Proposed Re-evaluation Decision PRVD2020-02

Cyromazine and Its Associated End-use Products

Consultation Document

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Proposed Re-evaluation Decision

Under the authority of the *Pest Control Products Act*, all registered pesticides must be regularly re-evaluated by Health Canada's Pest Management Regulatory Agency (PMRA) to ensure that they continue to meet current health and environmental standards and continue to have value. The re-evaluation considers data and information from pesticide manufacturers, published scientific reports, and other regulatory agencies. Health Canada applies internationally accepted risk assessment methods as well as current risk management approaches and policies.

Cyromazine is a systemic insecticide and insect growth regulator that is registered for commercial use for the control of a variety of pests on potatoes, greenhouse ornamentals, outdoor ornamentals, mushrooms, greenhouse vegetables, and field vegetables. Cyromazine is also registered for the importation of treated dry bulb and green onion seeds from the United States. Currently registered products containing cyromazine can be found in the Pesticide Label Search and in Appendix I.

This document presents the proposed regulatory decision for the re-evaluation of cyromazine including the proposed risk mitigation measures to further protect human health and the environment, as well as the science evaluation on which the proposed decision was based. All products containing cyromazine registered in Canada are subject to this proposed re-evaluation decision. This document is subject to a 90-day public consultation period, during which the public including the pesticide manufacturers and stakeholders may submit written comments and additional information to the PMRA. The final re-evaluation decision will be published taking into consideration the comments and information received.

Outcome of Science Evaluation

Cyromazine is the only active ingredient registered in Canada belonging to Insecticide Resistance Action Committee mode of action group 17. Its unique mode of action lends itself to rotation with other insecticides to delay the development of resistance in susceptible dipteran pests.

Cyromazine is a systemic insect growth regulator. It works by contact action, interfering with molting and pupation, so that dipteran insects do not develop. Cyromazine is valued as a tool to manage sciarid flies in mushroom houses, onion maggot in green onions, and leafminer in outdoor ornamentals.

With respect to human health, risks due to occupational exposure have not been shown to be acceptable for most uses of cyromazine. Therefore, cancellation of uses for potatoes, leafy vegetables, celery, leafy brassica vegetables, outdoor ornamentals grown for cut flowers, greenhouse ornamentals (including ornamentals grown for cut flowers), greenhouse lettuce and dry bulb onion seed is proposed. Mitigation measures are required for all remaining uses. Exposure from the remaining uses is unlikely to affect human health when used according to the proposed revised label directions.

Cyromazine enters the environment when used to control insects on crops, or when it is present in water discharged from greenhouses and mushroom houses. To mitigate potential risks to non-target organisms, spray buffer zones to protect sensitive aquatic and terrestrial habitats from spray drift and precautionary label statements to inform users of potential risks to the environment are required. When used according to the proposed label directions risks to the environment from cyromazine have been shown to be acceptable.

Proposed Regulatory Decision for Cyromazine

An evaluation of available scientific information found that certain uses of cyromazine products meet current standards for protection of human health and the environment when used according to proposed label directions, which include new mitigation measures. The following uses of cyromazine are proposed for cancellation as health risks were not shown to be acceptable: potatoes, leafy vegetables, leafy brassica vegetables, celery, outdoor ornamentals grown for cut flowers, greenhouse ornamentals, greenhouse lettuce and imported dry bulb onion seeds.

Under the authority of the *Pest Control Products Act*, Health Canada is proposing that continued registration of products containing cyromazine is acceptable when the proposed mitigation measures are in place.

Registered pesticide product labels include specific directions for use. Directions include risk mitigation measures to protect human health and the environment that must be followed by law. As a result of the re-evaluation of cyromazine, further risk mitigation measures for product labels are being proposed. The proposed label statements and mitigation measures are summarized below. Refer to Appendix XII for details.

Human Health

To protect human health, the following risk mitigation measures are proposed:

- Due to potential risks associated with workers handling or planting treated seed, cancellation of the following crop is proposed:
    - Treated onion seeds, dry bulb

- Due to potential postapplication worker risks, cancellation of the following crops is proposed:
    - Potatoes
    - Leafy Vegetables
    - Celery
    - Leafy Brassica Vegetables
    - Outdoor and Greenhouse Ornamentals Grown for Cut Flower Production
    - All Greenhouse Ornamentals Not Grown for Cut Flower Production
    - Greenhouse Lettuce

- For the remaining crops (mushrooms, green onion seeds and outdoor ornamentals not grown for cut flower production), the following mitigation is proposed:
    - Additional personal protective equipment (PPE)
    - Closed planting systems for green onion seeds
    - Revised restricted-entry intervals (REIs)
    - For mushroom applications, label statements to clarify use directions and minimize potential exposure to workers.

Environment

To protect the environment, the following proposed measures are required:

- Environmental hazard statements to inform users of the potential risks to birds and mammals (from cyromazine-treated seeds), beneficial insects, non-target terrestrial plants and aquatic organisms.
- As a precaution, the potential effects to bee reproduction and brood development will be indicated on the label, however when the product is used according to label directions no risk is expected. No restrictions to application timing are required to protect pollinators based on the risk assessment. Best practices will be recommended.
- Spray buffer zones are required on product labels (up to 3 m) to protect sensitive non-target terrestrial and aquatic organisms.
- A statement is required on product labels to inform users that residues of cyromazine (melamine) have the potential to carry over to the next season and leach to groundwater.
- To reduce the potential for runoff of cyromazine to adjacent aquatic habitats, precautionary label statements for sites with characteristics that may be conducive to runoff and when heavy rain is forecasted are required.

International Context

Cyromazine is currently acceptable for use in other Organisation for Economic Co-operation and Development (OECD) member countries, including Australia, the EU, Israel, Japan, New Zealand, Switzerland, United States and Turkey. No decision by an OECD member country to prohibit all uses of cyromazine for health or environmental reasons has been identified.

Next Steps

The public, including the registrants and stakeholders, are encouraged to submit additional information that could be used to refine risk assessments during the 90-day public consultation period[1] upon publication of this proposed re-evaluation decision.

[1] "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

All comments received during the 90-day public consultation period will be taken into consideration in preparation of re-evaluation decision document,[2] which could result in revised risk mitigation measures. The re-evaluation decision document will include the final re-evaluation decision, the reasons for it and a summary of comments received on the proposed re-evaluation decision with Health Canada's responses.

[2] "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

Science Evaluation

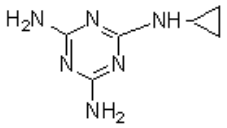
1.0 Introduction

Cyromazine is an insect growth regulator that is registered for use as a systemic insecticide on potatoes, greenhouse ornamentals, outdoor ornamentals, mushrooms, greenhouse vegetables and field vegetables. It is also registered for importation of cyromazine-treated dry bulb and green onion seeds from the United States. Cyromazine is the only active ingredient registered in Canada belonging to Insecticide Resistance Action Committee Mode of Action (MoA) Group 17 (dipteran moulting disruptor).

The registrant has indicated support for the re-evaluation of all cyromazine products and uses; all products and uses were therefore considered in the health and environmental risk assessments of cyromazine. Appendix I lists all products that contain cyromazine, as of 24 July 2019, that are registered under the authority of the *Pest Control Products Act*. A list of all commercial class uses for which cyromazine is currently registered is available in Appendix II.

