Since there are no residential uses of cyromazine, no chronic residential exposure is anticipated. RAB1 concludes that there is a reasonable certainty that no harm will result to infants and children from chronic aggregate exposure to cyromazine residues.

8. Data Requirements

a. Toxicology

There are no toxicology data gaps.

b. Residue Chemistry

The only residue chemistry data gap for the crops under consideration here is for cotton. The data requirements were detailed in the William Cutchin review of PP# 5F4546 dated 2/15/97. For cotton, a total of 11 field trials are required, one each in Regions 2 and 6, three in Region 4, and four in region 8. Also data on cotton gin byproducts (commonly called gin trash) are required. Until these data are submitted and reviewed, a time-limited tolerance for cottonseed is required.

To provide for the periodic evaluation of the anticipated residues and percent crop treated, the Agency will require under Section 408 (b) (2) (E) new information on those crops for which percent crop treated was used every five years as long as the proposed tolerances remain in force. Additional residue data for meat and milk will not be required since the tolerances are based on the methods limit of quantitation and not on the actual residues present which were used in the anticipated residue calculations.

c. Occupational/Residential Exposure

Post-application reentry exposure data are required consisting of Dislodgeable Foliar Residue data (132-1a) and Dermal and Inhalation exposure data (133-3 and 133-4 respectively). Other data gaps include the generation of mixer/loader/applicator data addressing the seed treatment

use of cyromazine. These guidelines are dermal exposure at an outdoor site (231) and inhalation exposure at an outdoor site (232). This registration should be considered conditional pending the submission of these data as well as the reentry data for potatoes. Until these data are submitted and reviewed, conditional registrations and time-limited tolerances for potatoes and onions are required.

Attachment I - DRES Run

cc: with attachment A. Rathman, DRES (B. Steinwand)
cc: without attachment PP#5E4450, 5F4576, 6F4613, 5F4546, 6F3332
RDI: Team(1/22/98),M.Morrow(3/10/98)
A.Rathman:804K:CM#2:(703)305-7330:7509C:RAB1:3/11/98

End of Document

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

PP# 6F4613

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

Date 12/11/97

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Subject: Cyromazine In/On Various Crops and Meat and Milk. Chemical # 121301.

From: Andrew R. Rathman, Chemist
Registration Action Branch I
Health Effects Division (7509C)

Through: Melba Morrow, Senior Scientist
Registration Action Branch I
Health Effects Division (7509C)

To: George Larocca, PM 13
Registration Division (7505C)

This memo covers the crop/tolerance combinations listed below. In the case of cotton, sweet corn and radishes, the tolerances are proposed as rotational crop tolerances with no purposeful use of cyromazine on those crops. The tolerance expression is for residues of cyromazine (N-cyclopropyl -1,3,5-triazine-2,4,6-triamine) and its metabolite, melamine (1,3,5-triazine-2,4,6-triamine) in or on the following raw agricultural commodities (RACs):

Petition Number	DP Barcode	RAC	Tolerance Level
PP# 5E4550	D236184	Mangoes	0.3 ppm
PP# 5F4576	D236189	Onions, green	3.0 ppm
		Onions, dry bulb	0.3 ppm
PP# 6F4613	D236190	Potato tubers	1.5 ppm
PP# 5F4546	D236187	Cottonseed	0.2 ppm
PP# 6F3332	D236185	Corn, sweet (K+CWHR)	0.5 ppm
		Corn, sweet, forage	0.5 ppm
		Corn, sweet, fodder	0.5 ppm
		Radish, root	0.5 ppm
		Radish, tops	0.5 ppm

Recycled/Recyclable • Printed with Vegetable Oil Based Inks on 100% Recycled Paper (40% Postconsumer)

In addition as part of PP# 6F3332 tolerances were proposed for residues of cyromazine and metabolite(s) in milk and tissues as listed below:

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	0.02 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	0.02 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

These tolerance expressions were proposed in Ciba's response to review of the tomato and carrot petitions submitted on 6/10/94. They are to be found in Volume 5 of the submission containing revised Sections B and F.
[See J. Stokes, memo, 2/13/95]

[The submission of 6/10/94 contains these additional comments in regard to the proposed animal tissue tolerances.]

The petitioner has previously withdrawn the request to establish a tolerance on carrot. The exclusion of carrot from the dairy and beef cattle diets greatly reduces the need expressed previously by CBTS to increase petitioner's proposed milk tolerances of 0.02 ppm for cyromazine and 0.02 ppm for melamine to 0.05 ppm. The petitioner agrees with CBTS that the other tolerances for meat and meat by-products should be established at 0.05 ppm, and not at the petitioner's proposal of 0.1 ppm.
[See J. Stokes, memo, 2/13/95]

As part of the February 17, 1997 submission, the petitioner is requesting that the tolerance for residues of cyromazine in milk be raised to 0.04 ppm.

The HED metabolism committee met to discuss cyromazine on 11/4/97. The conclusion of the committee was that only residues of cyromazine need to be regulated and used for risk

assessment at this time. As a result of this decision, we have reevaluated the tolerance requests for the petitions currently under consideration. At some future time all the established cyromazine tolerances will need to be reevaluated to determine if the established levels are excessive because of the removal of melamine as a residue of concern.

Conclusions

1. As a result of the decision of the HED Metabolism Committee, the tolerance expression currently in 180.414 and in the petitions under consideration here needs to be revised to include the parent cyromazine only.

2. For those crops where purposeful use is proposed the tolerance levels need to be revised for potatoes and onions; however, the level previously proposed for mangos is acceptable since essentially all residues detected consisted of cyromazine. The following tolerances should be proposed for residues of cyromazine:

Mango	0.3 ppm
Onion, green	2.0 ppm
Onion, bulb	0.1 ppm
Potato, tuber	0.8 ppm

3. For those crops where inadvertent tolerances are being requested, tolerances should be established in a separate subsection as follows:

> "Tolerances are established for the indirect or inadvertent residues of cyromazine (N-cyclopropyl-1,3,5-triazine-2,4,6-triamine), in or on the raw agricultural commodities when present therein as a result of the application of cyromazine to growing crops listed in paragraphs (x) of this section."

Cotton, undelinted seed	0.1 ppm
Corn, sweet, (K+CWHR)	0.5 ppm
Corn, sweet, forage	0.5 ppm
Corn, sweet, stover	0.5 ppm
Radish, root	0.5 ppm
Radish, tops (leaves)	0.5 ppm

4. No tolerances are required for the potato processing products chips and granules. Using the highest average field trial and the average concentration factor, residues in potato chips do not exceed the 0.8 ppm level required for potatoes and the concentration into potato granules is

below the 1.5X level where we generally set processed commodity tolerances.

5. For eggs and chicken tissue, the currently established tolerances should be revised by removing Section 180.414 (c) which is for residues of melamine in poultry tissue. The tolerances would be 0.25 ppm for eggs and 0.05 ppm for poultry meat, fat, and meat byproducts (from chicken layer hens and chicken breeder hens only).

