Cyromazine Summary Document: Registration Review

March 2007

Docket Number: EPA-HQ-EPA-2006-0108
www.regulations.gov

Cyromazine Summary Document
Registration Review: Initial Docket
March 2007

Cyromazine: Registration Review
Summary Document

Case Number 7439

Approved by: Debra Edwards

Debra Edwards, Ph. D.
Director
Special Review and Reregistration Division

Date: March 23, 2007

TABLE OF CONTENTS

I. Preliminary Work Plan

Introduction:

The Food Quality Protection Act of 1996 mandated a new program: **registration review**. All pesticides distributed or sold in the United States generally must be **registered** by EPA, based on scientific data showing that they will not cause unreasonable risks to human health, workers, or the environment when used as directed on product labeling. The new registration review program is intended to make sure that, as the ability to assess risk evolves and as policies and practices change, all registered pesticides continue to meet the statutory standard of no unreasonable adverse effects. Changes in science, public policy, and pesticide use practices will occur over time. Through the new registration review program, the Agency periodically reevaluates pesticides to make sure that as change occurs, products in the marketplace can be used safely. Information on this program is provided at: http://www.epa.gov/oppsrrd1/registration_review/.

The Agency has begun to implement the new Registration Review program, and plans to review each registered pesticide every 15 years to determine whether it continues to meet the FIFRA standard for registration. The public phase of registration review begins when the initial docket is opened for each case. The docket is the Agency's opportunity to state clearly what it knows about the pesticide and what additional risk analyses and data or information it believes are needed to make a registration review decision.

Anticipated Risk Assessment and Data Needs:

Ecological Risk

- The Agency anticipates needing the following data in order to conduct a complete ecological risk assessment, including an endangered species assessment, for all uses:
    - (GLN 850.1025) Estuarine/Marine Mollusk (Oyster) Acute Toxicity Test (Shell Deposition) for Cyromazine
    - (GLN 850.1350) Mysid (Shrimp) Chronic Toxicity (early life stage in fish) for Cyromazine

A detailed discussion of the value of these data for risk assessment purposes is provided in Table 5 (page 20) of this document.

Human Health Risk:

- The dietary assessments covering all current uses of cyromazine meet current standards, and the Agency has determined that there is no dietary risk that exceeds the Agency's level of concern.
- The occupational exposures to cyromazine estimated in past assessments indicate that risks are below the Agency's LOC. However, the Agency anticipates conducting a new

occupational risk assessment for the cyromazine uses that are not covered by previous occupational assessments.

- Because no dermal hazard is expected from the dermal route of exposure (see table 3.2 on page 36), only inhalation risk to occupational handlers is assessed for cyromazine. Current assessments rely on oral toxicity studies to assess risks to handlers. Though no risks of concern have been identified using this approach, a 21-day inhalation toxicity study is needed to reduce uncertainty. An unpublished study cited in a 1990 World Health Organization (WHO) monograph on cyromazine may, if submitted, be sufficient to meet the data need. If not, EPA will need to call-in a 28-day inhalation study in order to assess potential inhalation risks.

Timeline:

EPA has created the following estimated timeline for the completion of the cyromazine registration review.

Activities	**Estimated Month/Year**
Phase 1: Opening the docket	
Open Public Comment Period for Cyromazine Docket	March 2007
Close Public Comment Period	June 2007
Phase 2: Case Development	
Develop Final Work Plan (FWP)	August 2007
Issue DCI	June 2008
Data Submission	June 2010
Open Public Comment Period for Preliminary Risk Assessments	October 2011
Close Public Comment Period	December 2011
Phase 3: Registration Review Decision	
Open Public Comment Period for Proposed Reg. Review Decision	March 2012
Close Public Comment Period	May 2012
Final Decision and Begin Post-Decision Follow-up	September 2012
Total (years)	5.5

Guidance for Commenters:

The public is invited to comment on EPA's preliminary registration review work plan and rationale. The Agency will carefully consider all comments as well as any additional information or data provided prior to issuing a final work plan for the cyromazine case.

Through the registration review process, the Agency intends to solicit information on trade irritants and, to the extent feasible, take steps toward facilitating irritant resolution. Growers and other stakeholders are asked to comment on any trade irritant issues resulting from lack of MRLs or disparities between U.S. tolerances and MRLs in key export markets, providing as much specificity as possible regarding the nature of the concern.

Stakeholders are also specifically asked to provide information and data in the following areas.

There is specific information that will assist the Agency in refining the ecological risk assessment, including any species-specific effects determinations. The Agency is very much interested in obtaining the following information:

1. confirmation of the following label information
    a. sites of application
    b. formulations
    c. application methods and equipment
    d. maximum application rates
    e. frequency of application, application intervals, and maximum number of applications per season
    f. geographic limitations on use
2. use or potential use distribution (e.g., acreage and geographical distribution of relevant crops)
3. use history
4. median and 90th percentile reported use rates (lbs ai/acre) from usage data – national, state, and county
5. application timing (date of first application and application intervals) by crop – national, state, and county
6. sub-county crop location data
7. directly acquired county-level usage data (not derived from state level data)
    a. maximum reported use rate (lbs ai/acre) from usage data – county
    b. percent crop treated – county
    c. median and 90th percentile number of applications – county
    d. total pounds per year – county
    e. the year the pesticide was last used in the county/sub-county area
    f. the years in which the pesticide was applied in the county/sub-county area
8. typical application interval (days)
9. state or local use restrictions

10. ecological incidents (non-target plant damage and avian, fish, reptilian, amphibian and mammalian mortalities) not already reported to the Agency
11. monitoring data
12. Cyromazine is not identified as a cause of impairment for any waterbodies listed as impaired under section 303 (d) of the Clean Water Act, based on information provided at http://oaspub.epa.gov/tmdl/waters_list.impairments?p_impid=3 . However, the Agency invites submission of other existing water quality data for these chemicals. To the extent possible, data elements identified in Appendix A of the "OPP Standard Operating Procedure: Inclusion of Impaired Water Body and Other Water Quality Data in OPP's Registration Review Risk Assessment and Management Process" should be provided (reference: http://www.epa.gov/oppfead1/cb/ppdc/2006/november06/session1-sop.pdf), in order to ensure they can be used quantitatively or qualitatively in pesticide risk assessments.

Further, uncertainties in the environmental exposure assessment for use of cyromazine for fly control in poultry and horse manure could be reduced with additional information. Information related to the size and conditions of the operations, how much area is typically treated, and when and how is the manure removed would be very useful. Specifically, information in the following areas is of interest:

1. average size (area, ft^2) of poultry, horse housing facility
2. number of animals per house
3. manure production per animal per day
4. typical number of applications per year
5. amount (lbs) of cyromazine that is used annually for manure uses
6. percentage of animals kept outdoors (*i.e.*, not in a covered housing facility)
7. cyromazine concentration in manure (from feed-through and/or treated manure)
8. proportion of the feed lot area/manure that is treated.
9. amount (total lbs and lbs/acre) of manure treated with cyromazine that is used as a soil fertilizer supplement
10. frequency and nature of manure removal (*e.g.*, whether or not facilities are typically hosed out with water)

Next Steps:

After the comment period closes in June 2007, the Agency will prepare a Final Work Plan for this pesticide.

II. FACT SHEET

Background Information:

- Cyromazine registration review case number: 7439
- Cyromazine PC Code: 121301 CAS#: 66215-27-8
- Technical registrants: Syngenta Crop Protection, Inc., Novil, Inc., and Novartis Animal Health US Inc.
- First approved for use in a registered product in May 1985
- Cyromazine is not subject to reregistration (no Reregistration Eligibility Decision (RED))
- Tolerances for cyromazine were reassessed on September 24, 2003 (FR Vol. 68 No. 185). This final rule also established tolerances for leeks, garlic (bulb & great-headed bulb), rakkyo (bulb, green), shallot (bulb), cabbage (Abyssinian), cabbage (seakale), Hanover salad (leaves), kidney (cattle, goat, hog, horse & sheep), and meat-by-products.
- There are eleven active Section 3 registrations for cyromazine.
- Special Review and Reregistration Division Chemical Review Manager (CRM): James Parker: parker.james@epa.gov
- Registration Division Product Manager (PM): George LaRocca: larocca.george@epa.gov

Use & Usage Information: (For additional details, please refer to the BEAD Appendix A document in the cyromazine docket.)

- Cyromazine is an insecticide used on a variety of crops such as beans, celery, onions, root crops, leafy vegetables, and vegetable cucurbits.
- Cyromazine is also used as an insecticide for landscape and greenhouse ornamentals, as a seed treatment in bulb onions
- Cyromazine is registered for fly control in mushroom houses, and as a feed-through fly control agent for horse and chicken manure, and for fly larvae control in manure and floor areas of chicken facilities.
- There are no residential uses of cyromazine.
- Cyromazine is formulated as a wettable powder, soluble concentrate and a granular.
- Approximately 13,000 pounds of cyromazine are used annually on agricultural crops, with the highest usage in terms of percent crop treated on celery, spinach and lettuce.
- Cyromazine is typically applied in multiple applications to foliage by aerial or ground equipment; up to six times per year with application rates between 0.125 and 0.25 lbs ai/acre for a total of 0.75 lbs ai/acre.
- Cyromazine is applied as a feed through in horses at 300 mg/kg per day or 600 mg/kg every other day and as a 1% mix per ton for poultry in daily feed.
- Cyromazine is registered for control of the Colorado potato beetle, a variety of fly pest, fly larvae, leafminers, and maggots.