2.0 Technical Grade Active Ingredient

2.1 Identity

Common name		Cyromazine
Function		Insecticide
Chemical Family		Triazine
Chemical name		
1	**International Union of Pure and Applied Chemistry (IUPAC)**	*N*-cyclopropyl-1,3,5-triazine-2,4,6-triamine
2	**Chemical Abstracts Service (CAS)**	*N*-cyclopropyl-1,3,5-triazine-2,4,6-triamine
CAS Registry Number		66215-27-8
Molecular Formula		$C_6H_{10}N_6$
Structural Formula		
Molecular Weight		166.2
Purity of the Technical Grade Active Ingredient		97%

Registration Number 24463

Identity of relevant impurities of human health or environmental concern:

Based on the manufacturing process used, impurities of human health or environmental concern as identified in the *Canada Gazette*, Part II, Vol. 142, No. 13, SI/2008-67 (2008-06-25), including TSMP Track 1 substances, are not expected to be present in the product.

2.2 Physical and Chemical Properties

Property	Result
Vapour pressure at 25°C	4.48×10^{-4} mPa
Ultraviolet (UV) / visible spectrum	λ_{max} = 241 nm. Does not absorb > 300 nm.
Solubility in water at 25°C	13 g/L at pH 7.1
n-octanol–water partition coefficient (log K_{ow})	Log K_{ow}= -0.061 at pH 7
Dissociation constant (pK_a)	pK_a= 5.22

3.0 Human Health Assessment

3.1 Toxicology Summary

Cyromazine belongs to the s-triazine class of chemicals and is used as an insecticide and larvicide. Cyromazine is an insect growth regulator which interferes with moulting and pupation, though the precise mechanism of insecticidal action is unclear. Melamine is a mammalian and plant metabolite of cyromazine. It was identified as a metabolite of concern, and as such, was evaluated and addressed in the human health risk assessment of cyromazine. The human health risk assessments for cyromazine and melamine were based on an extensive toxicology database, including papers in the published scientific literature. The scientific quality of the available data was considered to be high and adequate to define the majority of the toxic effects which may result from exposure to cyromazine and its metabolites.

Cyromazine

Based on radiolabel studies in which rats and monkeys were administered a single or repeated oral dose, cyromazine was rapidly and extensively absorbed, distributed and eliminated; no significant sex, species or dose-related differences were observed. In radiolabel studies conducted in rats, the highest tissue concentrations were detected in liver and kidney, followed by blood, adrenal and thyroid, with low levels of radioactivity noted in brain and adipose tissues during and post-exposure to cyromazine. While cyromazine was not metabolized extensively in

rats or monkeys, the small amounts that were metabolized resulted in the formation of melamine, hydroxycyromazine and methylcyromazine. Administration of a single or repeated oral dose in rats and monkeys resulted in the elimination of most of the administered dose in urine within 24 hours. In the urine of both species, up to 97% of the radioactivity present was identified as unchanged cyromazine, and up to 6% was identified as the metabolite melamine. Smaller amounts of radioactivity were recovered in feces in both species, 24 hours after exposure.

Acute oral toxicity studies in rodents and rabbits conducted with cyromazine indicated low toxicity. Clinical signs of toxicity following acute oral exposure included decreased activity, salivation, tremors, ataxia, dyspnoea, diarrhea, piloerection, chromodacryorrhea, ptosis (drooping eyelid), exophthalmos (abnormal protrusion of the eye), curved position and ruffled fur. In acute dermal studies in rats, cyromazine was of low toxicity and induced clinical signs of toxicity (dyspnoea, curved position, ruffled fur) at high doses. Cyromazine produced low acute inhalation toxicity following nose-only exposure in rats. Clinical signs including decreased activity, piloerection and discoloration of the lungs were noted at the lowest administered concentration. Cyromazine produced mild eye and dermal irritation in rabbits, and was not a dermal sensitizer to guinea pigs following testing by the Maximization method. No significant sex-related differences in acute toxicity were noted.

In repeat-dose dietary toxicity studies, decreased body weight was a common finding among all species tested. Based on oral studies in rats and dogs, increased duration of dosing resulted in increased toxicity. Long-term dietary administration of cyromazine resulted in mammary gland and uterine histopathological changes in female rats, and altered organ weights and changes in clinical chemistry and hematological parameters in dogs. Other notable effects at higher oral doses in repeat-dose dietary studies included mortality in mice and dogs, clinical signs of toxicity in mice and dogs, mammary gland pathology in mice, testicular and ovarian effects in rodents and dogs and heart pathology in dogs.

Short-term nose-only inhalation exposure to cyromazine in rats produced clinical signs, which persisted in the recovery phase of the study, as well as reduced body weight and organ weight changes at the lowest administered concentration. Hematological and liver effects were observed at higher concentrations. Short-term dermal exposure to cyromazine did not result in systemic or dermal effects at the limit dose of testing in rabbits of either sex.

In an acute gavage neurotoxicity study in rats, decreased locomotor activity, decreased hind limb foot-splay and decreased body temperature were noted on the day of dosing. A short-term oral neurotoxicity study conducted with cyromazine was not available. Other potential signs of neurotoxicity in the database were observed at high doses and included tremors in the 7-week dietary study in mice and ataxia in the 6-month dietary study in dogs. Increased brain weight in rats and dogs was noted at exposure levels that were greater than those producing other toxicological effects. There was no evidence of neuropathology in the species tested.

In acceptable in vitro studies, cyromazine was negative for induction of gene mutation in Salmonella, E. coli, S. cerevisiae, mouse lymphoma cells and hamster V79 cells, and for DNA damage and unscheduled DNA synthesis in mouse hepatocytes. In supplemental in vitro studies, negative results were reported for unscheduled DNA synthesis in rat hepatocytes and

chromosomal aberrations in human lymphocytes. In the only acceptable in vivo study, cyromazine was negative for induction of micronuclei in mouse bone marrow cells. In supplemental in vivo studies, results were negative in the dominant lethal assay in mice and in an assay of nuclei anomalies in hamster bone marrow cells. An inconclusive result was noted in a supplemental mouse Spot Test. Overall, the weight of evidence indicates that cyromazine is not genotoxic.

In the two year dietary toxicity study in mice, a slight increase in the incidence of adenocarcinoma as well as the combined incidence of adenocarcinoma and adenoacanthoma was observed in the mammary gland of high-dose females. Although the increase was not statistically significant, the incidence of adenocarcinoma at the high-dose exceeded the historical control range; historical control data for the combined tumour incidences were not available. For these reasons, the evidence for carcinogenicity in female mice was considered to be equivocal.

There was a statistically significant (trend, pairwise analysis) increase in the combined incidence of mammary gland adenoma and adenocarcinoma in high-dose female rats treated in the diet with cyromazine for two years. The high-dose incidence exceeded concurrent and historical control values. A re-read of the pathology slides showed no increase in the incidence of mammary gland adenomas, but the incidence of mammary gland adenocarcinomas was marginally positive in a trend test, and was at the upper-end of the range of historical control data. The combined incidence of mammary gland tumours was not available from the pathology re-read. Although rarely seen in male rats, mammary gland tumours were also present in mid- and high-dose males, but they did not occur in a dose-related manner. The equivocal evidence of mammary gland tumours in female mice and male rats provided further support for the mammary gland tumours in female rats. Mammary non-neoplastic histopathological changes in female rats (hyperplasia, cysts), mice (hyperplasia) and dogs (nodules, increased secretory activity) and evidence of female, as well as male reproductive toxicity throughout the database contributed to the weight of evidence. Treatment-related mammary gland tumours have been reported with other structurally-related s-triazines. Although the increased combined incidence of mammary gland adenomas and adenocarcinomas in female rats in the two-year dietary study was considered treatment-related, it occurred at a dose level which exceeded the maximum tolerated dose (MTD) based on excessive body weight reductions, and as such, was not considered relevant for human health risk assessment.