6. As a result of the animal feed items potato waste and sweet corn forage being added to the animal diet at this time, the following meat and milk tolerances need to be proposed for residues of cyromazine: 0.05 ppm for milk; 0.05 ppm for meat, fat and meat byproducts of cattle, goats, hogs, horses, and sheep.

Recommendations

The petitioner should be requested to revise the Section F in all the petitions to remove melamine from the tolerance expression. Additionally, in many cases the levels being proposed need to be revised as a result of the removal of the metabolite melamine from consideration and the levels noted in Conclusions 2, 3 and 6 should be incorporated into the revisions.

Detailed Considerations

Mangoes (MRID# 4344703-01-08)

Data from six field trials conducted in Mexico showed residues of cyromazine ranging from 0.04 (below the limit of quantitation) to 0.25 ppm on day 0 and from <0.03 (non-detectable) to 0.10 ppm on day 28. No melamine residues were found in any sample. These results are contained in the data review of W. Cutchin (PP# 5E4450, 5/3/95). Therefore, the tolerance level of 0.3 ppm proposed is adequate with no revision needed.

Onions (MRID# 437631-01)

Data for onions (green and dry bulb) were submitted in connection with PP# 5F4576 and discussed in detail in the J. Stokes review dated 7/9/96. A total of eleven trials at the 1 and 2X application rate were submitted. Maximum cyromazine residues on green onions from the 1X rate were 1.7 ppm and from the 2X rate were 2.0 ppm. Cyromazine residues in dry bulb residues were a maximum of 0.06 ppm at the 1 rate and <0.05 ppm at the 2X rate. From these data we conclude that the tolerance level for onion, green should be 2.0 ppm and for onion, bulb the level should be 0.1 ppm.

Potatoes (MRID#'s 438262-02 and 438262-03)

Data for potatoes were reviewed in the J. Stokes memo of 9/12/96 in connection with PP# 6F4613. Residue levels in samples from field trials using the proposed 0.75 lb a.i./A (1X) rate

show average cyromazine residues of 0.23 ppm . The maximum value detected in the 1X samples was 0.75 ppm. Samples from the other application rates (0.75X-5X) show a fairly linear relationship with estimated (calculated) values of cyromazine residues all falling below 0.8 ppm. As a result, we conclude that the tolerance should be set at 0.8 ppm for potato, tuber.

Processing studies were conducted where potatoes were processed into wet and dry peel, potato chips and potato granules. Average concentration factors for the various processed products were calculated to be the following: Wet peel - 0.4; dry peel - 3; potato chips - 1.7; potato granules - 2.4. Since the concentration factors for potato chips and potato granules were greater than 1, we used the highest average residue in the field trials (HAFT = 0.48) to multiply by the mean concentration factors for these processed commodities to determine the highest expected residue in the processed items.

Potato chips	0.48 ppm x 1.7X = 0.8 ppm
Potato granules	0.48 ppm x 2.4X = 1.15 ppm

Since the maximum expected residue in potato chips is the same as the tolerance level required, no tolerances are needed for this processed commodity. For potato granules the concentration factor is below the 1.5X value that is generally used for setting tolerances for processed commodities.

Cottonseed (MRID# 436944-01)

The tolerance request for cottonseed is for inadvertent residues when cotton is planted as a rotational crop. A detailed review of the data is contained in the W. Cutchin memo of 2/15/96 of PP# 5F4546. Data are available from five studies conducted in CA(2), AZ(2) and TX. These studies show no detectable residues of cyromazine (<0.05 ppm) from a 1X application. These data were found deficient in that there were an inadequate number of studies and there were no data available for cotton gin byproducts (commonly called cotton gin trash). In a more recent review of this petition request (A. Rathman, 11/13/97), we had no objections to a time-limited rotational crop tolerance for residues of cyromazine and its metabolite melamine at 0.2 ppm noting the need for additional residue data and data for cotton gin byproducts for a permanent tolerance. Considering only residues of cyromazine, this time-limited rotational tolerance should be revised to 0.1 ppm. The company should be informed that the additional residue trials and data for cotton gin byproducts are still required.

Sweet Corn and Radishes

The data for sweet corn and radishes were originally reviewed in 1987 by A. Smith. Data of the level of parent vs. the metabolite melamine are not available in the branch files at this time. Therefore, we will use the levels found acceptable in the J. Garbus review of PP# 6F3332, 8/26/96 for the DRES calculations. These levels are the following:

Corn, sweet (K+CWHR)	0.50 ppm
Corn, sweet, forage	0.50 ppm
Corn, sweet, fodder*	0.50 ppm
Radishes, root	0.50 ppm
Radishes, tops	0.50 ppm

* Note: The proper terminology now for this tolerance is "corn, sweet, stover."

Meat, Milk, Poultry and Eggs

The only significant animal feed items from either published or proposed tolerances are potato culls, processed potato waste and sweet corn forage and stover. Since none of these items are fed to poultry, the established poultry tolerances need only be reevaluated on the basis of the established feed through use of Larvadex. Secondary residues could occur in meat, fat and meat byproducts of animals and in milk. Animal diets and the dietary burden to animals was discussed in detail in the J. Stokes review of PP# 6F4613, 9/12/96. At that time alfalfa was also a significant feed item, but has been removed from consideration (A. Rathman review dated 11/13/97). We have reexamined the animal diets considering only potato culls and sweet corn forage since this results in the highest dietary burden and find that maximum dietary burden for diary cattle would be 2.4 ppm and for beef cattle the maximum level would be 3.4 ppm; see the following table:

COMMODITY	PERCENT DM	PERCENT IN DIET	LEVEL IN COMMODITY, ppm	DAILY DIETARY BURDEN
BEEF CATTLE				
Potato culls	20	75	0.8	3.0
Sweet corn forage (rotational)	30	25	0.5	0.4
			Total	3.4
DAIRY CATTLE				
Potato culls	20	40	0.8	1.6
Sweet corn forage (rotational)	30	50	0.5	0.8
			Total	2.4

A ruminant feeding study has been reviewed (R. Lascola, 4/2/93). In this study residues in milk seemed to plateau by day seven. Residue analyses were conducted for parent and the metabolites melamine and 1-methylcyromazine. Since the metabolism committee has determined

that only residues of cyromazine need be considered in animal commodities unless the dietary burden to animals increases significantly, we have calculated the levels of cyromazine that might be present in milk, meat, liver and kidney. Very little residues were detected in fat, regardless of feeding level. Residue levels increase with increasing feeding levels and appear to be linear for milk and tissues (except fat). The table below shows the feeding levels and the amount of cyromazine detected along with calculations on the level of cyromazine to be expected for milk, meat, liver and kidney from the maximum dietary burdens from the table above.