Recent Actions:

- A final rule for cyromazine was issued on September 24, 2003 (FR Vol. 68 No. 185) which established tolerances for leeks, garlic (bulb & great-headed bulb), rakkyo (bulb,

green), shallot (bulb), cabbage (Abyssinian), cabbage (seakale), Hanover salad (leaves), kidney (cattle, goat, hog, horse & sheep), and meat by products.
- An amendment for an increased application rate for potatoes was approved in January 2007.
- There is a pending registration application for the use of cyromazine as a larvacide spray on manure in cattle and hog facilities.

Ecological Risk Assessment Status:

In order to meet current standards, new ecological risk assessments are needed for all registered outdoor uses. However, a preliminary screening level assessment indicates that acute and chronic risk quotients (RQs) for terrestrial animals are expected to exceed the Agency's levels of concern (LOCs) for some cyromazine uses. There is a presumption of risk to birds (surrogate for reptiles and terrestrial-phase amphibians) and mammals, including Federally-listed threatened or endangered species.

Previous assessments have not addressed potential indirect effects. Direct effects to birds and mammals have the potential to indirectly affect other species even if those other species may not be directly affected by cyromazine. For example, if use of cyromazine results in direct effects to birds, there is a possibility of indirect effects to endangered plants that rely on birds for pollination.

Human Health Risk Assessment Status:

Please refer to Section IV of this document, Human Health Effects Scoping Document, for a detailed discussion of the anticipated risk assessment needs for human health. A summary follows:

Dietary (Food and Water):
- No acute endpoint was identified, and therefore an acute dietary assessment is not needed.
- A chronic aggregate dietary exposure assessment was conducted in 2006, and indicated that dietary (food plus drinking water) exposure is below the Agency's LOC.

Residential:
- There are no residential uses cyromazine.

Occupational:
- The occupational exposures to cyromazine estimated in past assessments indicate that risks are below the Agency's LOC. However, to reduce uncertainty in the hazard component of these risk assessments, inhalation toxicity data are needed.
- The Agency anticipates conducting a new occupational risk assessment for some uses that are not covered by previous occupational assessments.

Tolerances:

- Codex and Canadian MRLs and Mexican tolerances are established for a number of cyromazine uses in/on agricultural commodities. A comparison of U.S. tolerances and other international standards for cyromazine is provided on pages 39-40 of this document.
- There are 71 U.S. tolerances that are listed under 40 CFR 180.414.

Data Call-In Status:

- A data call-in has not been issued for cyromazine.

Labels:

- A list of registration numbers may be found in this document on pages 30-32.

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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

PC Code: 121301
DP Barcode: 334907

MEMORANDUM

Subject: Cyromazine Registration Review: Ecological Risk Assessment Problem Formulation

To: James Parker
Special Review and Registration Division

From: Colleen Flaherty, Biologist
James Wolf, Environmental Scientist
Environmental Risk Branch 3
Environmental Fate and Effects Division (7507P)

Thru: Daniel Rieder, Branch Chief
Environmental Risk Branch 3
Environmental Fate and Effects Division (7507P)

Date: 23 March 2007

Attached is the Environmental Fate and Effects Division's (EFED) problem formulation document in support of the cyromazine (PC code 121301) registration review docket opening. This memorandum outlines (1) the methods that will likely be used in the ecological risk assessment of cyromazine, (2) a preliminary binning decision, (3) anticipated LOC exceedances, (4) data gaps, and (5) additional data needs.

1. Problem Formulation

1.1. Pesticide Type, Class, and Mode of Action

Cyromazine (*N*-cyclopropyl-1,3,5-triazine-2,4,6-triamine; **Figure 1**) is in the triazine family of pesticides. While most of the triazines have herbicidal qualities, cyromazine is an insect growth regulator and controls pest insects by inhibiting chitin synthesis.

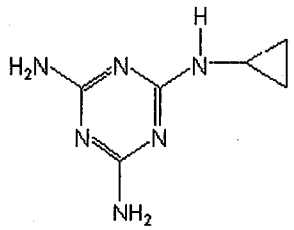


Figure 1. Chemical structure of cyromazine

1.2. Stressor Source and Distribution

Cyromazine (Armor®, Citation®, Trigard®) is an insecticide used on a variety of crops such as beans, celery, onions, root crops, leafy vegetables, vegetable cucurbits, and field grown chrysanthemums (**Appendix A**). Cyromazine is formulated as a wettable powder, soluble concentrate, and in a granular formulation. Cyromazine is registered for control of the Colorado potato beetle, a variety of fly pests, fly larvae, leafminers, and maggots. Cyromazine is typically applied in multiple applications to foliage by aerial or ground equipment, up to six times per year with application rates between 0.125 and 0.25 lbs ai/acre for a total of 0.75 lbs ai/acre.

Cyromazine (Flyzine™, Larvadex®, Solitude™ IGR) can also be used to control certain fly species which develop in poultry and horse manure. For the poultry manure use, cyromazine can be applied directly to the poultry feed (1% Flyzine/Larvadex premix per ton of feed) as a feed-through application and/or applied directly to the surface of the manure, as is the case for Larvadex 2SL. Poultry manure treated with cyromazine may be used as a soil fertilizer supplement, up to 4 tons manure per acre[1]. The label for the use of cyromazine as a feed-through application for horses[2] does not preclude the use of treated horse manure as a soil fertilizer supplement.

1.3. Overview of Pesticide Usage

Less than 13,000 pounds of cyromazine are used annually on agricultural crops with highest usage, in terms of percent crop treated, on celery (35%) and spinach (20%) (**Table 1**). It should be noted that the poultry and horse manure uses of cyromazine are not included in these estimates.

---

[1] According to the Larvadex 2SL [70585-2] label dated November 3, 2004.
[2] According to the Solitude™ IGR [1007-93] label dated January 17, 2006.

Table 1. Screening Level Estimates of Agricultural Uses of Cyromazine Sorted Alphabetically (USEPA/BEAD Screening Level Usage Analysis, dated December 5, 2006).

Crop		Pounds of Active Ingredient	Percent of Crop Treated	Maximum Percent of Crop Treated
Beans, Green		<500	<1	<2.5
Cantaloupes		<500	<1	5
Celery 3,000	35	60		
Chicory *		<500		
Lettuce		4,000	5	20
Onions <500	<1	<2.5		
Peppers		<500	5	5
Spinach		1,000	20	35
Tomatoes		2,000	5	15
Watermelons		<500	<1	<2.5

All numbers rounded.
'<500' indicates less than 500 pounds of active ingredient.
'<2.5' indicates less than 2.5 percent of crop is treated.
'<1' indicates less than 1percent of crop is treated.
* CA data only, but 95% or more of U.S. acres are in California
(data years 2000 to 2005)

The use of cyromazine on agricultural crops occurs primarily in California and Florida (**Figure 2**). This map does not include the manure uses of cyromazine.

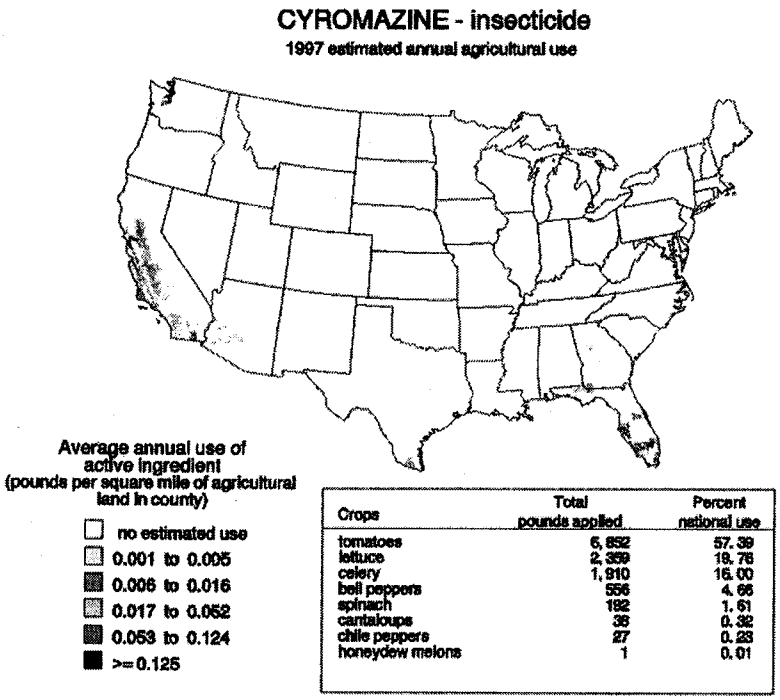


Figure 2. Estimated use of cyromazine insecticide in 1997 (http://ca.water.usgs.gov/pnsp/pesticide_use_maps/show_map.php?year=97&map=m6012)

1.4. Environmental Fate Summary

Based on previously submitted data, cyromazine is stable to hydrolysis and photolysis, and is quite persistent in aerobic soil ($t_{½}$ > 100 days). This was confirmed in field studies, where dissipation half-lives ranged from 93 to 240 days. Under anaerobic conditions, cyromazine may be somewhat less persistent. Soil adsorption coefficients are generally low with Freundlich adsorption coefficients ($K_{f\text{-}ads}$) of less than 20. Cyromazine is also highly soluble in water (1.36 x 10^5 mg/L). Based on this information, cyromazine has the potential to leach through soils, especially sand, fine sands, and loamy sands, or to be transported in solution in runoff water. Data suggest that cyromazine in manure is also quite persistent; cyromazine in chicken manure had a half-life of 439 days. Cyromazine in manure used as a soil amendment may be transported off site in runoff (Pote et al., 1994). Volatilization is not expected to be a major route of dissipation due to the relatively low vapor pressure.

The primary degradate of cyromazine is melamine. Aerobic metabolism studies indicate that melamine levels can be as much as 33% of the parent substance. The persistence ($t_{½}$), adsorption (K_d), and dissipation rate of melamine have not been specified, but in terrestrial field studies, melamine is shown to be more persistent and mobile than the parent, and may accumulate in soil with repeated uses.