There was an equivocal increase in the incidence of testicular interstitial cell tumours in high-dose male rats in the two-year dietary chronic toxicity/carcinogenicity study. Although the increased incidence at the high-dose was marginally-statistically significant, a positive test for trend was obtained. The high-dose incidence exceeded concurrent and historical control means, but was within the historical control range. Further support that these findings are likely treatment-related came from the finding of testicular effects (atrophy, organ weight changes) in rodents and dogs, and the occurrence of treatment-related interstitial cell tumours in rats treated with the structurally-related s-triazine, terbutryn (PMRA# 1158528). As the MTD was exceeded in high-dose males in the two-year dietary chronic toxicity/carcinogenicity study conducted with cyromazine, the testicular tumours were not considered relevant for human health risk assessment.

There was evidence of adverse effects on male mating performance (decreased copulation) and fertility in the dietary multi-generation reproductive toxicity study in rats conducted with cyromazine. Systemic toxicity in parental animals was similar to that observed in repeat-dose oral toxicity studies (decreased body weight) and was noted at dose levels which were similar to those administered to non-pregnant animals. At the lowest dose level tested, there was evidence of serious effects in the young in the presence of marginal reductions in maternal body weight, with only one eye (assumed to be anophthalmia or cyclopia) present in some F1/F2 offspring. At the highest dose level tested, decreased F1 pup viability up to post-natal day (PND) 4, decreased F1/F2 pup body weights up to PND 21, altered F1/F2 organ weights (testes, brain, kidney, heart) and lung nodules in F1 pups were noted in the presence of maternal toxicity (decreased body weight, organ weight changes). The decreased viability noted in F1 pups is a serious effect; however, concern for this finding was tempered by the fact that it was observed in the presence of maternal toxicity.

A number of gavage developmental toxicity studies were available for cyromazine including investigations conducted in two New Zealand White (NZW) rabbit colonies (Buckshire and Dutchland), Dutch Belted rabbits (Langshaw colony) and Sprague-Dawley rats. Strain- and colony-specific historical control data were available for each study and were included in the assessment of weight-of-evidence of developmental effects. An important finding in the developmental toxicity database was a treatment-related increase in the number of multiple eye/craniofacial malformations at low oral dose levels in NZW rabbits.

The rabbit, especially the NZW strain, is known to be a sensitive responder to some teratogens in the form of multiple eye/craniofacial malformations. This response involves a sequence of gradual reductions in facial and cranial bones and a decrease in the inter-ocular distance until a cyclopean condition is reached (PMRA# 2723045, 2727593). This holoprosencephaly (HPE) spectrum is caused by the impaired midline cleavage of the embryonic forebrain and incomplete separation of the two cerebral hemispheres. The HPE response is heterogeneous, producing brain malformations which are accompanied by a spectrum of highly variable midline facial anomalies. The HPE spectrum may also be associated with the spectrum of agnathia. The most severe variant of the HPE-agnathia-spectrum is alobar HPE (cyclopia with proboscis) with otocephaly (absent or small mouth and jaw, and ears displaced ventrally). Further reductions in craniofacial structure result in alobar HPE-otocephaly phenotypes which are also associated with a spectrum of severe skull/cranial effects (PMRA# 2722231, 2727593).

Increased incidences of external malformations and rare eye, craniofacial and skull malformations consistent with severe alobar HPE-otocephaly phenotypes were observed in the offspring of NZW (Buckshire colony) rabbits gavage-dosed with cyromazine. These findings occurred in the absence of maternal toxicity. Treatment-related eye and craniofacial malformations included cyclopia with proboscis, agnathia with no oral opening and pinnae located more ventrally than normal (otocephaly) and exencephaly, all occurring in the absence of maternal toxicity at dose levels ≥10 mg/kg bw/day (NOAEL = 5 mg/kg bw/day). At higher dose levels in this investigation, severe eye/craniofacial malformations were also noted in offspring including cyclopia with proboscis, exencephaly, nares absent, micrognathia (maxilla) and hydrocephaly in the absence of maternal toxicity. Although single incidences were noted for some of these observations, they represent a HPE response when considered collectively. At the

highest dose level tested in this investigation, open eyelid, skull anomaly (small nostrils, cleft palate) and accessory skull bones in the parietal or nasal sutures were seen in the presence of maternal toxicity. Cyanazine, a close structural analogue of cyromazine, also produced treatment-related eye malformations in NZW rabbits (microphthalmia) and F344 rats (microphthalmia, anophthalmia) which were not correlated with maternal toxicity (PMRA# 2722230, 2722222).

The findings of the NZW Buckshire rabbit teratology study were supported by the results of a second gavage NZW rabbit teratology study which utilized rabbits from the Dutchland colony. In this second study, increases in the number of external malformations and single incidences of rare eye malformations (microphthalmia/anophthalmia) were noted in the absence of maternal toxicity at 5 mg/kg bw/day cyromazine. Single incidences of other craniofacial malformations including agnathia and macroglossia, occurring in the absence of maternal toxicity, and pinnae misplaced/small or absent, occurring in the presence of maternal toxicity, were also noted at higher dose levels in this investigation.

In the post-natal phase of the NZW Dutchland rabbit study, cyclopia and cleft palate in one kit found dead, and an increased incidence of external malformations were noted at the highest dose level tested. The finding of cyclopia and other rare eye/craniofacial malformations at frequencies greater than those in concurrent and historical controls for two NZW rabbit colonies suggests that cyromazine produces alobar HPE-related malformations in the rabbit. It is noteworthy that these effects were observed despite the increased post-implantation loss, resorptions, abortions, small number of available fetuses per litter, and lack of reporting of external findings in all aborted fetuses.

A third gavage teratology study with cyromazine, conducted in Dutch Belted rabbits, also demonstrated an increased incidence of craniofacial malformations including dome-shaped head with hydrocephaly and skull anomaly (nasals, premaxillae and jugals malformed/small, bilateral) at the highest dose level tested. This dose level also resulted in maternal toxicity.

The cyromazine dietary reproductive toxicity study in rats presented evidence of a possible teratogenic effect (anophthalmia or cyclopia) as indicated by only one eye present (no additional details) in F1/F2 pups of both sexes. This finding occurred in the presence of a marginal maternal body weight reduction and is consistent with the rare eye malformations noted in rabbit developmental toxicity studies conducted with cyromazine. It is noteworthy that eye malformations have also been reported in rats or rabbits treated with structurally-related compounds including cyanazine and simazine (PMRA# 2722230, 2722222).

Soft tissue malformations in rabbits consisting primarily of abdominal wall closure defects were noted at dose levels which also resulted in increased numbers of external, eye/craniofacial and total malformations in this species. Increases in the number of soft tissue malformations and diaphragmatic hernia were noted in the NZW Buckshire and Dutchland rabbit colonies at $\geq$ 10 mg/kg bw/day. There was no indication of maternal toxicity at this dose in either colony. The NOAEL for these malformations was 5 mg/kg bw/day. At a higher dose level, an increased incidence of umbilical hernia was also noted in NZW Buckshire rabbits in the absence of maternal toxicity. At even higher dose levels in other developmental toxicity studies, there was an increased incidence of omphalocele in Dutch Belted rabbits and rats occurring in the presence

of maternal toxicity. Although abdominal wall closure defects were not observed in offspring in the rat reproductive toxicity study, the highest dose level in the reproductive toxicity study was considerably lower than that which produced omphalocele in the rat developmental toxicity study.