MEASURED RESIDUES FROM 10, 50, AND 100 PPM FEEDING LEVELS VS. CALCULATED VALUES		
Feeding level, ppm	Cyromazine residues detected	Calculated levels from 2.4 ppm dairy diet and 3.4 ppm beef cattle diet
Milk (Day 7)		
10	<0.04	<0.02
50	0.20	0.01
100	0.50	0.01
Meat (Day 28)		
10	<0.05	<0.02
50	0.12	0.01
100	0.25	0.01
Liver (Day 28)		
10	<0.05	<0.02
50	0.12	0.01
100	0.21	0.01
Kidney (Day 28)		
10	0.09	0.03
50	0.66	0.04
100	0.80	0.03

Since tolerances are currently being proposed for combined residues of cyromazine and melamine in milk and meat, fat and meat byproducts, a revised Section F will be required. While the limit of quantitation for the method is 0.05 ppm, the limit of detection is at or about 0.01 ppm. Based upon the limit of quantitation of the method, we recommend that the following tolerance levels be proposed for residues of cyromazine: 0.05 ppm for milk; 0.05 ppm for meat, fat and meat byproducts of cattle, goats, hogs, horses, and sheep. If anticipated residues are required for risk assessment, we recommend the following levels be used: 0.01 ppm for milk; 0.01 ppm for

meat, fat and meat byproducts (other than kidney) of cattle, goats, hogs, horses and sheep. And a level of 0.04 ppm in the kidney of cattle, goats, hogs, horses, and sheep.

For eggs and chicken tissue, the currently established tolerances should be revised by removing Section 180.414 (c) which is for residues of melamine in poultry tissue. The tolerances would be 0.25 ppm for eggs and 0.05 ppm for poultry meat, fat, and meat byproducts (from chicken layer hens and chicken breeder hens only).

cc: PP#s 5E4550 ,6F3332, 5F4546, 6F4613 5F4576, Rathman (2 copies)
RDI:G.Kramer:12/10/97:M.Morrow:12/11/97
7509C:RAB1:ARR:12/11/97

End of Document

PP# 5F4576

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

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

SEP 12 1996

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Memorandum

Subject: PP#6F4613. Cyromazine In/On Potato. Residue Data and Analytical Methodology. MRID#'s 438262-00, 438262-02 and 438262-03. DP Barcode# D220675. CBTS#16444. Chemical No. 121301.

From: Jerry B. Stokes, Chemist
Chemistry Branch I/Tolerance Petition Team 2
Health Effects Division (7509C)

Jerry B. Stokes

Through: Elizabeth Haeberer, Acting Chief
Chemistry Branch I/Tolerance Petition Team 2
Health Effects Division (7509C)

Elizabeth T. Haeberer 9/12/96

To: Debbie McCall, Acting Section Head
Risk Characterization and Analysis Branch
Health Effects Division (7509C)

CIBA-GEIGY Corporation, Agricultural Division proposes that 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), all expressed as cyromazine, be established in/on the raw agricultural commodity (RAC) potato at 1.5 ppm. The petitioner has requested a 0.04 ppm milk tolerance based on the proposed use. Tolerances for the combined residues of cyromazine and melamine are established under 40 CFR §180.414. Currently there are no cyromazine food additive tolerances. No Registration Standard for cyromazine has been issued.

CONCLUSIONS

1. All product chemistry data requirements have been previously and adequately addressed. No additional data are needed for the proposed use.

2a. The petitioner has proposed the use of Trigard® containing 75% cyromazine active ingredient (a.i.) on potato. The submitted field residue data support the proposed 7-day PHI.

Recycled/Recyclable • Printed with Vegetable Oil Based Inks on 100% Recycled Paper (40% Postconsumer)

2b. Tolerances have been recommended (See memo of 08/26/96, J. Garbus), but are not yet established for sweet corn and radishes as rotational crops (pending PP#6F3332). Rotation to sweet corn and radishes with a 1 month plantback interval will only be allowed if these tolerances are established. Provided these tolerances are established, a revised Section B is needed to reflect this proposed 1-month plantback interval.

3. The nature of the residue in plants is adequately understood for the proposed use. The primary route for cyromazine metabolism is dealkylation of cyromazine to form melamine and cyclopropane. The HED Metabolism Committee will determine the residues of concern.

4. The nature of the residue in ruminants is adequately understood for the proposed use. The primary route for cyromazine metabolism is dealkylation of cyromazine to form melamine and cyclopropane. Metabolite 1- methylcyromazine is found in the liver and kidney. The HED Metabolism Committee will determine the residues of concern.

5a. There are adequate residue analytical methods in Pesticide Analytical Manual (PAM), Vol-II to determine residues of cyromazine and its metabolite melamine in/on potato.

5b. Data for cyromazine and its metabolites melamine and 1-methylcyromazine through the FDA multiresidue methods have been previously submitted for the FDA Pesticide Analytical Manual. Melamine and 1-methylcyromazine are not recovered by these methods. Cyromazine gives marginal recovery using Protocol D.

5c. Methodology is available to determine cyromazine and melamine residues in meat, fat, and meat byproducts at or above 0.05 ppm.

5d. Methodology is available to determine 1-methylcyromazine residues in meat byproducts (liver and kidney) above 0.05 ppm and in milk above 0.10 ppm. Estimated residues are expected to be below this level following the proposed use. If the HED Metabolism Committee determines that 1-methylcyromazine is to be regulated in meat byproducts, then Agency and independent lab validations will be necessary.

5e. The methodology AG-403 allows detection of cyromazine and melamine residues in milk at 0.01 ppm. Until the HED Metabolism Committee determines whether residues of metabolites melamine and/or 1-methylcyromazine are to be regulated in milk, CBTS reserves comments on this methodology. However, Agency validation of this method for residues of cyromazine in milk will likely be required.

6. Residues of cyromazine and melamine are stable in frozen storage from 9 to 24 months in head lettuce, leaf lettuce, celery, mushrooms, and tomatoes. The treated potato field trial samples in this petition were stored from 5.5 to 12 months. Storage stability data are adequate to support the proposed use.

7. Field trial residue data are from the major potato-growing states. The submitted field trial data are adequate to support the proposed use. The proposed 1.5 ppm tolerance for the RAC potato will cover any expected residues from the proposed use. However, the residue data suggests that the proposed 1.5 ppm tolerance could be decreased to 1.0 ppm and still adequately cover any residues. No additional field trial data are needed. The HED Metabolism Committee will determine the residues of concern. After this determination a revised Section F may be needed.

8. The processing study is adequate to support the proposed use. There is concentration of combined residues of cyromazine and its metabolite melamine in potato granules/flakes and potato chips. Separate tolerances may be needed for potato granules/flakes and potato chips. The HED Metabolism Committee will determine the residues of concern. After this determination a revised Section F may be needed.

9a. Cull potatoes and processed potato waste are considered significant feedstuffs for beef and dairy cattle. Secondary residues are expected in dairy and beef cattle meat, fat, meat byproducts, and milk from the proposed use. Potato commodities are not significant poultry feedstuffs.

9b. A tolerance for the RAC potato will cover residues in the processed potato waste.