Ground and Surface Water Concerns

A small-scale prospective ground-water (PGW) study on tomatoes in Florida showed no cyromazine residues in ground-water. However, low levels of melamine, the primary degradate, were detected in shallow ground water. Leaching during the PGW was limited due to a (artificial) high water table and upward water movement (flux) due to high evapotranspiration. Available environmental fate data also indicate that this chemical and the degradate (melamine) have potential to accumulate in soils and leach into ground water over repeated applications and years of uses. Cyromazine losses in runoff could be enhanced by the certain agricultural practice (e.g., plastic sheeting).

1.5. Ecological Effects Summary

Cyromazine has been shown to be practically non-toxic to freshwater fish (*i.e.*, rainbow trout, bluegill sunfish, channel catfish) and freshwater invertebrates (*i.e.*, water flea) on an acute basis (MRID 0070912). Chronic toxicity studies are also available for freshwater animals. Cyromazine significantly reduced fathead minnow length and weight at 36 mg/L (NOAEC = 14 mg/L) in a fish early life stage toxicity test (MRID 00073085). A freshwater invertebrate lifecycle test (MRID 00073085) concluded that cyromazine significantly affected daphnid growth and reproduction at 0.64 mg/L (NOAEC = 0.31 mg/L). There are no saltwater (estuarine/marine) animal toxicity data available for consideration in this cyromazine ecological risk assessment. Given that cyromazine acts as a chitin synthesis inhibitor, there is a potential for chronic effects to estuarine/marine invertebrate survivorship, growth, and/or reproduction.

Acute oral and dietary avian toxicity studies suggest that cyromazine is no more than slightly toxic to birds (MRID 00070912). Chronic toxicity effects on birds have been demonstrated with two species. Cyromazine significantly reduced the number of normal mallard duck hatchlings at 300 ppm (NOAEC = 75 ppm). In another study, there may have been a slight treatment related increase in the number of male bobwhite quails that exhibited regressing testes at 300 ppm cyromazine (NOAEC = 75 ppm).

An acute oral test with laboratory rat (MRID 00098384) indicates that cyromazine is practically non-toxic to small mammals on an acute oral basis. In a rat two-generation reproductive study (MRID 00103197), cyromazine decreased pup growth and number per litter and increased fetotoxicity at 3000 ppm (NOAEC = 1000 ppm).

Cyromazine is practically non-toxic to honey bees based on an acute contact toxicity study (MRID 43152601). However, given that cyromazine is an insecticide and acts as a chitin synthesis inhibitor, there is a potential for adverse effects to non-target terrestrial invertebrates.

There are no aquatic or terrestrial plant toxicity data available for consideration in this ecological risk assessment for cyromazine. However, risks to plants are presumed to be minimal given the mode of action (*i.e.*, inhibition of chitin synthesis) and the fact that cyromazine is applied to foliage of crop species.

No aquatic or terrestrial toxicity data are available for melamine, the primary degradate of cyromazine. If melamine acts as a chitin synthesis inhibitor like the parent cyromazine, aquatic and terrestrial invertebrates may be particularly sensitive.

1.6. Ecosystems at Risk

The terrestrial ecosystems potentially at risk as a result of cyromazine field treatments or land application of poultry or horse manure containing cyromazine include the treated area and areas immediately adjacent to the treated area that might receive drift or runoff. These areas could include other cultivated fields, fencerows and hedgerows, meadows, fallow fields or grasslands, woodlands, riparian habitats and other uncultivated areas. For Tier 1 assessment purposes, risk will be assessed to terrestrial animals that are assumed to feed on and otherwise occupy the treated area. Exposure to animals off the treated site is also possible, but exposure and risk estimates are not likely to be higher than on the treated site.

Aquatic ecosystems potentially at risk include water bodies adjacent to or downstream from the treated field or fields treated with poultry or horse manure containing cyromazine and might include impounded bodies such as ponds, lakes and reservoirs, or flowing waterways such as streams or rivers. For uses in coastal areas, aquatic habitat also includes marine ecosystems, including estuaries. For tier 1 assessment purposes, risk will be assessed to aquatic animals assumed to occur in small, static ponds receiving runoff and drift from treated areas. These ponds are used as surrogates for a number of small vulnerable water bodies that occur near the

headwaters of watersheds including swamps, bogs, prairie potholes, vernal pools, playa lakes, and first-order streams.

As stated above, risks to aquatic and terrestrial plants will not be assessed and are assumed to be negligible.

1.6.1 Assessment Endpoints

For cyromazine, ecological measures of effect are based on a suite of registrant-submitted toxicity studies. Other lines of evidence, including studies from the open literature, field studies, and ecological incident reports, are not available for consideration in this problem formulation. A summary of the assessment endpoints and measures of ecological effect selected to characterize potential ecological risks associated with exposure to cyromazine is provided in **Table 2.**

Table 2. Summary of Ecological Risk Assessment Endpoints for Cyromazine

Assessment Endpoint	Effects Measurement Endpoint
1. Survival, reproduction and growth of **birds** (Birds are surrogates for reptiles and terrestrial-phase amphibians)	1a. Oral LD_{50} (mallard duck, bobwhite quail) 1b. Dietary LC_{50} (mallard duck, bobwhite quail) 1c. Reproductive NOAEC (mallard duck, bobwhite quail)
2. Survival, reproduction and growth of **mammals**	2a. Oral LD_{50} (lab rat) 2b. Reproductive NOAEC (lab rat)
3. Survival, reproduction, and growth of **freshwater fish and invertebrates** (Fish are surrogates for aquatic-phase amphibians)	3a. Fish LC_{50} (rainbow trout, bluegill sunfish, channel catfish) 3b. Fish Reproductive NOAEC, LOAEC (fathead minnow) 3c. Invertebrate LC_{50} *(Daphnia magna)* 3d. Invertebrate Reproductive NOAEC *(Daphnia magna)*
4. Survival, reproduction, and growth of **saltwater fish and invertebrates**	No data available. Acceptable saltwater animal toxicity data would reduce the uncertainty in the risk assessment.
5. Survival of **beneficial insects**	5a. Contact LD_{50} honeybee acute

LC_{50} = Lethal concentration to 50% of the test population.
LD_{50} = Lethal dose to 50% of the test population.
NOAEC = No observed adverse effect level.

1.7. Conceptual Model

The conceptual model (**Figure 3**) assumes that once released from agricultural sprayers, most cyromazine will settle on the target site, and some will drift off site. That which settles on the target site (either post-spray or via application with manure) will either remain there, percolate into the soil, or runoff with surface water. Volatilization is not expected to be a major route of dissipation due to the relatively low vapor pressure and is not depicted in the conceptual model.

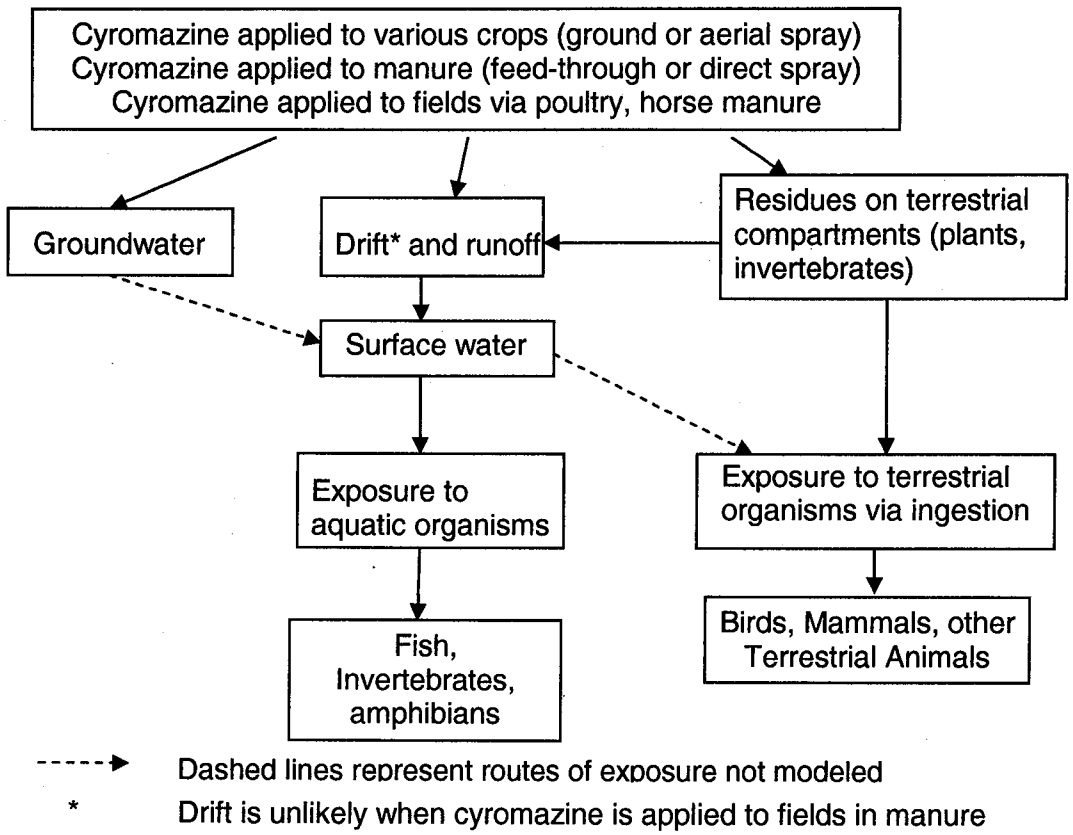


Figure 3. Conceptual model for the cyromazine ecological risk assessment.