A possible genetic link between the findings of cyclopia/related head malformations in NZW Buckshire rabbits and the use of a specific buck, and diaphragmatic hernia in NZW Dutchland rabbits and the use of a different buck was proposed by the registrant. However, these theories were not supported by the available data.

Treatment with cyromazine resulted in skeletal defects in rats and rabbits at maternally-toxic dose levels which also increased external, eye/craniofacial, soft tissue and total malformations. These included fused sternebrae in NZW Buckshire rabbits and Dutch Belted rabbits, cleft sternum in Dutch Belted rabbits, vertebral/rib anomaly and 13th rudimentary rib in NZW Buckshire rabbits, and reduced skull and skeletal ossification in rats.

It is noteworthy that the incidence of total malformations was increased in Dutch Belted rabbits, in the absence of maternal toxicity. Total malformations were also increased in NZW Buckshire rabbits in the absence of maternal toxicity, and in rats at a maternally toxic dose level.

An increase in pre-and/or post-implantation loss in rats and rabbits, an increase in abortions in rabbits, and a decrease in viable fetuses in rabbits were also noted at maternally toxic dose levels in developmental toxicity studies.

No specific endocrine-related toxicity studies were available for cyromazine; however, there are indications in the database that the endocrine system may be a target of toxicity. Notably, pathological changes and/or weight alterations were observed in mammary tissue, ovaries, uterus and testes following repeated dietary administration. Effects on reproductive performance in the rat 2-generation reproductive toxicity study, along with effects on pre- and/or post-implantation loss in the rat and rabbit developmental toxicity studies, and number of abortions and viable fetuses in rabbit developmental toxicity studies, contribute to the weight of evidence.

The toxicology reference values used for the human health risk assessment of cyromazine are summarized in Appendix III, Table 2. The results of toxicology studies conducted in laboratory animals with cyromazine are summarized in Appendix III, Table 1.

Melamine

As previously mentioned, melamine was identified as a metabolite of concern for cyromazine. The toxicology database for melamine is well-described (PMRA# 2722771, 2722772, 2722773). In short, melamine is not acutely toxic via the oral route in rodents. With repeated dietary exposure, the urinary bladder in rats, mice and dogs and the kidney in rats were target organs. These same target organs were identified in Chinese infants consuming melamine-tainted formula in 2008 and in domestic pets consuming melamine-adulterated pet food in 2007. Melamine was not considered to be genotoxic. With long-term dietary exposure, an increased incidence of urinary bladder tumours was seen in male rats. The bladder tumours in rats were

associated with exposure to high oral doses of melamine, were preceded by the formation of melamine-containing calculi, irritation and hyperplastic changes in the bladder, and are widely recognized to have a threshold-based MoA. Accordingly, a threshold approach for the carcinogenic risk assessment was supported. In gavage developmental toxicity studies in the rat, fetal effects (reduced viability and bodyweight, and increased variations and ossification delays) were noted at dose levels which resulted in significant maternal toxicity (clinical signs and histopathological changes in the kidney).

Reference doses that have been established for melamine by Health Canada (HC) and Environment and Climate Change Canada (ECCC) (PMRA# 2722772) and WHO (PMRA# 2722773) are higher than those established for cyromazine. Therefore, the human health risk assessment for cyromazine is expected to adequately protect for toxicological concerns related to melamine present as a result of the metabolism of cyromazine. Nonetheless, for refinement purposes of the cyromazine dietary risk assessment (Section 3.2), the tolerable daily intake value for melamine of 0.2 mg/kg bw/day from the HC and ECCC assessment under the Chemicals Management Plan (PMRA# 2722772) was used for the assessment of acute and chronic dietary risk from melamine formed as a result of the metabolism of cyromazine.

3.1.1 *Pest Control Products Act* Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to take into account the completeness of the data with respect to the exposure of, and toxicity to, infants and children as well as potential pre- and post-natal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the cyromazine toxicology database for the assessment of risk to infants and children, the standard complement of required studies for risk assessment were available including gavage developmental toxicity studies in rats and rabbits and a dietary multi-generation reproductive toxicity study in rats.

With respect to pre- and post-natal toxicity, there is evidence of treatment-related malformations in the absence of maternal toxicity in rabbit gavage developmental toxicity studies. In these studies, there was an increase in the incidence of total malformations, particularly soft tissue malformations, and those of the eye/craniofacial region.

In the gavage rat developmental toxicity study, a similar increase in the incidence of total and soft tissue malformations was noted at maternally-toxic dose levels. Evidence of eye malformations in the presence of marginal maternal toxicity was also present in the rat reproductive toxicity study.

At the highest dose level tested in the dietary rat reproductive toxicity study, decreased F1 pup viability up to PND 4, decreased F1/F2 pup body weights up to PND 21, altered F1/F2 organ weights (testes, brain, kidney, heart) and lung nodules in F1 pups were noted in the presence of maternal toxicity (decreased body weight and organ weight changes). The decreased viability noted in F1 pups is a serious effect; however, concern for this finding was tempered by the fact that it was observed in the presence of maternal toxicity.

Overall, the database is adequate for determining the sensitivity of the young and effects on the young are well characterized. There is concern for sensitivity of the young. The malformations, occurring in the absence of maternal toxicity, in rabbit developmental toxicity studies were considered serious endpoints. Therefore, the 10-fold *Pest Control Products Act* factor (PCPA factor) was retained for scenarios in which these endpoints were used to establish the point of departure for assessing risk to women of reproductive age. There is also concern for sensitivity of the young based on evidence of decreased viability in the young in the presence of maternal toxicity in the dietary rat reproductive toxicity study. Therefore, a threefold PCPA factor was retained for scenarios in which this endpoint was used to establish the point of departure for assessing risk to children. For other exposure scenarios, the risk was considered to be well-characterized and the PCPA factor was reduced to onefold.

3.2 Dietary Exposure and Risk Assessment

In a dietary exposure assessment, the PMRA determines how much of a pesticide residue may be ingested with the daily diet. Exposure to cyromazine from potentially treated domestic and imported foods was considered in the assessment. The dietary exposure and risk from melamine as a result of cyromazine uses in Canada and other countries was also assessed. Melamine is a major metabolite of cyromazine in food and drinking water. Dietary exposure assessments are age-specific and incorporate the different eating habits of the population at various stages of life (infants, children, adolescents, adults and seniors). For example, the assessments take into account differences in children's eating patterns, such as food preferences and the greater consumption of food relative to their body weight when compared to adults. Dietary risk is then determined by the combination of the exposure and the toxicity assessments. High toxicity may not indicate high risk if the exposure is low. Similarly, there may be risk from a pesticide with low toxicity if the exposure is high.

The PMRA considers limiting use of a pesticide when exposure exceeds 100% of the reference dose. PMRA's Science Policy Note, SPN2003-03 *Assessing Exposure from Pesticides: A User's Guide*, presents detailed risk assessment procedures.

Residue estimates used in the dietary risk assessment may be based conservatively (in other words, are high-end estimates) on the maximum residue limits (MRLs) or the field trial data representing the residues that may remain on food after treatment at the maximum label rate. Surveillance data representative of the national food supply may also be used to derive a more accurate estimate of residues that may remain on food when it is purchased.