9c. Tolerances may be needed for animal commodities of milk, meat, fat, and meat byproducts for the proposed use. This is based on not only the proposed use, but on pending petitions, e.g., PP#6F3332, PP#6F3422, PP#5F4546. The petitioner has proposed a 0.04 ppm milk tolerance. The HED Metabolism Committee will determine the residues of concern. After this determination a revised Section F may be needed.

10. Compatibility problems exists between Codex and Mexican limits and the proposed US tolerances. With Codex and Mexican limits only cyromazine is the residue of concern; the metabolite melamine is not included in the residue expression. There are no established cyromazine limits for the RAC potato, or the processed commodities, potato granules/flakes, or chips, or the feedstuff, processed potato waste. There is a 0.01 ppm (at or about the limit of determination) Codex limit in milks.

RECOMMENDATION

CBTS cannot recommend for the requested 1.5 ppm cyromazine (plus metabolite melamine) tolerance on the RAC potato because of **conclusions 2b, 3, 4, 5d, 5e, 7, 8, and 9c.** A revised Section B reflecting the proposed 1-month plantback interval to sweet corn and radishes should be submitted providing the tolerances are established for sweet corn and radish.

DETAILED CONSIDERATIONS

PRODUCT CHEMISTRY/CHEMICAL IDENTITY

All product chemistry data for cyromazine have been previously submitted and adequately reviewed (see memos in PP# 9G2230, A. Rathman, 11/14/79; and in PP# 5F3177, E. Haeberer, 02/13/85). 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 expect a residue problem in the RAC potato for the impurities identified at or above 0.1% in the TGAI cyromazine when the formulation Trigard® is used as directed.

DIRECTIONS FOR USE

The petitioner proposes use of Trigard®OMC, a wettable powder containing 75% a.i. cyromazine as a seed treatment and folair applications to control Colorado potato beetle and leafminer for potato crops. Trigard®OMC is applied to seed potatoes at the rate of one-sixth lb/A (2.7 oz) to one-third lb/A (5.3 oz) of formulated product for the Colorado potato beetle. Foliar application can be made 10 to 14 days later. The label states a minimum PHI of 7 days to control leafminer. Both pest control directions allow up to 1.0 lb of the formulation/A/season (0.75 lb a.i./A/season). The formulation should be applied in sufficient water to obtain full foliage coverage by ground equipment, and in a minimum of 5 gallons of water/A when applying by air.

The submitted field residue data support a 7-day PHI. (See discussion in Magnitude of the Residues, this memo.)

Rotational crop restrictions:

The submitted label for Trigard®OMC allows 0-day plantback to those crops listed on the label, i.e., celery, head and leaf lettuce, spinach, Chinese mustard and cabbage (Florida use only), peppers, and cucurbits. The label allows a 3-month plantback for sweet corn and radishes.

Cyromazine and/or melamine residues in the soil would be adequately covered by the established tolerances on these individual crops.

Tolerances have been recommended (See memo of 08/26/96, J. Garbus), but are not yet established for sweet corn and radishes as rotational crops (pending PP#6F3332). Rotation to sweet corn and radishes with a 1 month plantback interval will only be allowed if these tolerances are established. Provided these tolerances are established, a revised Section B is needed to reflect this proposed 1-month plantback interval.

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 memo of 02/04/85, E. Haeberer; memos of 02/08/85 and 03/20/85, C. Deyrup; memo of 01/28/87, A. Smith).

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. Cyromazine residues in the soil are taken up by crops and translocated to the edible portion of the plants. Melamine forms rapidly. The nature of the residue in plants is adequately understood. The HED Metabolism Committee will determine the residues of concern.

NATURE OF THE RESIDUE - LIVESTOCK: MRID# 422243-02

No new livestock cyromazine metabolism studies are submitted in this petition. Processed potato waste is considered a significant feedstuff.

CIBA-GEIGY has previously submitted an animal metabolism study (MRID# 422243-02). This metabolism study has been reviewed by CBTS (See memo of 04/02/93, R. Lascola). Two lactating goats were dosed once daily with 150mg of uniformly triazine ring-labeled 14C cyromazine for four days. Feed was available at all times and feed consumption was monitored. The first goat, numbered #86 in the study, received 107 ppm; the second goat, numbered #85, received 75 ppm. Milk was collected twice daily and tissues 6 hours after the last dose was administered. C14-Activity was characterized for milk, liver, kidney, tenderloin, omental fat, and bile. Identification of the various metabolites was made by TLC, with MS confirmation.

Residues in milk samples were analyzed by HPLC/LSC. 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. Milk solids

containing residues which were not released by the methanol were dissolved in water; however, these residues were not characterized.

Liver samples from both goats were extracted with acetonitrile/water, the extracts 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 acetonitrile/water, and then sequentially with acetone, water, and methanol, before a final combustion analysis of the remaining residue. Activity from the second acetonitrile/water and water extractions was also characterized. The acetone and methanol extractions (<0.5%) did not permit characterization of residues.

Kidney and tenderloin samples were extracted in the same manner as the 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 acetonitrile, which released 97% of the activity. For kidney, muscle, and fat, only samples from goat #86 were analyzed. The similarity of the residue profiles from the liver and milk samples suggest that the residues in the goat #85 would be similar.

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 #86, Day 1	46%				26%	11%[c]
Goat #86, Day 4	63%	<3%[a]	ND[b]	ND	22%	11%
Goat #85, Day 4	53%				22%	12%
(avg. ppm)	(0.66)	(0.03)				
Liver (Goat #86)[d]						
Acetonitrile - 1	32%	7%	42%	ND	14%	28%
Acetonitrile - 2	ND	ND	<1%	<1%	3%	---
H_2O	ND	ND	<<1%	<<1%	1%	---
combustion	---	---	---	---	---	8%
Liver (Goat #85)						
Acetonitrile - 1	33%	4%	39%	ND	23%	14%
Acetonitrile - 2	ND	ND	<2%	ND	<2%	---
H_2O	ND	ND	<1%	<<1%	<3%	---
combustion	---	---	---	---	---	3%
(avg. ppm)	(0.93)	(0.16)	(1.2)			
Kidney[e]	83%	27%	7%	ND	1%	<<1%
(avg. ppm)	(3.8)	(1.2)	(0.31)			
Tenderloin[f]	85%	3%	4%	ND	14%	5%
(avg. ppm)	(0.79)	(0.03)	(0.03)			
Omental Fat[g]	49%	ND	ND	ND	48%	N/A
(avg. ppm)	(0.11)					

[a] Melamine level reported is the average of the three samples.
[b] ND: Not Detected (<0.02 ppm).
[c] Milk solids were subjected to further extraction; however, recovered activity was too low for characterization.
[d] Acetone extraction after second acetonitrile extraction, and methanol extraction after water extraction, each yielded <0.5% of activity, and were not characterized.
[e] Overall recovery was higher 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. Assignments based on retention times of HPLC peaks.
[g] Several minor peaks were not identified, due to low levels of activity.

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 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 acetonitrile, acetone, water, and methanol. Adequate steps were taken to release these residues.