1.8. Risk Hypothesis

Hypothesis: *Non-target terrestrial and aquatic animals are at risk of direct and indirect effects resulting from labeled uses of cyromazine.*

1.9. Analysis Plan

1.9.1. Measures of Exposure

Environmental exposure concentrations for the drinking water assessment will be estimated only for the parent cyromazine since the primary degradate, melamine, is no longer a residue of concern for human health (USEPA/HED, FR Vol 65 No. 87).

Risks to aquatic species from the use of cyromazine on crops will be based on estimated environmental concentrations of cyromazine in surface water calculated using the Tier 1 aquatic exposure model, GENEEC2. Aquatic exposures will be estimated for the maximum application rate scenario for cyromazine – 3 applications, 7 days apart, at a rate of 0.25 lbs a.i./A. Aquatic exposures of cyromazine were estimated for this application scheme in the ecological risk assessment for cyromazine use on potatoes (D324410). Based on that assessment, the peak aquatic EEC was approximately 30 µg/L cyromazine.

For the poultry manure use, cyromazine exposure is possible at the application site and when cyromazine-treated manure is removed from poultry operations and applied as a soil amendment. Potential risk to aquatic animals (*i.e.*, fish, aquatic invertebrates, and aquatic-phase amphibians) as a result of the use of cyromazine in manure will be revisited, taking into account the most current tools, models, and methodologies. Aquatic exposures for this use will be estimated using GENEEC2, with the assumption that cyromazine is applied at a maximum rate of 4.92 lbs. a.i./A (converted from Larvadex 2SL label rate of 0.0113 lbs a.i./100 sq. ft.), with a minimum application interval of 21 days. In the event that aquatic exposure estimates need to be refined for any cyromazine use, the Tier 2 models, PRZM and EXAMS, will be employed.

Ingestion of granules or magnitude of residues in or on selected potential dietary sources for mammals and birds (*e.g.*, vegetation, insects) that could be ingested by these organisms will be estimated using the conceptual approach given in the Tier 1 model, T-REX (v 1.3.1, 2006). Terrestrial exposures will be estimated for the maximum application rate scenario for cyromazine – 3 applications, 7 days apart, at a rate of 0.25 lbs a.i./A. Terrestrial exposures of cyromazine were estimated for this application scheme in the ecological risk assessment for cyromazine use on potatoes (D324410). Based on that assessment, the predicted cyromazine residues on avian and mammalian food items ranged from approximately 10 to 158 ppm.

For the manure uses, terrestrial exposures of cyromazine are possible at the application site as well as when the manure is used as a soil amendment. Potential risk to terrestrial animals (*i.e.*, birds, mammals, and terrestrial-phase amphibians) as a result of this cyromazine use will be revisited. Terrestrial exposures for the poultry and horse manure uses will also be estimated using the T-REX model, with the assumption that cyromazine is applied at a maximum rate of 4.92 lbs. a.i./A (converted from Larvadex 2SL label rate of 0.0113 lbs a.i./100 sq. ft.), with a minimum application interval of 21 days.

1.9.2. Measures of Effect

Ecotoxicity data are available for several assessment endpoints. **Table 3** summarizes the specific toxicity values that will be used to assess acute and chronic risk to receptors.

Table 3. Summary of assessment endpoints and proposed measures of effects for screening level risk assessment of cyromazine

Assessment Endpoint	Measurement Endpoint
1. Survival, reproduction, and growth of **birds**	Acute oral LD_{50} = 1785 mg/kg bw (bobwhite quail) 5-day dietary LC_{50} >5620 ppm (bobwhite quail, mallard duck) Avian reproduction NOAEC = 75 ppm (bobwhite quail, mallard duck)
2. Survival, reproduction, and growth of **mammals**	Acute oral LD_{50} = 3387 mg/kg bw Reproduction NOAEC = 1000 ppm
3. Survival and reproduction of **freshwater fish** and **invertebrates**	Fish, Acute 96-hr LC50 > 89.7 mg/L (rainbow trout, bluegill sunfish) Fish Early life stage NOAEC = 14 mg/L (fathead minnow) Invertebrate, Acute 48-hr EC50 > 92.8 mg/L (daphnid) Invertebrate, Chronic NOAEC = 0.31 mg/L (daphnid)
4. Survival, reproduction of **estuarine/marine fish** and **invertebrates**	No data available
5. Survival of beneficial insect populations	Acute contact LD50 = 25 µg/bee

1.9.3. Preliminary Identification of Data Gaps

Fate

With respect to drinking water, the environmental fate data are adequate. This is based on the assumption that estimated drinking water concentrations (EDWCs) are conservative (over-estimated) (D317886). Specific information on the application rate for the use of cyromazine for fly control in poultry and horse manure would be useful to refine the exposure assessments (see **Section 1.14**).

Currently, a default value of 35-days as the foliar dissipation half-life is used in the TREX model. Additional data could be provided by the registrant to determine whether or not this is a reasonable assumption; however, these data are not being requested for submission.

Effects

Table 4 presents an evaluation of the uncertainty resulting from each ecotoxicity data gap. There is inherent uncertainty associated with not receiving data to fulfill data gaps. However, the submission of some studies to address specific data gaps is unlikely to affect conclusions in the risk assessment, whereas some data gaps are more critical. This determination is made on a case-by-case basis.

Table 4. Summary of ecotoxicity data gaps for cyromazine		
Assessment endpoint with data gap	**Value of Additional Data***	**Rationale**
Acute toxicity to estuarine/marine invertebrates (72-3; oyster shell deposition test)	**High**	Shell growth may be particularly sensitive to cyromazine given the mode of action (*i.e.*, chitin synthesis inhibition). Risk to this taxon has not been previously assessed. The value of an additional study would be in refining risks to estuarine/marine invertebrates including defining an action area for endangered species. Risk mitigation strategies (*e.g.*, determining maximum cyromazine application rate that results in an RQ below the LOC) cannot be evaluated without these data.
Acute toxicity to estuarine/marine invertebrates (72-3; mysid shrimp)	Low	Given the available data for freshwater invertebrates and mode of action, *acute* risk to saltwater invertebrates is unlikely.
Acute toxicity to estuarine/marine fish (72-3)	Low	Given the available data for freshwater fish and mode of action, acute risk to saltwater fish is unlikely.
Survivorship, reproduction, and growth (chronic toxicity) of estuarine/marine invertebrates (72-4)	**High**	Saltwater invertebrates may be particularly sensitive to cyromazine given the mode of action (*i.e.*, chitin synthesis inhibition). Risk to this taxon has not been previously assessed. Chronic toxicity was observed in freshwater animal studies. The value of an additional study would be in refining risks to estuarine/marine invertebrates including defining an action area for endangered species. Risk mitigation strategies (*e.g.*, determining maximum cyromazine application rate that results in an RQ below the LOC) cannot be evaluated without these data.
Survivorship, reproduction, and growth (chronic toxicity) of estuarine/marine fish (72-4)	Low	Given the available data for freshwater fish and mode of action, chronic risk to saltwater fish is unlikely.
Perpetuation of non-target terrestrial plants, crops and non-crop species (122-1, vegetative vigor and seedling emergence)	Low	Given the mode of action and the fact that cyromazine is applied to crop foliage, risk to terrestrial plants is unlikely.
Maintenance and growth of aquatic plants from standing crop or biomass (122-2, aquatic plant growth)	Low	Given the mode of action and the fact that cyromazine is applied to crop foliage, risk to aquatic plants is unlikely.

* In terms of reducing uncertainty in the risk assessment

1.10. Open Literature

Before requesting that new ecological effects studies be conducted by the registrant to fulfill these potential data gaps, the Agency will conduct a search of the open literature to determine if the data are indeed already available. If so, an evaluation will be made as to whether or not the data are adequate for use in a risk assessment. The Agency uses the ECOTOX database as its mechanism for searching the open literature; however, a scan of the on-line ECOTOX database

(http://www.epa.gov/ecotox) shows that the only applicable data in that system are those that are currently in the EFED files.

1.11. Binning Decision

EFED needs additional data (or will apply alternative effects assumptions) and would need to conduct new assessments for all registered outdoor uses. Therefore, cyromazine is recommended to be assigned to Bin 1. The new assessments are needed because:

a) Previous assessments did not consider acute or chronic risks to estuarine/marine invertebrates, which may be particularly sensitive to cyromazine
b) Previous assessments for some cyromazine uses were not done with current models and risk assessment calculations
c) Previous assessments did not include open literature as identified by EPA's ECOTOX literature search program
d) Indirect effects to endangered species have not previously assessed
e) Risks were not refined with regard to proximity and probability of effects to endangered species

1.12 Summary of Ecological Risks

Expected LOC exceedances for cyromazine are summarized in **Table 5** below. At this time, acute and chronic risk quotients (RQs) for terrestrial animals are expected to exceed the Agency's LOCs for some cyromazine uses. There is a presumption of risk to birds (surrogate for reptiles and terrestrial-phase amphibians) and mammals, including Federally-listed threatened or endangered species. Additional discussion of anticipated LOC exceedances is in Section 1.12.2. All conclusions are preliminary and may change during the risk assessment process.

Table 5. Preliminary identification of LOC exceedances for cyromazine*

Stressor	Exposure	Birds	Mammals	Terr. Plants	Insects	Fish	FW Inverts	SW Inverts	Aquatic Plants
Cyromazine	Acute	✓	✓					Unknown	
	Chronic	✓	✓					Unknown	

* All risk conclusions are preliminary and may change over the course of the risk assessment process
✓ RQ is anticipated to be greater than the Agency's LOC
Blank cells indicate no anticipated LOC exceedance

1.12.1 Risks to Aquatic Organisms

Acute and chronic risks to freshwater fish and invertebrates as a result of cyromazine use on agricultural crops at the maximum label rate appear to be minimal. Previous EFED ecological risk assessments for cyromazine use on crops at the current label rate indicate that no risk quotients (RQs) exceed the Agency's aquatic levels of concern (LOCs) (**Table 6**).