These include the Canadian Food Inspection Agency's (CFIA) National Chemical Residue Monitoring Program and the United States Department of Agriculture Pesticide Data Program (USDA PDP). Specific and empirical processing factors as well as specific information regarding percent of crops treated may also be incorporated to the greatest extent possible.

Sufficient information was available to assess the dietary risk from exposure to cyromazine and its metabolite melamine. Acute and chronic dietary exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model - Food Commodity Intake Database™ (DEEM-FCID™, Version 4.02, 05-10-c) program, which incorporates consumption data from the National Health and Nutrition Examination Survey, What We Eat in America for the years 2005-2010 available through the Centers for Disease Control and Prevention's National Center for Health Statistics. Further details on the consumption data are available in the Science Policy Note, SPN2014-01 *General Exposure Factor Inputs for Dietary, Occupational and Residential Exposure Assessments*. For more information on dietary risk estimates and the residue chemistry information used in the dietary assessment, see Appendices IV and V.

Canadian MRLs for cyromazine are currently specified for a wide range of commodities and no changes are being proposed as a result of this re-evaluation. Where no specific MRL has been established, a default MRL of 0.1 ppm applies, which means that pesticide residues in a food commodity must not exceed 0.1 ppm. The current MRLs and enforcement residue definition for cyromazine can be found on the Pesticides section of Canada.ca website

3.2.1 Determination of Acute Reference Dose

Acute Reference Dose (ARfD)

Females 13 to 49 Years of Age

To estimate acute dietary risk for females 13 to 49 years of age, the developmental NOAEL of 5 mg/kg bw/day from the developmental toxicity study conducted with cyromazine in NZW Buckshire rabbits was selected based on increased incidences of malformations at the LOAEL of 10 mg/kg bw/day. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As outlined in the *Pest Control Products Act* Hazard Characterization section, the 10-fold PCPA factor was retained when the endpoint of malformations from the rabbit developmental toxicity study was used for risk assessment purposes. Thus, the CAF was 1000.

$$\textbf{ARfD} = \frac{\textbf{NOAEL}}{\textbf{CAF}} = \frac{\textbf{5 mg/kg bw/day}}{\textbf{1000}} = \textbf{0.005 mg/kg bw}$$

General Population (excluding Females 13 to 49 Years of Age)

To estimate acute dietary risk for the general population, the maternal NOAEL of 10 mg/kg bw/day cyromazine was selected based on early maternal body weight loss at the LOAEL of 30 mg/kg bw/day in developmental toxicity studies conducted in Dutch Belted rabbits and NZW Dutchland rabbits.

Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the PCPA factor was reduced to onefold. Thus, the CAF was 100.

$$\textbf{ARfD} = \frac{\textbf{NOAEL}}{\textbf{CAF}} = \frac{\textbf{10 mg/kg bw/day}}{\textbf{100}} = \textbf{0.1 mg/kg bw}$$

3.2.2 Acute Dietary Exposure and Risk Assessment

The acute dietary risk was calculated considering the highest ingestion of cyromazine and its metabolite melamine that would be likely on any one day, and using food and drinking water consumption and residue values. The expected intake of residues is compared to the ARfD, which is the dose at which an individual could be exposed on any given day and expect no adverse health effects. When the expected intake of residues is less than the ARfD, the acute dietary exposure has been shown to be acceptable.

Acute food residue estimates for cyromazine and melamine were based on CFIA and PDP monitoring data, Canadian MRLs, American Tolerances, or Codex MRLs. Residues in drinking water were estimated using environmental modelling discussed in Section 3.3. Chemical specific processing factors were applied where available. The assessment considered all foods that may potentially be treated with cyromazine including foods that may be treated in other countries and imported to Canada. Percent crop treated information was available but not used in the assessment as this refinement was not necessary. A deterministic approach was used to conduct the acute assessment and the 95th percentile of exposure was reported.

When the combined exposure to residues of cyromazine and melamine were compared to the ARfD of cyromazine, the exposure was greater than the ARfD. This was primarily due to the residues of melamine occurring in drinking water as a transformation product of cyromazine (see Section 3.3). Therefore, for refinement purposes (that is, to have more accurate assessments of exposure and risk), separate dietary assessments were conducted for cyromazine and melamine. As noted in section 3.1, the tolerable daily intake value for melamine of 0.2 mg/kg bw/day from the HC and ECCC assessment under the Chemicals Management Plan was selected for the assessment of acute and chronic dietary risk from melamine formed as a result of the metabolism of cyromazine.

The acute dietary (food and drinking water) exposure estimate for cyromazine was less than 80% of the ARfD for females 13 to 49 years of age. For all other population groups, the acute dietary exposure estimates were less than 10% of the ARfD. Thus, the acute dietary exposure and risks to cyromazine were shown to be acceptable.

The acute dietary (food and drinking water) exposure estimates for melamine were less than 20% of the TDI for all population groups and were shown to be acceptable.

The acute dietary risks for cyromazine and melamine were not combined as a common mechanism of toxicity was not identified for these chemicals.

3.2.3 Determination of Acceptable Daily Intake

Acceptable Daily Intake (ADI)

Females 13 to 49 Years of Age

To estimate the risk from repeated dietary exposure for females 13 to 49 years of age, the developmental NOAEL of 5 mg/kg bw/day from the developmental toxicity study conducted with cyromazine in NZW Buckshire rabbits was selected based on increased incidences of malformations at the LOAEL of 10 mg/kg bw/day. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As outlined in the *Pest Control Products Act* Hazard Characterization section, the 10-fold PCPA factor was retained when the endpoint of malformations from the rabbit developmental toxicity study was used for risk assessment purposes. Thus, the CAF was 1000.

$$\textbf{ADI} = \frac{\textbf{NOAEL}}{\textbf{CAF}} = \frac{\textbf{5 mg/kg bw/day}}{\textbf{1000}} = \textbf{0.005 mg/kg bw/day}$$

The ADI provides a margin of >90,000 to the dose level which resulted in an equivocal increase in mammary gland tumours in female mice, and a margin of >2900 to the dose level which resulted in an equivocal increase in mammary gland tumours in male rats.

General Population (Excluding Females 13 to 49 Years of Age)

To estimate the risk from repeated dietary exposure for the general population, the NOAEL of 1.4 mg/kg bw/day in the rat chronic toxicity/carcinogenicity study was selected based on decreased body weight and histopathological changes in the mammary gland and uterus in females at the LOAEL of 18.8 mg/kg bw/day. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the PCPA factor was reduced to onefold. Thus, the CAF was 100.

$$\textbf{ADI} = \frac{\textbf{NOAEL}}{\textbf{CAF}} = \frac{\textbf{1.4 mg/kg bw/day}}{\textbf{100}} = \textbf{0.014 mg/kg bw/day}$$

The ADI provides a margin of > 30 000 to the dose level which resulted in an equivocal increase in mammary gland tumours in female mice, a margin of >1000 to the dose level which resulted in an equivocal increase in mammary gland tumours in male rats, and a margin of > 12 000 to the dose level which resulted in decreased viability in the young observed in the presence of maternal toxicity in the dietary rat reproductive toxicity study.

3.2.4 Cancer Assessment

Long-term dietary administration of cyromazine resulted in treatment-related mammary gland tumours in female rats at a dose level exceeding the MTD. An equivocal increase in mammary gland and testicular tumours in male rats was also noted at the MTD. These tumours were not considered relevant for risk assessment due to the administration of excessive doses. At non-

excessive dose levels, an equivocal increase was noted for mammary gland tumours in female mice and mammary gland tumours in male rats. The ADI and the selected toxicological reference values for occupational and residential exposure are protective of these findings.