The major residues in milk and meat are cyromazine and melamine. The major residues in liver and kidney are cyromazine, melamine, and 1-methylcyromazine. The HED Metabolism Committee will determine the residues of regulatory concern.

RESIDUE ANALYTICAL METHODS: MRID#437631-01

Methods AG-408 and AG-417A are the tolerance enforcement methodology as published in PAM, Vol II. These methodologies combined, and with minor modifications is Method AG-621. The residue data on the treated potatoes was analyzed by these methods. The crop matrix is extracted at reflux in methanol:water, acidified after cooling with dilute acid, partitioned with organic solvents, and then the water solubles are passed through an ion exchange column and a silica gel column for final cleanup before GLC analysis. The limit of quantitation is 0.05 ppm for cyromazine and 0.05 ppm for melamine expressed as cyromazine equivalents. These extraction and cleanup procedures are similar to the Methods AG-408 and AG-417, but AG-621 uses a gas chromatography for analysis, while the other methods use high pressure liquid chromatography for determination of cyromazine and melamine levels in the crop matrix. Recovery data for potato tubers and the processing fractions fortified at levels ranging from 0.05 ppm to 50 ppm for cyromazine and from 0.04 ppm to 50 ppm for melamine, averaged 107 ± 21% for cyromazine, and 89 ± 19% for melamine.

Methods AG-408 and AG-417 as listed in FDA's Pesticide Analytical Manual (PAM), Vol-II are adequate to enforce the proposed tolerance. AG-621 is acceptable to support the crop field trial residue data for cyromazine and its melamine metabolite on the RAC

potato. Data for cyromazine and its metabolites melamine and 1-methylcyromazine through the FDA multiresidue methods have been previously submitted for the FDA Pesticide Analytical Manual. Melamine and 1-methylcyromazine are not recovered by these methods. Cyromazine gives marginal recovery using Protocol D.

In the proposed use on the RAC potato, secondary residues of cyromazine, melamine, and 1-methylcyromazine could occur in animal commodities from the feeding of potato culls and potato processed waste. Methodology is available to determine 1-methylcyromazine residues in meat byproducts (liver and kidney) above 0.05 ppm and in milk above 0.10 ppm. Estimated residues are expected to be below this level following the proposed use. CBTS has previously commented on the need for analytical methodology for 1-methylcyromazine. However, since the HED Metabolism Committee will determine the residues of regulatory concern, CBTS will reserve comments on this methodology until after the committee review. Agency and independent lab validations may be needed to support the proposed use on potato.

The petitioner has not submitted a copy of the analytical methodology (AG-403) used to analyze the milk samples. EPA has validated this methodology in the Agency laboratory for chicken meat and eggs. This method is very similar to the Method I in PAM II referenced in the petitioner submissions as AG-417 or AG-417A. The only major difference between the two methods is the use of a gel permeation chromatography (AG-403) vs. ion exchange chromatography (AG-417) for additional sample cleanup after the first ion exchange chromatographic sample cleanup common to both methods. Method AG-403 has been radiovalidated for milk from a 14C goat metabolism. Methodology (AG-403) is referenced as MRID#00128232 in the Agency files. The methodology AG-403 allows detection of cyromazine and melamine residues in milk at 0.01 ppm.

Until the HED Metabolism Committee determines whether residues of metabolites melamine and/or 1-methylcyromazine are to be regulated in milk, CBTS reserves comments on this methodology. However, Agency validation of this method for residues of cyromazine in milk will likely be required.

The PAM II enforcement methodology for the determination of cyromazine and melamine residues limit of quantitation (LOQ) is 0.05 ppm for each compound in meat, fat, and meat byproducts. Based on the estimation of expected cyromazine and melamine residues in animal commodities (See discussion Meat, Milk, Poultry, and Eggs, this memo), residues could be below the LOQ.

STORAGE STABILITY: MRID#437631-01

Storage stability data have been previously submitted for other crops and reviewed (See memo 01/28/87, A. Smith). 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. Samples removed from storage and reanalyzed reflected no significant changes in the residues. Residues of cyromazine and melamine are stable in frozen storage for at least 24 months. The treated potato field trial samples in this petition were stored from 5.5 to 12 months. The existing storage stability data for the listed crops are adequate to support the proposed use.

MAGNITUDE OF THE RESIDUE: MRID#'s 438262-02 and 438262-03

Field trial residue data from the major potato-growing states have been submitted accounting for >80% of the US potato production. Residue data are submitted for both the tuber and foliage. Only the tuber data is discussed in this memo. (See summary table below).

Summary Table: Potato Field Trials					
Site	Application Rate, lb a.i./A	PHI, days	Cyromazine residue	Melamine residue	Combined residue
NY (05-IR-003-91)	6 x 0.125 (1X)	7	0.07, 0.10	0.08, 0.08	0.15, 0.18
"	6 x 0.25 (2X)	7	0.28	0.16	0.44
ID (OW-IR-613-92)	6 x 0.125	25	0.06, <0.05	0.09, 0.07	0.15, <0.12
"	3 x 0.25 (1X)	25	<0.05, <0.05	0.07, 0.07	<0.12, <0.12
"	3 x 0.50 (2X)	25	<0.05	0.06	<0.11
"	3 x 0.75 (3X)	25	0.07	0.09	0.16
"	3 x 1.25 (5X)	25	0.14	0.10	0.24
ID (OW-IR-614-92)	6 X 0.125	23	0.09, 0.07	0.13, 0.11	0.22, 0.18
"	3 x 0.25	23	<0.05, <0.05	<0.05, <0.05	<0.10, <0.10
"	6 x 0.25	23	0.20	0.15	0.35
WA (OW-IR-615-92)	6 x 0.125	32	0.18, 0.27	0.17, 0.23	0.34, 0.50
"	3 x 0.25	32	0.21, 0.75	0.22, 0.38	0.43, 1.13
MI (NE-IR-101-92)	6 x 0.125	18	0.27, 0.30	0.38, 0.37	0.65, 0.67
"	3 x 0.25	18	0.34, 0.24	0.27, 0.18	0.61, 0.42
ND (MW-IR-501-92)	6 x 0.125	46	0.22, 0.20	0.16, 0.16	0.38, 0.36
"	3 x 0.25	46	0.36, 0.47	0.23, 0.28	0.59, 0.75