Potential risks to aquatic animals for the poultry and horse manure uses of cyromazine cannot be precluded at this time. Assuming a maximum application rate of 4.92 lbs. a.i./A (converted from

Larvadex 2SL label rate of 0.0113 lbs a.i./100 sq. ft.), with a minimum application interval of 21 days, aquatic EECs may exceed acute and/or chronic aquatic toxicity thresholds. Specific usage information for the manure uses would reduce the level of uncertainty in the exposure estimates (see Section 1.14).

No toxicity data are currently available to assess the potential risks to saltwater (estuarine/marine) fish or invertebrates. Given that cyromazine acts as a chitin synthesis inhibitor, risk to estuarine/marine invertebrates cannot be precluded. Risks to aquatic plants are assumed to be minimal given the mode of action of this chemical.

Table 6. Aquatic EECs and RQs for cyromazine use on crops; based on 3 applications, 7 days apart, at a rate of 0.25 lbs a.i./A

Taxa	Toxicity	EEC	RQ
Fish	96-hr LC50 > 89.7 mg/L (rainbow trout, bluegill sunfish)	Peak 1-in-10 year EEC = 29.74 µg/L	< 0.05
	Chronic NOAEC = 14 mg/L (fathead minnow)	60-day EEC = 28.74 µg/L	< 1
Aquatic Invertebrate	48-hr EC50 > 92.8 mg/L (daphnid)	Peak 1-in-10 year EEC = 29.74 µg/L	< 0.05
	Chronic NOAEC = 0.31 mg/L (daphnid)	21-day EEC = 29.39 µg/L	< 1
Estuarine/marine invertebrates	No data available		
	No data available		

1.12.2 Risks to Terrestrial Organisms

Based on estimated dietary exposures of cyromazine and available toxicity information, acute risk to birds as a result of the use of cyromazine on crops appears to be minimal (**Tables 7-8**). The acute endangered species level of concern (LOC) is narrowly exceeded in one scenario (*i.e.*, 20-g bird that eats short grass exclusively). However, cyromazine use on crops at the assessed application rate may pose a chronic risk to birds (**Table 9**). Chronic RQs for birds that consume short grass and/or broadleaf plants/small insects exceed the Agency's LOC.

Given that some avian RQs exceed LOCs for the agricultural crop uses and that the maximum application rate for the poultry manure use is considerably higher (*i.e.*, 4.92 lbs. a.i./A for the manure use versus 0.25 lbs. a.i./A for the crop uses), risks to birds and terrestrial-phase amphibians as a result of the manure uses of cyromazine are presumed at this time. Specific usage information for the manure uses would reduce the level of uncertainty in the exposure estimates (see Section 1.14).

Table 7. Upper 90th Percentile Kenaga, Acute Avian Dose-Based Risk Quotients									
Size Class (grams)	Adjusted LD50	EECs and RQs							
		Short Grass		Tall Grass		Broadleaf Plants/ Small Insects		Fruits/Pods/ Seeds/ Large Insects	
		EEC	RQ	EEC	RQ	EEC	RQ	EEC	RQ
20	1285.97	179.61	0.14*	82.32	0.06	101.03	0.08	11.23	0.01
100	1637.10	102.42	0.06	46.94	0.03	57.61	0.04	6.40	0.00
1000	2312.47	45.86	0.02	21.02	0.01	25.79	0.01	2.87	0.00
* Risk quotient exceeds the acute endangered species level of concern									

Table 8. Upper 90th Percentile Kenega, Subacute Avian Dietary Based Risk Quotients								
	EECs and RQs							
	Short Grass		Tall Grass		Broadleaf Plants/ Small Insects		Fruits/Pods/Seeds/ Large Insects	
LC50	EEC	RQ	EEC	RQ	EEC	RQ	EEC	RQ
>5620	157.70	<0.03	72.28	<0.01	88.71	<0.02	9.86	<0.00
Size class not used for dietary risk quotients								

Table 9. Upper 90th Percentile Kenega, Chronic Avian Dietary Based Risk Quotients								
	EECs and RQs							
	Short Grass		Tall Grass		Broadleaf Plants/ Small Insects		Fruits/Pods/Seeds/ Large Insects	
NOAEC (ppm)	EEC	RQ	EEC	RQ	EEC	RQ	EEC	RQ
75	157.70	2.10*	72.28	0.96	88.71	1.18*	9.86	0.13
Size class not used for dietary risk quotients								
* Risk quotient exceeds the chronic level of concern								

Acute and chronic risks to mammals as a result of cyromazine use on crops appear to be minimal (**Tables 10-11**). None of the acute dose-based or chronic dietary-based RQs exceed the Agency's LOCs for mammals. Risks to mammals as a result of the manure uses of cyromazine cannot be precluded at this time. Specific usage information for the manure uses would reduce the level of uncertainty in the exposure estimates (see Section 1.14).

Table 10. Upper 90th Percentile Kenaga, Acute Mammalian Dose-Based Risk Quotients											
Size Class (grams)	Adjusted LD50	EECs and RQs									
		Short Grass		Tall Grass		Broadleaf Plants/ Small Insects		Fruits/Pods/ Seeds/ Large Insects		Granivore	
		EEC	RQ	EEC	RQ	EEC	RQ	EEC	RQ	EEC	RQ
15	7444.05	150.36	0.02	68.91	0.01	84.58	0.01	9.40	0.00	2.09	0.00
35	6023.03	103.92	0.02	47.63	0.01	58.45	0.01	6.49	0.00	1.44	0.00
1000	2605.15	24.09	0.01	11.04	0.00	13.55	0.01	1.51	0.00	0.33	0.00

Table 11. Upper 90th Percentile Kenega, Chronic Mammalian Dietary Based Risk Quotients								
NOAEC (ppm)	EECs and RQs							
	Short Grass		Tall Grass		Broadleaf Plants/ Small Insects		Fruits/Pods/Seeds/ Large Insects	
	EEC	RQ	EEC	RQ	EEC	RQ	EEC	RQ
1000	157.70	0.16	72.28	0.07	88.71	0.09	9.86	0.01

Size class not used for dietary risk quotients

1.13. Additional Uncertainties

In addition to known data gaps for taxonomic groups for which the Agency normally has data, there is a possibility that through public comment and literature searches, additional data may be found that identifies different adverse effects, effects to other taxonomic groups or effects at lower exposure levels. Currently, the Agency conducts searches of the open literature to locate potentially useful data that may provide additional information on the potential effects of pesticides. Previous assessments did not include a search of open literature for such information.

Previous assessments have not addressed potential indirect effects. Direct effects to birds and mammals have the potential to indirectly affect other species even if those other species may not be directly affected by cyromazine. For example, if use of cyromazine results in direct effects to birds, there is a possibility of indirect effects to endangered plants that rely on birds for pollination.

In addition to the need to assess risk to taxonomic groups for which data were not available, some of the currently registered uses (*e.g.*, poultry and horse manure uses) have not been assessed according to current tools and models which would be required to bring the Agency assessment on cyromazine into compliance with current Agency guidance on ecological risk assessments for pesticides. Some recent changes to the methods of ecological risk assessment include a revised mammalian exposure model which tends to result in higher tier 1 risk quotients. Aquatic modeling is more refined with additional regionally specific scenarios that take into account local runoff and meteorological conditions. Drift has not been assessed using Agdrift, which is a drift model that takes into account several relevant factors such as wind speed, release height and droplet size.

A critical aspect of risk assessments that comply with current policy is risk refinements. If a screening level risk assessment indicates potential risk to endangered species (direct or indirect effects), the assessment must be refined at a local level to determine if potential exposures are likely to adversely affect or not likely to adversely affect the listed species. None of the potential risks identified for cyromazine have been refined. For example, the potential risk of reproductive effects to birds has not been refined to determine if endangered birds are likely to be exposed, and if that exposure might adversely affect the species.

1.14 Other Information Needs

There is specific information that will assist the Agency in refining the ecological risk assessment, including any species-specific effects determinations. The Agency is interested in obtaining the following information:

1. confirmation on the following label information
    a. sites of application
    b. formulations
    c. application methods and equipment
    d. maximum application rates
    e. frequency of application, application intervals, and maximum number of applications per season
    f. geographic limitations on use
2. use or potential use distribution (e.g., acreage and geographical distribution of relevant crops)
3. use history
4. median and 90th percentile reported use rates (lbs ai/acre) from usage data – national, state, and county
5. application timing (date of first application and application intervals) by crop – national, state, and county
6. sub-county crop location data
7. directly acquired county-level usage data (not derived from state level data)
    a. maximum reported use rate (lbs ai/acre) from usage data – county
    b. percent crop treated – county
    c. median and 90th percentile number of applications – county
    d. total pounds per year – county
    e. the year the pesticide was last used in the county/sub-county area
    f. the years in which the pesticide was applied in the county/sub-county area
8. typical application interval (days)
9. state or local use restrictions
10. ecological incidents (non-target plant damage and avian, fish, reptilian, amphibian and mammalian mortalities) not already reported to the Agency
11. monitoring data

Further, uncertainties in the environmental exposure assessment for use of cyromazine for fly control in poultry and horse manure could be reduced with additional information. Information related to the size and conditions of the operations, how much area is typically treated, and when and how is the manure removed would be very useful. Specifically, information in the following areas is of interest:

1. average size (area, ft^2) of poultry, horse housing facility
2. number of animals per house
3. manure production per animal per day

4. typical number of applications per year
5. amount (lbs) of cyromazine that is used annually for manure uses
6. percentage of animals kept outdoors (*i.e.*, not in a covered housing facility)
7. cyromazine concentration in manure (from feed-through and/or treated manure)
8. proportion of the feed lot area/manure that is treated
9. amount (total lbs and lbs/acre) of manure treated with cyromazine that is used as a soil fertilizer supplement
10. frequency and nature of manure removal (*e.g.*, whether or not facilities are typically hosed out with water)