3.2.5 Chronic Dietary Exposure and Risk Assessment

The chronic dietary risk was calculated using the average consumption of different foods and drinking water and the average residue values on those foods and in drinking water. The estimated exposure was then compared to the ADI, which is an estimate of the level of daily exposure to a pesticide residue that, over a lifetime or life stage, is believed to have no significant harmful effects. When the estimated exposure is less than the ADI, the chronic dietary exposure has been shown to be acceptable.

Chronic food residue estimates for cyromazine and melamine were based on CFIA and PDP monitoring data, Canadian MRLs, American Tolerances, or Codex MRLs. Residues in drinking water were estimated using environmental modelling discussed in Section 3.3. Chemical specific processing factors were applied where available. The assessment considered all foods that may potentially be treated with cyromazine including foods that may be treated in other countries and imported to Canada. Percent crop treated information were available but not used in the assessment as this refinement was not necessary.

Similar to the approach used for the acute dietary exposure and risk assessment in Section 3.2.2, separate chronic dietary assessments were conducted for cyromazine and melamine.

The chronic dietary (food and drinking water) exposure estimate for cyromazine was 30% of the ADI for females 13 to 49 years of age. For all other population groups, the chronic exposure estimates were less than 20% of the ADI. Thus, the chronic dietary exposure and risks to cyromazine were shown to be acceptable.

The chronic dietary (food and drinking water) exposure estimates for melamine were less than 10% of the TDI for all population groups and were shown to be acceptable.

The chronic dietary risks for cyromazine and melamine were not combined as a common mechanism of toxicity was not identified for these chemicals.

3.3 Exposure from Drinking Water

Residues of cyromazine and melamine in potential drinking water sources were estimated from modelling.

3.3.1 Concentrations in Drinking Water

Estimated environmental concentrations (EECs) of cyromazine and melamine (and the sum of their concentrations) in potential drinking water sources (groundwater and surface water) were generated using the Pesticides in Water Calculator (PWC v. 1.52). EECs in surface water were calculated by simulating pesticide runoff from a treated field into an adjacent water body (a small reservoir) and the fate of a pesticide within that water body. EECs in groundwater were

calculated by selecting the highest EEC from several scenarios representing different regions of Canada. All modelling used 5 applications of 141 g a.i./ha with a maximum cumulative application rate of 705 g a.i./ha per year over a 50-year period, with initial application dates between March and October. A summary of the use pattern and modelling parameters is provided in Table 3.3.1. The main transformation product of cyromazine, melamine, was included in the modelling for drinking water by considering that 97-100% of cyromazine transforms into melamine (depending on the type of degradation).

Results of the modelling are presented in Table 3.3.2. Cyromazine and melamine specific EECs were used in separate dietary assessments. The highest daily EECs (29 µg a.i./L for cyromazine and 122 µg a.i./L for melamine) were used in the acute dietary assessments. The highest yearly EECs (24 µg a.i/L for cyromazine and 122 µg a.i./L for melamine) were used in the chronic dietary assessment. Combined estimates were generated but not used in the assessment.

Table 3.3.1 Summary of Use Pattern Modelled for the Level 1 Assessment of cyromazine

Parameter	Cyromazine	Melamine
Application Information		
Maximum application rate per year (g a.i./ha)	705	NA
Maximum rate of each application (g a.i./ha)	141	NA
Maximum number of applications per year	5	NA
Minimum interval between applications (days)	7	NA
Method of application	ground - foliar spray	NA
Environmental Fate Characteristics		
Hydrolysis half-life at pH 7 (days)	stable	stable
Photolysis half-life in water (days)	stable	stable
Adsorption K_d (mL/g)	1.1	2
Aerobic soil biotransformation half-life at 20 ºC (days)	73[1]	822
Aerobic aquatic biotransformation half-life at 20 ºC (days)	449[1]	stable
Anaerobic aquatic biotransformation half-life at 25 ºC (days)	104	162

1 90th percentile of the confidence interval on the mean of four half-lives adjusted (with Q_{10} of 2.0) to 20ºC.

Table 3.3.2 Level 1 Estimated Environmental Concentrations of Cyromazine and Melamine (as Parent Equivalent) in Potential Sources of Drinking Water

Chemical	Groundwater (µg a.i./L)		Surface Water µg a.i./L)	
	Daily[1]	Yearly[2]	Daily[3]	Yearly[4]
Cyromazine	24	24	29	6.2
Melamine	122	122	1.9	0.86
Combined	134	134	30	6.7

1 90th percentile of daily average concentrations
2 90th percentile of 365-day moving average concentrations
3 90th percentile of the peak concentrations from each year
4 90th percentile of yearly average concentrations

3.3.2 Water Monitoring Data

In addition to water modelling, a search for water monitoring data on cyromazine and its transformation product, melamine, in groundwater and surface water from Canada or the United States was undertaken as part of this review. Melamine is present in the environment from other sources, so detections in water are not necessarily the result of transformation from cyromazine.

The PMRA regularly communicates with the Federal, Provincial and Territorial representatives from all of the provinces and territories in Canada along with Environment and Climate Change Canada, the Department of Fisheries and Oceans and the drinking water subcommittee through Health Canada to acquire monitoring data that would be relevant to current re-evaluation programs. Limited monitoring data from Canada was available for cyromazine and melamine in ground and surface waters from agricultural regions of Ontario and Quebec. Of the 192 samples analysed, there was only one detection of cyromazine (0.021 µg/L) in a groundwater sample from Woodstock, Ontario. Melamine was detected in 31 of the 192 samples (13.5 %) with a maximum concentration of 0.59 µg/L. No data from the United States was available for analysis.

Due to the limited water monitoring data available, drinking water exposure could not be estimated using monitoring data. For the drinking water human health dietary risk assessment, concentrations of cyromazine and melamine determined through water modelling were considered.

3.3.3 Drinking Water Exposure and Risk Assessment

Exposure from drinking water and food sources were combined to determine the total dietary exposure and risk. Refer to Sections 3.2.2 and 3.2.5 for the results of the acute and chronic dietary exposure and risk assessments.

3.4 Occupational and Non-Occupational Exposure and Risk Assessment

Occupational and residential exposure is estimated by comparing potential exposures with the most relevant endpoint from toxicology studies to calculate a margin of exposure (MOE). This is compared to a target MOE incorporating uncertainty factors protective of the most sensitive subpopulation. If the calculated MOE is less than the target MOE, it does not necessarily mean that exposure will result in adverse effects, but mitigation measures to reduce risk would be required.

3.4.1 Toxicological Reference Values

Short-, Intermediate- and Long-term Dermal for Adults

For short-, intermediate- and long-term dermal risk assessment, the developmental NOAEL of 5 mg/kg bw/day in the developmental toxicity study conducted with cyromazine in NZW Buckshire rabbits was selected, based on increased incidences of malformations at the LOAEL of 10 mg/kg bw/day. The available repeat-dose dermal toxicity study conducted in rabbits was not selected for risk assessment purposes since it did not assess the endpoint of concern (that is, malformations).

For residential scenarios, the target margin of exposure (MOE) selected for this endpoint is 1000. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As outlined in the *Pest Control Products Act* Hazard Characterization section, the 10-fold PCPA factor was retained when the endpoint of malformations from the rabbit developmental toxicity study was used for risk assessment purposes. The selection of this study and target MOE is considered to be protective of all populations, including the unborn children of exposed women.