Summary Table: Potato Field Trials					
Site	Application Rate, lb a.i./A	PHI, days	Cyromazine residue	Melamine residue	Combined residue
"	3 x 0.50 (2X)	46	0.79	0.45	1.24
"	3 x 0.75 (3X)	46	1.11	0.61	1.72
"	3 x 1.25 (5X)	46	1.55	0.86	2.41
MN (MW-IR-502-92)	6 x 0.125	49	0.21, 0.20	0.18, 0.20	0.38, 0.40
"	3 x 0.25	49	0.21, 0.20	0.28, 0.27	0.49, 0.47
WI (MW-IR-703-92)	6 x 0.125	14	0.26, 0.36	0.17, 0.19	0.42, 0.56
"	3 x 0.25	14	0.16, 0.21	0.09, 0.10	0.24, 0.32
NY (05-IR-001-92)	6 x 0.125	14	0.43, 0.28	0.15, 0.16	0.62, 0.43
"	3 x 0.25	14	0.37, 0.23	0.16, 0.15	0.53, 0.38
"	6 x 0.125	21	0.25, 0.29	0.17, 0.16	0.42, 0.45
"	3 x 0.25	21	0.49, 0.30	0.19, 0.16	0.68, 0.46
"	6 x 0.125	68	0.30, 0.35	0.15, 0.14	0.45, 0.49
"	3 x 0.25	68	0.22, 0.29	0.16, 0.17	0.37, 0.46
CO (MW-IR-301-92)	6 x 0.125	43	0.14, <0.05	<0.05, <0.05	<0.19, <0.10
"	3 x 0.25	43	0.42, 0.18	0.07, <0.05	0.49, <0.23
CA (02-IR-004-92)	6 x 0.125	14	0.21, 0.14	0.29, 0.23	0.50, 0.37
"	3 x 0.25	14	0.18, 0.20	0.26, 0.28	0.44, 0.48
"	6 x 0.125	21	0.19, 0.23	0.34, 0.53	0.53, 0.76
"	3 x 0.25	21	0.27, 0.16	0.44, 0.27	0.71, 0.43
"	6 x 0.125	23	0.18, 0.23	0.27, 0.49	0.45, 0.72
"	3 x 0.25	23	0.15, 0.27	0.27, 0.44	0.42, 0.71
"	6 x 0.25	23	0.53	0.81	1.34
"	3 x 0.50	23	0.36	0.62	0.98
ME (NE-IR-402-92)	3 x 0.25	20	0.26, 0.31	0.12, 0.11	0.38, 0.41
ID (OW-IR-303-93)	0.25 + 2(0.125) (0.75X)	48	0.11, 0.16	0.17, 0.22	0.28, 0.38
"	0.50 + 2(0.25) (1.3X)	48	0.36	0.30	0.66
"	0.75 + 2(0.375) (2X)	48	0.52, 0.56	0.42, 0.49	0.95, 1.05
"	1.25 + 2(0.625) (3.3X)	48	1.20, 1.32	0.66, 0.81	1.86, 2.12
ID (OW-IR-303-93)	0.25 + 2(0.125) (0.75X)	48	0.20	0.21	0.41

Summary Table: Potato Field Trials					
Site	Application Rate, lb a.i./A	PHI, days	Cyromazine residue	Melamine residue	Combined residue
"	0.75 + 2(0.375) (2X)	48	0.60	0.42	1.02
"	1.25 + 2(0.625) (3.3X)	48	1.15	0.72	1.87
ND (MW-IR-501-93)	0.25 + 2(0.125) (0.75X)	47	0.28, 0.43	0.28, 0.45	0.56, 0.88
"	0.50 + 2(0.25) (1.3X)	47	1.09	1.08	2.18
"	0.75 + 2(0.375) (2X)	47	1.42, 1.57	1.23, 1.28	2.65, 2.85
"	1.25 + 2(0.625) (3.3X)	47	1.25, 1.06	1.02, 1.13	2.27, 2.19
ND (MW-IR-501-93)	0.25 + 2(0.125) (0.75X)	47	0.40	0.35	0.75
"	0.75 + 2(0.375) (2X)	47	0.85	0.95	1.80
"	1.25 + 2(0.625) (3.3X)	47	1.12	1.30	2.41
MI (NE-IR-107-93)	0.25 + 2(0.125) (0.75X)	45	0.06, 0.07	0.09, 0.07	0.15, 0.14
PA (NE-IR-504-93)	0.25 + 2(0.125) (0.75X)	42	0.25, 0.30	0.10, 0.11	0.35, 0.41

Conclusions:

Field trial residue data are presented for application rates of 0.5 lb a.i./A (0.67X), 0.75 lb a.i./A (1X), 1.0 lb a.i./A (1.3X), 1.5 lb a.i./A (2X), 2.25 lb a.i./A (3X), 2.5 lb a.i./A (3.3X), and 3.75 lb a.i./A (5X). The PHI's for the various applications ranged from 7 to 68 days. Samples were analyzed for cyromazine and its metabolite melamine, and residue levels for each plus the combined total are reported. The residue levels do not appear to be related to the reported PHI's. For example, samples from the same field trial analyzed at 14, 21, and 68 days after the last application did not show dissipation of the cyromazine or melamine residues. In addition the residues observed from different field trials with different PHI's are similar.

Therefore CBTS concludes that at the same application rate, the residue levels are independent of the PHI's and that the proposed 7-day PHI is adequate even though much of the field trials were conducted at higher PHI's.

Residue levels in samples from field trials using the proposed 0.75 lb a.i./A (1X) rate show averaged combined residues of 0.43 ppm. In all (58 samples) but one sample (1.13 ppm), the combined residue levels are below 1.0 ppm. In addition, samples from field trials using higher application rates showed residue in proportion to the proposed 0.75 lb a.i./A treatment rate. For example, samples (11 samples) from the 2X application averaged 1.22 ppm and this could be extrapolated for a 1X treatment, i.e. 1.22 ppm/2 = 0.61 ppm. Similar linear relationships can be shown for the other treatment levels, with all estimated residues falling below 1.0 ppm if

extrapolated to the 1X rate, e.g., 3-3.3X, ave. 1.82 ppm; 1.82/3.3 = 0.55 ppm; 5X, 2.41 ppm; 2.41/5 = 0.48 ppm).

Therefore, CBTS concludes that the proposed 1.5 ppm tolerance for the RAC potato is too high based on the proposed maximum label rate and the determined 7-day PHI. No additional field trial data are needed. CBTS will reserve comments on this proposed tolerance level until after the HED Metabolism Committee review of cyromazine. A revised Section F may be needed for the RAC potato.

Processed Commodities:

The petitioner submitted residue data from the four trials for processing field-treated potato tuber into potato chips and dehydrated potato granules. The field trial and processing data are summarized in following table.