Appendix A. Summary Table of Registered Uses

Reg. Number	% a.i.	Uses	Use Instructions
100-667 [Citation Insecticide]	75	Chrysanthemums	**General Use** - Apply 2.66 oz./A in minimum of 100 gals. of water as a foliar spray to runoff when stippling first appears. Repeat applications at 7-day intervals if necessary to maintain control. Do not make more than six (6) applications of Citation per crop. **Special Preaution** - Citation should not be used as the only control for leafminers. Make no more than three (3) applications at 7 day intervals then switch to Avid as an alternative control for the same period.
70585-6 [Cyromazine]	97	Technical	For use only in the formulation of end-use products used in layer and breeder chicken operations
75066-2 [Flyzine]	96.8	Technical	For use only in the formulation of end-use products used in layer and breeder chicken operations.
75066-1 [Flyzine 1% premix]	1.0	Intended for use only in poultry (chickens) layer and breeder operations	**Dosage and use**- Mix 1 lb. of Flyzine 1% premix per ton of feed. Feed the treated feed as a daily ration. Begin feeding when adult flies become active and continue the treatment as prescribed through the fly season. Feed Flyzine 1% continuously as directed for four (4) to six (6) weeks. Then carefully examine manure pits. If little or no activity is observed in the manure, discontinue the use of Flyzine 1% premix. **During winter months or during periods of low fly pressure**, discontinue Flyzine 1% use for at least four (4) consecutive months per year **Note** – Do not feed Flyzine 1% treated feed to broiler poultry. Flyzine 1% use in poultry is limited to use as a feed-through in chicken layer and breeder operations only and may not be fed to any other poultry species **Manure** from chickens fed Flyzine 1% may be used as a soil fertilizer supplement. Do not apply more than three (3) tons of manure per acre per year. Do not apply to small grain crops that will be harvested or grazed or illegal residues may result. Do not feed manure from chickens fed Flyzine to animals. **To avoid illegal residues**, Flyzine treated feed must be removed at least three days (72 hours) before slaughter. **Important Note to Feed Mill Operators**: Flyzine feed formulators (those mixing as a service to customers) must inform the feed user that treated feed must be removed from layers and breeders at least (3) days before slaughter.
70585-2 [Larvadex 2SL]	2	Fly control in Poultry Operations, Including Layer and Breeder Chickens	**Mixing Applications** – Dilute Larvadex 2SL with water to make a 0.1% spray. Apply 1 gallon of finished spray per 100 sq. ft. of area over surface of manure. Manure storage areas, spilled feed and other sites where maggots are active. **Do not** - apply Larvadex 2SL more frequently than once every 21 days. **Do not** apply Larvadex 2SL directly to poultry or poultry feed as illgal residues may result. **Do not** feed manure treated with Larvadex 2SL to animals **To avoid illegal residues**, allow 1 day (24 hours) between last application and slaughter **Do not use** Larvadex 2SL in conjunction with Larvadex 1% premix. If chickens have been fed Larvadex – treated feed, do not apply Larvadex 2SL to manure Manure treated with Larvadex 2SL may be used as a soil fertilizer supplement. **Do not apply** more than 4 tons of manure treated with Larvadex 2SL per acre per year.
1007-93 [Solitude IGR fly control pellets]	2.12	Equine (Horse) Operations	**Do not use** on Horses intended for slaughter for food. This product is to be fed top-dressed on grain or mixed with the horse's total ration to provide 300mg (1 scoop) of cyromazine per horse per day or 600 mg (2 scoops) of cyromazine per horse every other day. Note: Each scoop equivalent to ½ oz.
100-790 [Trigard OMC]	75.0	Seed treatment for onion maggot control in bulb onions.	**Do not use** on agricultural establishments in hopper-box, planter-box, slurry-box, or other seed-treatment applications at or immediately before planting. Trigard OMC is for use only by licensed commercial seed treatment companies. **Apply Trigard** OMC to seed at the rate of 6.6 lbs. of product per 100 lbs. of seed (4.5 lbs.) active ingredient per 100 lbs. of seed).
100-667 [Citation Insecticide]	75.0	Landscape ornamentals, container grown ornamentals, greenhouse, lath and shadehouse grown ornamental bedding plants and ornamental crops and	**For control** of Dipterous leafminers, apply 2.66 oz./A in a minimum of 100 gals. water as a foliar spray to the point of runoff when slippling first appears. Repeat application at 7- day intervals or as necessary to maintain control. Do not make more than a total of 6 applications to one crop For control of fungus gnats and shore flies apply 2.66 oz. of Citation in 100 gals of water as a spray or drench to all surfaces where insect pests may breed. This includes the potting media surfaces, bench tops, undersides of benches, and the areas under benches that may be contaminated with potting media or algae. Repeat application on a 7 to 14 day schedule to minimize manifestation

		interiorscapes; and shore flies only in greenhouse ornamental crops and interiorscapes	
100-656 [Armor]	5	Used on treated spent mushroom compost to land on which food crops are grown.	**Apply in sufficient** water for uniform distribution at rates at a concentration of 5 parts per million (ppm) of active ingredient.
100-632 [Cyromzine Technical]	97	Technical	**Crops** = Abyssinian cabbage, Brassica leafy vegetables, bulb vegetables, cucurbits, dry beans, Hanover salad, leafy vegetables, tomatoes, peppers; seakale cabbage, and turnip greens. **Ornamentals** = Chrysanthemums; container-grown ornamentals; greenhouse, lathhouse, and shade house-grown ornamental crops; interiorscapes and landscape ornamentals. **Other** = layer and breeder chicken operations, mushroom compost
100-654 [Trigard 75W]	75	Leafy vegetables (except Brassica vegetables), succulent lima beans, peppers, cucurbits, tomatoes, Chinese mustard (Florida Use Only), and Chinese cabbage (Florida Use Only)	**Add 2/3 of the required** amount of water to the spray or mixing tank. With the agitator running, drop the required number of unopened soluble packets of Trigard into the tank. One 2.66 oz. water-soluble packet of Trigard will treat one acre of leafy vegetables, lima beans, peppers, cucurbits, tomatoes, Chinese mustard (Florida Use Only), or Chinese cabbage (Florida Use Only). Continue agitation while adding the remainder of the water. **To avoid spray drift**, do not apply under windy conditions **Aerial application** should be used only when conditions exist that prohibit application by ground equipment.
		Chinese Mustard (Forida use only) and Chinese Cabbage (Florida use only)	**For leafminer control**, apply 2.66 oz. (one packet) of Trigard per acre as a foliar spray when leafminers first appear. Apply by air in a minimum of 5 gals. of water per acre, or by ground in a minimum of 10 gals. of water per acre, using sufficient carrier to achieve adequate coverage. Repeat applications at 7-day intervals or as necessary to maintain control. **Notes:** 1 Do not make more than 6 applications to one crop of Chinese mustard or Chinese cabbage, and 2 Do not make the last application within 7 days of harvest, or illegal residues may result.
		Cucurbits	**Cucurbits include** balsam pear (bittermelon), Chinese waxgourd (Chinese preserving melon), citron melon, cucumber, gherkin, edible gourds, melons (including hydrids; cantaloupe, casaba, Crenshaw, honeydrew melons, honey balls , mango melon, muskmelon, Persian melon), pumpkin, summer squash, winter squash, and water melon (including hybrids). **For leafminer control**, apply 2.66 oz. (one packet) of Trigard per acre as a foliar spray when leafminers first appear. Apply by air in a minimum of 5 gals. of water per acre or by ground in a minimum of 10 gals of water per acre, using sufficient carrier to achieve adequate coverage. Repeat applications at 7-day intervals or as necessary to maintain control. **Note** To avoid possible illegal residues, 1 Do not make more than 6 applications per growing season to cucurbits and 2 Curcurbits may be harvested on the same day of the last application
		Leafy Vegetables (except Brassica Vegetables)	**Leafy vegetable include:** Amaranth, arugula, cardoon, celery, celtuce, chervil chrysanthemum, corn salad, cress, dandelion, dock, endive, fennel, lettuce, orach, parsley, purslane, radicchio, rhubarb, spinach, and Swiss chard. **For leafminer control**, apply 2.66 oz. (one packet) of Trigard per acre as a foliar spray when leafminers first appear. Apply by air in a minimum of 5 gals. of water per acre or by ground in a minimum of 10 gals of water per acre, using sufficient carrier to achieve adequate coverage. Repeat applications at 7-day intervals or as necessary to maintain control. **Notes:** Do not make more than 6 applications to one crop of celery or head lettuce 2 For all other leafy vegetable crops do not make more than 5 applications per crop, and 3 Do not make the application within 7-days of harvest, or illegal residues may result
		Succulent Lima Beans	**For leafminer control**, apply 2.66 oz. (one packet) of Trigard per acre as a foliar spray when leafminers first appear. Apply by air in a minimum of 5 gals. of water per acre or by ground in a minimum of 10 gals of water per acre, using sufficient carrier to achieve adequate coverage. Repeat applications at 7-day intervals or as necessary to maintain control. **Notes:** 1 Do not make more than 6 applications to one of lima beans 2 Do not apply more than 0.88 lb (0.66 lb active ingredient) to one crop, and 3 Do not make the last application with-in 7-days of harvest or illegal residues may occur
		Peppers	**For leafminer control**, apply 2.66 oz. (one packet) of Trigard per acre as a foliar

			spray when leafminers first appear. Apply by air in a minimum of 5 gals. of water per acre or by ground in a minimum of 10 gals of water per acre, using sufficient carrier to achieve adequate coverage. Repeat applications at 7-day intervals or as necessary to maintain control. **Notes** 1 Do not make more than 6 applications to one crop of peppers, and 2 Peppers may be harvested on the same day of the last application
		Tomatoes	**For leafminer control**, apply 2.66 oz. (one packet) of Trigard per acre as a foliar spray when leafminers first appear. Apply by air in a minimum of 5 gals. of water per acre or by ground in a minimum of 10 gals of water per acre, using sufficient carrier to achieve adequate coverage. Repeat applications at 7-day intervals or as necessary to maintain control. **Notes:** 1 Do not make more than 6 applications to one crop of tomatoes and 2 Tomatoes may be harvested on the same day of the last application.
70585-1 [Lavardex 1% premix]	1	Caged or slatted flooring layer chicken operations Breeder Chicken Operations	**Blending and Feeding Laradex 1% Premix Housefly, solder fly, lesser housefly:** Mix 1lb of Larvadex 1% Premix per ton of feed. Feed the treated feed as a daily ration. Begin feeding when adult flies become active and continue treatment as prescribed through the fly season.