For occupational scenarios, the target MOE for this endpoint is 1000. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As the worker population could include pregnant women, it is necessary to afford adequate protection of the fetus that may be exposed via its mother. In light of the concerns regarding prenatal toxicity, as outlined in the *Pest Control Products Act* Hazard Characterization section, an additional 10-fold factor was applied to this endpoint to protect for a sensitive subpopulation, namely females 13 to 49 years of age.

Short-term Dermal for Children

For short-term residential dermal risk assessment for children, an offspring NOAEL of 51 mg/kg bw/day from the rat dietary reproductive toxicity study was selected. This NOAEL was based on decreased F1 pup viability up to PND 4, altered F1/F2 organ weights (testes, brain, kidney, heart), and lung nodules in F1 pups at 169 mg/kg bw/day, observed in the presence of maternal toxicity in the form of decreased body weight and organ weight changes. Decreases in F1/F2 pup body weight were also noted at dose levels of 51 mg/kg bw/day and greater. However, the results from the reproductive toxicity study provided evidence that the body weight effects occurred at similar dose levels in the young and adult animal. Therefore, since there were no body weight effects noted in the 21-day dermal toxicity study in rabbits, it was concluded that body weight was not an endpoint of concern via the dermal route for the young or adult animal. There was, however, concern for the toxicological effects noted in offspring at 169 mg/kg bw/day (that is, decreased viability, organ weight changes and lung nodules) which were not observed in the adult. Effects in the young animal were not assessed via the dermal route, thus necessitating the use of an oral study. As outlined in the *Pest Control Products Act* Hazard Characterization section, the PCPA factor was retained but reduced to threefold when the endpoint of decreased viability in the young was used for risk assessment purposes. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied to the offspring NOAEL of 51 mg/kg bw/day, resulting in a target MOE of 300.

Short-, Intermediate- and Long-term Inhalation for Adults

For short-, intermediate- and long-term inhalation risk assessment, the developmental NOAEL of 5 mg/kg bw/day in the developmental toxicity study conducted with cyromazine in NZW Buckshire rabbits was selected, based on increased incidences of malformations at the LOAEL of 10 mg/kg bw/day. The repeat-dose inhalation toxicity study in rats was not selected since the LOAEC of 0.055 mg/L (~11 mg/kg bw/day) was not considered protective for potential malformations.

For residential scenarios, the target MOE for this endpoint is 1000. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As outlined in the *Pest Control Products Act* Hazard Characterization section, the 10-fold PCPA factor was retained when the endpoint of malformations from the rabbit developmental toxicity study was used for risk assessment purposes. The selection of this study and target MOE is considered to be protective of all populations, including the unborn children of exposed women.

For occupational scenarios, the target MOE for this endpoint is 1000. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As the worker population could include pregnant women, it is necessary to afford adequate protection of the fetus that may be exposed via its mother. In light of the concerns regarding prenatal toxicity, as outlined in the *Pest Control Products Act* Hazard Characterization section, an additional 10-fold factor was applied to this endpoint to protect for a sensitive subpopulation, namely females 13–49 years of age.

Dermal Absorption

A dermal absorption value of 27% was determined for cyromazine based on the results of the rat in vivo study.

3.4.2 Occupational Exposure and Risk Assessment

There is potential for exposure to cyromazine in occupational scenarios from workers handling cyromazine products during mixing/loading and application activities, from handling and planting treated seeds, and from workers entering treated areas. Potential exposure to melamine was also considered for each of these scenarios.

3.4.2.1 Mixer, Loader, and Applicator Exposure and Risk Assessment

For commercial-class products, there are potential exposures to cyromazine for mixers, loaders, applicators and other handlers. The following scenarios were assessed:

- Mixing/loading of wettable powders (WP) in water soluble packaging (WSP);
- Groundboom application to potatoes, leafy vegetables, leafy brassica vegetables, celery and outdoor ornamentals;
- Airblast application to outdoor ornamentals;
- Mixing, loading and applying by backpack to greenhouse lettuce and greenhouse ornamentals;
- Mixing, loading and applying by manually pressurized handwand (MPHW) to greenhouse lettuce and greenhouse ornamentals;
- Mixing, loading and applying by mechanically pressurized handgun (MPHG) to greenhouse lettuce and greenhouse ornamentals;
- Mixing, loading and applying cyromazine to compost in mushroom houses, based on a MPHW exposure scenario;
- Mixing, loading and applying by MPHW to mushroom bed casing layer;
- Planting/handling treated onion seeds (dry bulb and green onions).

Handlers may also potentially be exposed to melamine while using cyromazine products. The human health risk assessment for cyromazine is expected to adequately protect for toxicological concerns related to melamine (as explained above in Section 3.1).

Personal Protective Equipment:

The exposure estimates for mixer/loaders and applicators are based on different levels of personal protective equipment (PPE) and engineering controls:

- Baseline PPE: Long-sleeved shirt, long pants, and chemical-resistant (CR) gloves.
- Mid-level PPE: Cotton coveralls over long-sleeved shirt, long pants, and CR gloves.
- Engineering Controls: Represents the use of appropriate engineering controls, such as closed cab tractor or closed mixing/loading systems.
- Chemical-Resistant Headgear. Chemical-resistant headgear that covers the neck (for example, sou'wester hat, rain hat).

Exposure Data:

No chemical-specific handler exposure data were available for cyromazine; therefore, dermal and inhalation exposures were estimated using data from the Pesticide Handlers Exposure Database (PHED) Version 1.1, and the Agricultural Handler Exposure Task Force (AHETF).

The PHED is a compilation of generic mixer/loader applicator passive dosimetry data with associated software which facilitates the generation of scenario-specific exposure estimates based on formulation type, application equipment, mix/load systems and level of PPE. The open cab airblast and open cab groundboom studies from AHETF were also used. While there are limitations in the use of generic data, these exposure data represent the best available data currently available.

Cyromazine is registered for planting imported, treated onion seeds. PHED scenarios were not considered to be representative of exposure to workers handling or planting treated seeds. A surrogate commercial planting exposure study was used to estimate worker exposure (PMRA# 1571553). These are the best data available for the assessment of worker exposure during the handling and planting of treated onion seeds.

Cyromazine is also registered for application to the compost and casing layers during mushroom production. Application of cyromazine to the compost layer will occur after compost has matured. Information from the registrant indicates that a conveyor will move mature compost from a bunker toward a truck bed. While the compost is moved along the conveyor, inoculated mycelium will be added and cyromazine will be applied via a downward facing, horizontal boom using a low pressure, coarse drench spray. A worker may be present during application. This method of application may occur in large or mechanized mushroom production facilities. Adequate exposure studies are not available to estimate dermal and inhalation exposure for workers using this method of application. In addition, the use of hand-held equipment by workers may occur in smaller, less mechanized facilities.

Therefore, to estimate exposure to workers applying cyromazine to compost, the PHED liquid, open pour mix/load and apply MPHW scenario was used. This PHED scenario was also used to estimate exposure of cyromazine to workers treating the casing layer of mushroom beds.

Exposure Durations:

Based on the number of applications and timing of application, workers applying cyromazine would have a short-term (<30 days) duration of exposure, except for greenhouse ornamental crops, greenhouse lettuce and mushroom houses, where there is potential for intermediate- to long-term (up to several months) duration of exposure.