Potato Processing Studies, MRID#438262-02				
Commodity	Residues, ppm			Concentration factors
	Cyromazine	Melamine	Combined	
OW-IR-303-93 (Idaho), 0.5 lb a.i./A (0.7X), 48-day PHI				
mature tuber	0.20	0.21	0.41	--
wet peel	0.09	0.10	0.19	0.5
dry peel	0.40	0.33	0.73	1.8
potato chips	0.07	0.82	0.89	2.2
potato granules	0.57	0.46	1.02	2.5
OW-IR-303-93 (Idaho), 1.5 lb a.i./A (2X), 48-day PHI				
mature tuber	0.60	0.42	1.02	--
wet peel	0.22	0.14	0.36	0.4
dry peel	0.85	0.55	1.4	1.4
potato chips	0.69	1.17	1.86	1.8
potato granules	1.73	0.91	2.65	2.6
OW-IR-303-93 (Idaho), 2.5 lb a.i./A (3.3X), 48-day PHI				
mature tuber	1.15	0.72	1.87	--
wet peel	0.42	0.20	0.62	0.3
dry peel	1.88	0.88	2.76	1.5
potato chips	1.71	1.48	3.20	1.7
potato granules	3.51	1.43	4.94	2.6
MW-IR-501-93 (North Dakota), 0.5 lb a.i./A (0.7X), 47-day PHI				
mature tuber	0.40	0.35	0.75	--
wet peel	0.14	0.15	0.29	0.4
dry peel	0.64	0.61	1.26	1.7
potato chips	0.70	0.68	1.37	1.8

Potato Processing Studies, MRID#438262-02				
Commodity	Residues, ppm			Concentration factors
	Cyromazine	Melamine	Combined	
potato granules	0.77	0.83	1.60	2.1
MW-IR-501-93 (North Dakota), 1.5 lb a.i./A (2X), 47-day PHI				
mature tuber	0.85	0.95	1.80	--
wet peel	0.46	0.30	0.76	0.4
dry peel	1.84	1.22	3.06	1.7
potato chips	0.47	0.40	0.86	0.5
potato granules	2.76	1.97	4.73	2.6
MW-IR-501-93 (North Dakota), 2.5 lb a.i./A (3.3X), 47-day PHI				
mature tuber	1.12	1.30	2.41	--
wet peel	0.44	0.33	0.77	0.3
dry peel	1.87	1.18	3.05	1.3
potato chips	3.11	2.30	5.41	2.2
potato granules	3.25	1.99	5.24	2.2
OW-IR-613-92 (Idaho), 0.75 lb a.i./A (1X), 25-day PHI				
mature tuber	<0.05	<0.05	<0.10	--
wet peel	<0.05 (a) <0.05 (s)	<0.05 <0.05	<0.10 <0.10	1 1
dry peel	0.08 (a) 0.12 (s)	<0.05 0.12	<0.13 0.24	1.3 2.4
potato chips	0.07 (a)	0.08	0.15	1.5
potato granules	<0.05 (s)	<0.05	<0.10	1
OW-IR-613-92 (Idaho), 2.25 lb a.i./A (3X), 25-day PHI				
mature tuber	0.11	<0.05	<0.16	--
wet peel	<0.05 (a) <0.05 (s)	<0.05 <0.05	<0.10 <0.10	0.6 0.6
dry peel	0.19 (a) 0.32 (s)	0.11 0.15	0.31 0.47	1.9 2.9
potato chips	0.15 (a)	0.14	0.29	1.8
potato granules	0.25 (s)	0.11	0.36	2.3
OW-IR-613-92 (Idaho), 3.75 lb a.i./A (5X), 25-day PHI				
mature tuber	0.16	<0.05	<0.21	--
wet peel	0.05 (a) 0.07 (s)	<0.05 <0.05	<0.10 <0.12	0.5 0.6
dry peel	0.47 (a) 0.81 (s)	0.11 0.21	0.58 1.02	2.8 4.6
potato chips	0.33 (a)	0.17	0.50	2.4

Potato Processing Studies, MRID#438262-02				
Commodity	Residues, ppm			Concentration factors
	Cyromazine	Melamine	Combined	
potato granules	0.56 (s)	0.15	0.71	3.4
MW-IR-501-92 (North Dakota), 0.75 lb a.i./A (1X), 7-day PHI				
immature tuber	0.38	0.25	0.63	--
wet peel	0.14 (a) 0.11 (s)	0.07 0.07	0.21 0.17	0.3 0.3
dry peel	1.16 (a) 1.55 (s)	0.53 0.69	1.69 2.24	2.7 3.6
potato chips	1.11 (a)	0.31	1.42	2.3
potato granules	0.31 (s)	0.14	0.45	0.7
MW-IR-501-92 (North Dakota), 2.25 lb a.i./A (3X), 7-day PHI				
immature tuber	1.04	0.44	1.48	--
wet peel	0.47 (a) 0.27 (s)	0.14 0.11	0.61 0.38	0.4 0.3
dry peel	7.03 (a) 4.44 (s)	1.25 1.58	8.28 6.02	5.6 4.1
potato chips	2.67 (a)	0.67	3.34	2.3
potato granules	1.90 (s)	1.64	3.54	2.4
MW-IR-501-92 (North Dakota), 3.75 lb a.i./A (5X), 7-day PHI				
immature tuber	1.87	0.70	2.57	--
wet peel	0.50 (a) 0.40 (s)	0.17 0.14	0.67 0.54	0.3 0.2
dry peel	6.96 (a) 9.31 (s)	1.37 2.40	8.34 11.72	3.2 4.6
potato chips	3.72 (a)	0.98	4.70	1.8
potato granules	5.71 (s)	1.92	7.63	3.0
Highest/lowest residues (1X rate)				Average concentration factors (all application rates)
mature tuber	0.38/<0.05	0.25/<0.05	0.63/<0.10	--
wet peel	0.14/<0.05	0.07/<0.05	0.21/<0.10	0.5
dry peel	1.55/0.08	0.69/<0.05	2.24/<0.13	2.7
potato chips	1.11/0.07	0.31/0.08	1.42/0.15	1.9
potato granules	0.31/<0.05	0.14/<0.05	0.45/<0.10	2.3

Conclusions:

Combined residues of cyromazine and melamine do not concentrate in wet peel, commonly called processed potato waste, a significant

feedstuff. The tolerance on the RAC potato will cover processed potato waste as a result of the proposed use. Residues, however, concentrate in potato chips and granules. Thus, separate tolerances may be needed for potato granules/flakes and potato chips. A revised Section F may be needed. CBTS will reserve comments on these tolerances until after the HED Metabolism Committee review of cyromazine.

MEAT, MILK, POULTRY, AND EGGS

Potato culls and processed potato waste are considered significant feedstuffs for beef and dairy cattle. Secondary residues of cyromazine and melamine could occur in cattle meat, fat, meat byproducts, and milk. Since potato culls and processed potato waste are not poultry feedstuffs, then no secondary residues are expected in poultry or eggs from the proposed use.

Estimated daily dietary burden:

A ruminant feeding study has also been reviewed (See memo of 04/02/93, R. Lascola). Residues in milk seemed to plateau by day 7. No residues of 1-methylcyromazine (LOD, <0.05 ppm) were found in milk. In tissues, no residues were found at levels greater than 0.15 ppm, the combined quantitation 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.