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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

March 21, 2007

SUBJECT: Cyromazine: Registration Review Scoping Document for Human Health Assessments; PC Code 121301; DP Barcode 337096

FROM: Ray Kent, Chief
Sue Hummel, Chemist
Jerry Stokes, Chemist
Reregistration Branch 4
Health Effects Division (7509P)

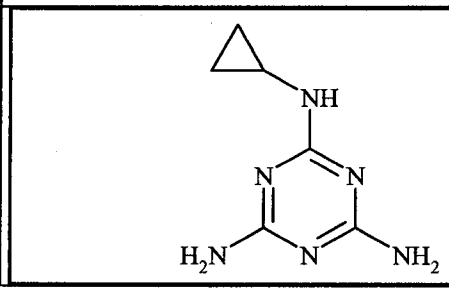
TO: James Parker
Reregistration Branch 1
Special Review and Reregistration Division (7508P)

Attached is the human health scoping/problem formulation document to support the registration review of the insect growth regulator, cyromazine.

.Introduction.

Cyromazine is currently registered for use on dry bean, lima beans, sweet corn, cotton, garlic, hanover salad, leafy vegetables, except brassica, leek, mango, mushroom, onion, pepper, Rakkyo bulb, shallot bulbs, shallot fresh leaves, tomato, turnip greens, Brassica leafy vegetables, and cucurbit vegetables, chrysanthemum (edible), wax beans, garbanzo beans, lupine, guar, beans (field), poultry, poultry premises, poultry manure, horses, horse premises. Tolerances are established in 40 CFR 180.414 for these commodities, and commodities of cattle, goats, hogs, and sheep, from secondary residues resulting from the feeding of treated commodities to livestock. Non food uses include ornamental plants. There are no registered homeowner uses. Use on potatoes is pending, although the tolerance has already been established. Uses on cattle and swine premises and manure are pending and require no new tolerances.

Section 1. Chemical Identity

Table 1.1 Chemical Identity	
Common Name	Cyromazine (ANSI)
IUPAC name	N-cyclopropyl-1,3,5-triazine-2,4,6-triamine
CAS name	N-cyclopropyl-1,3,5-triazine-2,4,6-triamine
PC Code	121301
CAS registry number	66215-27-8
Registration Review Case No.	7439
Chemical Structure	

Section 2. Toxicology

No toxicity studies have been received since the last human health risk assessment in 2003 (Wassell, 2003). A comprehensive search of the open literature was not done primarily because a screening Google search (Google Scholar) and a Science Direct search indicated little new information relevant to human health risk assessment has been published on this herbicide that had not already been considered in previous assessments.

Cyromazine targets the hematological system in dogs (6- month chronic), but otherwise does not exhibit target organ toxicity (decreased body weight and food consumption in dogs, mice, rats and rabbits). No neurotoxicity studies with cyromazine are available, but there is no evidence of neurotoxic potential for cyromazine in any of the available studies.

Acceptable developmental toxicity studies in the rat and rabbit and a two-generation reproduction study in the rat are available. In the prenatal developmental toxicity study in rats, the NOAEL (300 mg/kg/day) for developmental toxicity was higher than the Maternal NOAEL (100 mg/kg/day). In the developmental toxicity study in rabbits, no evidence of developmental toxicity was noted at the highest dose tested of 60 mg/kg/day. In the two-generation reproduction study in rats, no reproductive effects were observed at the NOAEL of 150 mg/kg/day.

A FQPA Safety factor of 1x is appropriate because there is no evidence of increased susceptibility (quantitative or qualitative) to rats or rabbits following *in utero* exposure or to postnatal exposure to rats and no residual uncertainties concerning pre/postnatal toxicity.

Table 2.1 Toxicological Doses and Endpoints for Cyromazine for Use in Dietary and Non-Occupational Human Health Risk Assessments

Exposure Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (All populations)	An appropriate endpoint attributable to a single dose (exposure) of cyromazine was not observed in oral toxicity studies. Thus, an acute dietary endpoint was not chosen.			
Chronic Dietary (All populations)	NOAEL= 7.5 mg/kg/day	UF_A = 10x UF_H = 10x FQPA SF = 1x	Chronic RfD = 0.075 mg/kg/day cPAD = 0.075 mg/kg/day	Chronic Oral Toxicity in Dogs. LOAEL = 75 mg/kg/day based on alterations in hematological parameters [hematocrit and hemoglobin (males)], decreased body weight/body weight gain and increases in several organ weights.
Cancer (oral, dermal, inhalation)	Group E carcinogen - evidence of non-carcinogenicity for humans.			

Table 3.2 Summary of Toxicological Doses and Endpoints for Cyromazine for Use in Occupational Human Health Risk Assessments

Exposure Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Short-, Intermediate- and Long-Term Dermal	No hazard was identified via the dermal route of exposure. No dermal or systemic toxicity was seen following repeated dermal application at 2000 mg/kg/day for 21 days to rabbits.			
Short-Term Inhalation (1 to 30 days)	Oral NOAEL= 10 mg/kg/day (inhalation absorption rate = 100%)	UF_A = 10x UF_H = 10x	Occupational LOC for MOE<100	Developmental Toxicity-Rabbit LOAEL=30 mg/kg/day based on decreases in maternal body weight gain and food consumption
Intermediate-Term Inhalation (1 to 6 months)	Oral NOAEL= 7.5 mg/kg/day (inhalation absorption rate = 100%)	UF_A = 10x UF_H = 10x	Occupational LOC for MOE<100	Chronic Oral Toxicity in Dogs. LOAEL = 75 mg/kg/day based on alterations in hematological parameters [hematocrit and hemoglobin (males)], decreased body weight/body weight gain and increases in several organ weights.
Long-Term Inhalation (>6 months)	Oral NOAEL= 7.5 mg/kg/day (inhalation absorption rate = 100%)	UF_A = 10x UF_H = 10x	Occupational LOC for MOE<100	Chronic Oral Toxicity in Dogs. LOAEL = 75 mg/kg/day based on alterations in hematological parameters [hematocrit and hemoglobin (males)], decreased body weight/body weight gain and increases in several organ weights.
Cancer (oral, dermal, inhalation)	Group E carcinogen - evidence of non-carcinogenicity for humans.			

Section 3. Current Dietary Assessments

As indicated above, no acute endpoint was identified and therefore an acute dietary assessment is not needed. A chronic aggregate dietary exposure assessment was carried out recently (Deschamp, 2006). However, a dietary exposure assessment has not been completed to support the pending use in livestock facilities. The Agency is waiting for additional information from the registrant to refine the water exposure assessment. The most recently conducted assessment was conservative (Tier1) in assuming that 100% of the crops on which cyromazine is registered have been treated with cyromazine and that cyromazine is present on the treated commodities at the

tolerance level. A conservative estimate of drinking water exposure has also been incorporated into the analysis. The results of the chronic dietary exposure analyses are given in Table 2. The most highly exposed population subgroup is children 1-2 years old, at 14.1% of the cPAD. This level of dietary exposure is not of concern.

Since the last risk assessment, a study (MRID 46238801) on the magnitude of the residue in lima beans has been received by the Agency, but not yet reviewed. It is unlikely to have a significant impact on the dietary exposure assessment.

Table 2. Results of the Chronic Dietary (Food and Water) Exposure Analysis for Cyromazine.

Population Subgroup	cPAD (mg/kg/day)	Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.075	0.006576	8.8
All Infants (< 1 year old)	0.075	0.004951	6.6
Children 1-2 years old	0.075	0.010588	14.1
Children 3-5 years old	0.075	0.009737	13.0
Children 6-12 years old	0.075	0.007024	9.4
Youth 13-19 years old	0.075	0.005355	7.1
Adults 20-49 years old	0.075	0.006052	8.1
Adults 50+ years old	0.075	0.006807	9.1

Section 4. Aggregate and Cumulative Exposure

There are no residential uses for cyromazine. An aggregate dietary risk assessment from exposure to cyromazine in food and water is presented in Section 3.

Cyromazine contains a symmetrical triazine substructure like the herbicides atrazine and simazine, but atrazine and simazine are halotriazines, and the toxicity of these herbicides is associated with the presence of halogens on the triazine ring. Cyromazine is not a halotriazine. There is no basis as this time to believe that cyromazine has a mechanism of toxicity like any other pesticide.

Section 5. Occupational Exposure

Occupational exposures may be short-term (up to 30 days), or intermediate-term (1 to 6 months). Handlers may be exposed by dermal and inhalation routes from mixing, loading and applying cyromazine. Postapplication workers may be exposed dermally from harvesting and other crop-tending activities in treated areas. There are no concerns regarding exposure through the

inhalation route for postapplication workers. In 2002, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) re-evaluated toxicity endpoints for use in occupational risk assessments and concluded that dermal exposure does not result in a systemic dermal hazard (HIARC Report, 2002). Since then, only inhalation exposure to occupational handlers has been assessed.