The feedstuffs potato culls (20% DM) and processed potato waste (15% DM) are both fed to beef and dairy cattle at maximums of 75% and 40%, respectively. Based on a 1.0 ppm tolerance on the RAC potato as recommended in this memo by CBTS, feeding of feedstuffs from the RAC potato, and the proposed rotations to other crops such as sweet corn (proposed 0.5 ppm tolerance for inadvertent residues on sweet corn forage, PP#6F3332) and alfalfa (proposed 1.0 ppm tolerance for inadvertent residues on alfalfa forage, PP#5F4546), the estimated daily dietary burdens would be the following:

COMMODITY	PERCENT DM	PERCENT IN DIET	PROPOSED TOLERANCE, ppm	DAILY DIETARY BURDEN
BEEF CATTLE				
Potato culls	20	75	1.0	3.8
Sweet corn forage (rotational)[a]	30	25	0.5	0.4
			Total	4.2
Potato culls	20	75	1.0	3.8
Alfalfa forage (rotational)[a]	35	25	1.0	0.7
			Total	4.6
Processed potato waste	15	75	0.5[b]	2.5
Sweet corn forage (rotational)[a]	30	25	0.5	0.4
			Total	2.9
Processed potato waste	15	75	0.5[b]	2.5
Alfalfa forage (rotational)[a]	35	25	1.0	0.7
			Total	3.2
DAIRY CATTLE				
Potato culls	20	40	1.0	2.0
Sweet corn forage (rotational)[a]	30	50	0.5	0.8
			Total	2.8
Potato culls	20	40	1.0	2.0
Alfalfa forage (rotational)[a]	35	60	1.0	1.7
			Total	3.7
Processed potato waste	15	40	0.5[b]	1.3
Sweet corn forage (rotational)[a]	30	50	0.5	0.8
			Total	2.1
Processed potato waste	15	40	0.5[b]	1.3
Alfalfa forage (rotational)[a]	35	60	1.0	1.7
			Total	3.0

[a] Pending proposed tolerance for rotational crop [sweet corn (PP#6F3332) and alfalfa (PP5F4546)]

[b] The average residue of combined cyromazine and melamine is 0.5 ppm from the submitted potato processing studies.

Therefore, based on the estimated maximum daily dietary burdens of 4.6 ppm for beef cattle and 3.7 ppm for dairy cattle, and extrapolating from the 10, 50 and 100 ppm feeding study, residues of cyromazine, melamine, and 1-methylcyromazine in the animal commodities are shown below.

MEASURED RESIDUES FROM 10, 50, and 100 PPM FEEDING LEVELS VS. ESTIMATED DAILY DIETARY BURDEN[a]					
Feeding level, ppm	Cyromazine	Melamine	Combined total[b]		1-Methylcyromazine
Milk (Day 7)					
10	<0.04	<0.03	<0.07		<0.01
50	0.20	0.1	0.3		<0.01
100	0.50	0.13	0.63		<0.01
Best estimate for 3.7 ppm dietary burden	<0.02	<0.01	<0.03		<0.005
Meat (Day 28)					
10	<0.05	<0.05	<0.10		<0.05
50	0.16	0.07	0.23		<0.05
100	0.25	0.08	0.33		<0.05
Best estimate for 4.6 ppm dietary burden	<0.02	<0.02	<0.04		<0.02
Liver (Day 28)					
10	<0.05	<0.05	<0.10		<0.05
50	0.12	0.11	0.23		0.11
100	0.21	0.16	0.37		0.13
Best estimate for 4.6 ppm dietary burden	<0.02	<0.02	<0.04		<0.02
Kidney (Day 28)					
10	0.09	0.05	<0.14		<0.05
50	0.66	0.11	<0.77		<0.05
100	0.80	0.12	0.92		0.05
Best estimate for 4.6 ppm dietary burden	<0.04	<0.02	<0.06		<0.02

[a] For example, at the 10 ppm feeding level, <0.04 ppm of cyromazine residues were found. Therefore extrapolation to a 3.7 ppm diet in dairy cattle would give an estimated cyromazine residue of <0.02 ppm.

[b] Cyromazine and its metabolite melamine only; the total does not include metabolite 1-methylcyromazine.

Conclusion:

Residues of cyromazine, melamine, and 1-methylcyromazine may be present in animal commodities from the proposed use. The expected levels may be below the limits of quantitation (0.05 ppm) in livestock meat and meat byproducts for the existing analytical methodologies. The petitioner has proposed a 0.04 ppm milk tolerance for the combined residues of cyromazine and melamine. Since quantifiable cyromazine residues including its metabolite melamine, and in some cases, its metabolite 1-methylcyromazine are found in the 50 ppm feeding study (ca. 10X estimated dietary burden), and based on not only the proposed use, but on pending petitions, e.g., PP#6F3332, PP#6F3422, PP#5F4546, CBTS has determined that tolerances may be needed for meat, fat, meat byproducts, and milk. However, the tolerance expression can only be accurately defined after the HED Metabolism Committee has reviewed the active ingredient cyromazine to determine the residues of regulatory concern. After this determination a revised Section F may be needed.

OTHER CONSIDERATIONS

Compatibility problems exists between Codex and Mexican limits and the proposed US tolerances. With Codex and Mexican limits only cyromazine is the residue of concern; the metabolite melamine is not included in the residue expression. There is not a Canadian limit on any crop for cyromazine or cyromazine and its metabolite melamine. There are no established cyromazine or its metabolite melamine tolerances for the RAC potato, processed potato granules, flakes, potato chips, or the feedstuff, processed potato waste. There is a 0.01 ppm (at or about the limit of determination) residue Codex limit for cyromazine in milks.

Presently US tolerances for raw agricultural commodities are expressed in terms of the combined residues of cyromazine and melamine [See 40 CFR 180.414 (d), (e), and (f). Separate tolerances for poultry (chicken layers and breeders only) fat, meat, and meat byproducts are established for cyromazine (180.414 (b)] and melamine [180.414 (c)]. Formerly CBTS has determined that the tolerance expression should include cyromazine and its metabolite melamine for plant commodities, and for animal commodities of meat and milk. For meat byproducts the tolerance expression should include cyromazine, melamine and 1-methylcyromazine. (See memos of 02/12/87, A. Smith, 04/02/93, R. Lascola, 08/20/96; review memos in PP6F3332, PP6F3422, and PP5F4546). Therefore, since whenever possible, CBTS chooses to harmonize the proposed US tolerances with Codex maximum residue limits, CBTS will submit cyromazine to the HED Metabolism Committee that they might determine the residue(s) of regulatory concern in plant and animal commodities. CBTS will reevaluate the established and proposed US tolerances after the committee review.

cc: PP#5F4576, J. Stokes, RD (G. LaRocca), RF, Circu.
RDI: TPT2:09/96:RLoranger:09/11/96:EHaeberer:09/12/96
7509C:CBTS:JStokes/js:CM#2:Rm803:305-7561:09/12/96

END OF DOCUMENT

13544

R062746

Chemical:	**Cyromazine**
PC Code:	**121301**
HED File Code	**11500 Petition Files Chemistry**
Memo Date:	**07/25/2003 12:00:00 AM**
File ID:	**DPD254881; DPD242798; DPD242799; DPD242801; DPD242802; DPD236184; DPD236189; DPD236190; DPD236187; DPD236185; DPD220675**
Accession Number:	**412-04-0144**

HED Records Reference Center
06/29/2004