Section 6. Anticipated Data Needs

Since there are inhalation exposures associated with uses of cyromazine and the Agency has not received any inhalation studies in order to assess inhalation risks, HED previously recommended requiring a 28-day inhalation study (HIARC, 2002). However, the following study cited in a 1990 World Health Organization (WHO) monograph on cyromazine may be sufficient to meet the data need:

Hartmann, H.R., Schneider, M., Gretener, P., Froehlich, E., Malinowski, W., Krinke, A. and Gfeller, W., (1988). CGA-72662 tech. - 28 day aerosol inhalation toxicity in the rat - final report. Unpublished report, project no. 861472 from CIBA-GEIGY Ltd., Basle, Switzerland.

If this study is submitted to EPA, and if the results are consistent with those reported in the WHO monograph, the Agency does not anticipate needing additional data. Otherwise, EPA will need to call-in a 28-day inhalation study in order to assess potential inhalation risks.

Section 7. Tolerances

The following table lists the current U.S. tolerances for cyromazine (40 CFR 180.414)

Commodity	Tolerance (ppm)
Bean, dry, except cowpea	3
Bean, lima	1
Broccoli	1
Cabbage, abyssinian	10
Cabbage, seakale	10
Cattle, fat	0.05
Cattle, kidney	0.2
Cattle, meat byproducts, except kidney	0.05
Cattle, meat	0.05
Corn, sweet, forage	0.5
Corn, sweet, kernels plus cob with husks removed	0.5
Corn, sweet, stover	0.5
Cotton, undelinted seed	0.1
Egg	0.25
Garlic, bulb	0.2

Commodity	Tolerance (ppm)
Garlic, great-headed, bulb	0.2
Goat, fat	0.05
Goat, kidney	0.2
Goat, meat byproducts, except kidney	0.05
Goat, meat	0.05
Hanover salad, leaves	10
Hog, fat	0.05
Hog, kidney	0.2
Hog, meat byproducts, except kidney	0.05
Hog, meat	0.05
Horse, fat	0.05
Horse, kidney	0.2
Horse, meat byproducts, except kidney	0.05
Horse, meat	0.05
Leafy vegetables (except Brassica)	7
Leek	3
Mango	0.3
Milk	0.05
Mushroom	1
Onion, dry bulb	0.2
Onion, green	3
Onion, potato	3
Onion, tree	3
Onion, welsh	3
Pepper	1
Potato	0.8
Poultry, fat (from chicken layer hens and chicken breeder hens only)	0.05
Poultry, meat (from chicken layer hens and chicken breeder hens only)	0.05
Poultry, meat byproducts (from chicken layer hens and chicken breeder hens only)	0.05
Radish, root	0.5
Radish, tops (leaves)	0.5
Rakkyo, bulb	0.2
Shallot, bulb	0.2
Shallot, fresh leaves	3
Sheep, fat	0.05
Sheep, kidney	0.2
Sheep, meat byproducts, except kidney	0.05
Sheep, meat	0.05
Tomato	0.5
Turnip, greens	10
Vegetable, brassica, leafy, group 5, except broccoli	10

Commodity	Tolerance (ppm)
Vegetable, cucurbit, group 9	1

There are Codex and Canadian MRLs and Mexican tolerancias for cyromazine. The following table lists only those RACs with both US tolerances and MRLs from other countries.

	Tolerances or MRLs (ppm)					
RAC	US	Codex	Canada	Australia	EU	Mexico
cauliflower	10	--	--	--	0.05	10
celery	7	5	10	--	2	7
cucumber	1	0.2	1	--	1	1
endive	7				15	
lettuce, head	7	5	4	--	15	7
melon	1	0.2 (except watermelon)	1	--	0.3	1
mushroom	1	5	8	--	5	
onion, bulb	0.2	--	0.3	--	0.05	
onion, green	3	--	3	--	0.05	3
pepper	1	1	3	--	--	1
potato	0.8	--	0.5	--	1	0.8
spinach	7	--	10	--	0.05	7
tomato	0.5	0.5	1	--	1	0.5
eggs	0.25	0.2	--		--	
poultry	0.05 meat, fat, liver, kidney	0.05 (meat only)	--	0.05 (meat, fat, liver, kidney)	0.05 meat, fat, liver, kidney	--
sheep	0.05(meat, fat, liver), 0.2 (kidney)	0.05 (meat only)	--	0.2 (liver, kidney)	0.05 meat, 0.3 fat, 0.2 liver, kidney	--
cattle	0.05(meat, fat, liver), 0.2 (kidney)	--	--	0.05 (meat, fat, liver, kidney)	0.05 meat, fat, liver, kidney	--
milk	0.05	0.01	--	0.01	0.02	--
pig/hog	0.05(meat, fat, liver),	--	--	0.05 (meat, fat,	0.05 meat, fat, liver,	--

	Tolerances or MRLs (ppm)					
RAC	US	Codex	Canada	Australia	EU	Mexico
	0.2 (kidney)			liver, kidney)	kidney	

Section 8. Overall Conclusions

The risk assessments for dietary and occupational exposure are up to current standards. The dietary risk assessment may be updated if the residue chemistry study (for lima beans), received but not yet reviewed (MRID 46238801), indicates that a revision is appropriate. However, given the small percentage of the cPAD occupied, this is unlikely to indicate a concern. The Hartmann et al. (1988) inhalation study should be obtained and reviewed. Occupational risk assessments may be revised based on the outcome of the review.

Section 9. Reference Memoranda

Table 9.1. HED Memoranda Relevant to Registration Review

Author	Barcode	Date	Title
W. Wassell	D284528	7/16/03	Cyromazine in/on Bulb Vegetables (Group 3), Leafy Brassica Vegetables (Group 5) and Turnip Greens. HED Human Health Risk Assessment.
HIARC Report (W. Tehseen & W. Greear)	N/A	5/28/02	CYROMAZINE - Report of the Hazard Identification Assessment Review Committee.
A. Rathman	D242798, D242799, D242801, D242802	3/11/98	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).
P. Deschamp	D324408	12/26/06	Cyromazine: (R35) Application to Add Potatoes to EPA Reg. No. 100-654.
TES Report 2 (S. Dapson)	N/A	1/10/97	TOXICOLOGY ENDPOINT SELECTION DOCUMENT
W. Wassell	D256716	7/14/99	PP#7E4905. Human Health Risk Assessment for Cyromazine in/on Lima Bean and Reassessment of Established Tolerances

V. GLOSSARY of TERMS and ABBREVIATIONS

ai	Active Ingredient
AR	Anticipated Residue
CFR	Code of Federal Regulations
cPAD	Chronic Population Adjusted Dose
CSF	Confidential Statement of Formula
CSFII	USDA Continuing Surveys for Food Intake by Individuals
DCI	Data Call-In
DEEM	Dietary Exposure Evaluation Model
DFR	Dislodgeable Foliar Residue
DNT	Developmental Neurotoxicity
DWLOC	Drinking Water Level of Comparison
EC	Emulsifiable Concentrate Formulation
EDWC	Estimated Drinking Water Concentration
EEC	Estimated Environmental Concentration
EPA	Environmental Protection Agency
EUP	End-Use Product
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FFDCA	Federal Food, Drug, and Cosmetic Act
FQPA	Food Quality Protection Act
FOB	Functional Observation Battery
GENEEC	Tier I Surface Water Computer Model
IR	Index Reservoir
LC_{50}	Median Lethal Concentration. A statistically derived concentration of a substance that can be expected to cause death in 50% of test animals. It is usually expressed as the weight of substance per weight or volume of water, air or feed, e.g., mg/l, mg/kg or ppm.
LD_{50}	Median Lethal Dose. A statistically derived single dose that can be expected to cause death in 50% of the test animals when administered by the route indicated (oral, dermal, inhalation). It is expressed as a weight of substance per unit weight of animal, e.g., mg/kg.
LOC	Level of Concern
LOAEL	Lowest Observed Adverse Effect Level
µg/g	Micrograms Per Gram
µg/L	Micrograms Per Liter
mg/kg/day	Milligram Per Kilogram Per Day
mg/L	Milligrams Per Liter
MOE	Margin of Exposure
MRID	Master Record Identification (number). EPA's system of recording and tracking submitted studies.
MUP	Manufacturing-Use Product
NA	Not Applicable
NAWQA	USGS National Ambient Water Quality Assessment
NPDES	National Pollutant Discharge Elimination System
NR	Not Required
NOAEL	No Observed Adverse Effect Level
OPP	EPA Office of Pesticide Programs
OPPTS	EPA Office of Prevention, Pesticides and Toxic Substances
PAD	Population Adjusted Dose
PCA	Percent Crop Area
PDP	USDA Pesticide Data Program
PHED	Pesticide Handler's Exposure Data

PHI	Preharvest Interval
ppb	Parts Per Billion
PPE	Personal Protective Equipment
ppm	Parts Per Million
PRZM/EXAMS	Tier II Surface Water Computer Model
Q_1*	The Carcinogenic Potential of a Compound, Quantified by the EPA's Cancer Risk Model
RAC	Raw Agriculture Commodity
RED	Reregistration Eligibility Decision
REI	Restricted Entry Interval
RfD	Reference Dose
RQ	Risk Quotient
SCI-GROW	Tier I Ground Water Computer Model
SAP	Science Advisory Panel
SF	Safety Factor
SLN	Special Local Need (Registrations Under Section 24©) of FIFRA)
TGAI	Technical Grade Active Ingredient
USDA	United States Department of Agriculture
UF	Uncertainty Factor
WPS	Worker Protection Standard