Risk Assessment Outcomes:

For agricultural uses, calculated MOEs exceeded target MOEs for all mixing, loading, and application scenarios and therefore, risks were shown to be acceptable, provided engineering controls, personal protective equipment, and limitations on amount handled per day are used, as summarized in Appendix VI.

For planting imported, treated green onion seeds, calculated MOEs exceeded target MOEs and risks were, therefore, shown to be acceptable for green onion, provided engineering controls and PPE are used. For planting imported, treated dry bulb onion seeds, calculated MOEs were below target MOE and risks were, therefore, not shown to be acceptable. To mitigate this risk, cancellation of this use is proposed (Summarized in Appendix VI).

For use on mushroom house compost and casing treatments, risks were shown to be acceptable. Calculated MOEs exceeded the target MOEs, provided current label restrictions and additional PPE are added to the labels, as summarized in Appendix VI.

3.4.2.2 Postapplication Worker Exposure and Risk Assessment

The postapplication occupational risk assessment considers exposures to workers entering treated sites to conduct agronomic activities involving contact with treated material (for example foliage, soil). For outdoor agricultural crops, there is potential for short- to intermediate-term exposure for workers based on the amount of applications per growing season. For greenhouse ornamental and lettuce uses, there is potential for long-term exposure, as there is potential for treatment of many different types of ornamentals and multiple crop cycles per year. For mushroom houses, postapplication exposure would also be long-term due to multiple and concurrent crop cycles.

Agricultural Scenarios Not Including Mushrooms

For all scenarios except mushrooms, potential dermal exposure to postapplication workers was estimated using updated activity-specific transfer coefficients (TCs) and dislodgeable foliar residue (DFR) data. The DFR refer to the amount of residue that can be dislodged or transferred from a surface, such as leaves of a plant. The TC is a measure of the relationship between exposure and DFRs for individuals engaged in a specific activity, and is calculated from data generated in field exposure studies. The TCs are specific to a given crop and activity combination (for example, hand harvesting apples, scouting late season corn) and reflect standard agricultural

work clothing worn by adult workers. Activity-specific TCs from the Agricultural Re-Entry Task Force (ARTF) were used. For more information about estimating worker postapplication exposure, refer to PMRA's Regulatory Proposal PRO2014-02 (*Updated Agricultural Transfer Coefficients for Assessing Occupational Exposure to Pesticides*).

Since no chemical-specific DFR studies were available for cyromazine, default values were used (peak DFR of 25% of the application rate for all crops, with 10%, 2.3% and 0% dissipation per day for outdoor crops, greenhouse crops and greenhouse ornamentals, respectively). For further information on these default values, refer to PMRA's Science Policy Note SPN2014-02, *Estimating Dislodgeable Foliar Residues and Turf Transferable Residues in Occupational and Residential Post-application Exposure Assessments.*

For workers entering a treated site, restricted-entry intervals (REIs) are calculated to determine the minimum length of time required before people can safely enter after application. An REI is the duration of time that must elapse before residues decline to a level where performance of a specific activity results in exposures above the target MOE.

Exposure would be predominantly dermal for workers performing postapplication activities in crops treated with a foliar spray. Based on the vapour pressure of cyromazine, inhalation exposure would be low, provided that the minimum 12-hour REI is followed.

For melamine, no data were available regarding the formation of melamine on foliage following application of cyromazine, and whether such melamine residues would be dislodgeable resulting in worker exposure. However, the postapplication risk assessment conducted for cyromazine would be protective of potential melamine residues due to a) conservative inputs used to estimate potential worker exposure to cyromazine dislodgeable residues as described above, and b) use of the cyromazine toxicology reference doses is expected to adequately protect for toxicological concerns related to melamine present as a result of the metabolism of cyromazine (as explained above in section 3.1).

Table 1 in Appendix VII summarizes the postapplication risk assessment including the REIs determined for each crop and activity combination. For agricultural scenarios, REIs range from 12 hours to 149 days. For most uses, these REIs are not agronomically feasible. Therefore, the following crops are proposed for cancellation: potatoes, leafy vegetables, celery, leafy brassica vegetables, greenhouse ornamentals including ornamentals grown for cut flower production, outdoor ornamentals grown for cut flower production and greenhouse lettuce. Risks were shown to be acceptable for outdoor ornamentals not grown for cut flower production with an REI of 12 hours for most activities and an REI of 18 days for handset irrigation involving foliar contact.

The risk assessment was conducted according to current label directions and the best data available at this time. To refine the risk assessment, the registrant can propose alternate use directions which may result in lower exposures, such as reduced rates, lower number of applications, increased time between applications, and/or limiting applications to specific growth stages. Alternatively, or in addition, the registrant can submit chemical-specific studies (for example, dislodgeable foliar studies) to more accurately characterize potential exposures.

Mushrooms

Based on the current label directions, cyromazine is applied to compost and casing; it is not directly applied to mushrooms. Potential dermal exposure to cyromazine and melamine from contact with the compost, casing and mushrooms was considered in the risk assessment and is discussed below.

For the compost, after it is inoculated, treated and stored, workers turn the treated compost to allow for oxygen incorporation. Since the compost was previously treated, there is potential for dermal exposure to workers performing this task. This exposure scenario was assessed using estimates of dermal exposure to chemicals in soil outlined in the USEPA 2004 Risk Assessment Guidance for Superfund (RAGS). Calculated dermal MOEs exceeded the target MOE and therefore, risks were shown to be acceptable. See Appendix VII, Table 2 for more information.

For the casing layer, most postapplication activities are considered low contact (checking and manipulating growing media temperature, humidity, carbon dioxide and water content). The only high contact postapplication activity following application of cyromazine to the casing layer is harvesting. Exposure from potential contact with the casing layer would be less than that for the treated compost, since the rate of application to the casing is lower (56.25 vs 14 g cyromazine/100 m^2, respectively) and most activities are considered low contact. Since postapplication worker risks were shown to be acceptable for the compost, potential risks would also be acceptable for the casing.

For the mushrooms that grow in the treated compost or through the treated casing layer, the major postapplication worker activity is hand harvesting. Although the mushrooms are not directly treated, in supervised field trials required for the dietary assessment, cyromazine and melamine residues were present in/on mushrooms when the compost or casings were treated, and residues increased with longer pre-harvest intervals (PHIs). In the Canadian field trial, residues up to approximately 2 ppm were detected, with melamine accounting for approximately 80% of the residues. It appears that the mushrooms are absorbing these residues from the media and/or could also be metabolizing absorbed cyromazine to melamine. It is uncertain whether these residues would be dislodgeable or available to workers hand harvesting mushrooms. However, it is expected that potential dermal risks to workers would be acceptable, since the cyromazine MOE determined for workers in direct contact with treated compost at a concentration of 5 ppm was very high (approximately 150 000 with a target MOE of 100), indicating that residues dislodged from the mushroom surface would have to be very high in order to reach exposure levels close to the target MOE. Based on the Canadian field trial, total residues are not expected to exceed 2 ppm. In addition, the health risk assessment for cyromazine is expected to adequately protect for toxicological concerns related to melamine present as result of the metabolism of cyromazine.

As noted above, cyromazine is not directly applied to the surface of mushrooms. In order to minimize residues of cyromazine and melamine on mushrooms and thus minimize further exposure during hand harvesting, best-practice label statements are proposed to clarify that cyromazine is only to be applied to compost and casings, and not when mushrooms are present.

For all mushroom house scenarios, inhalation exposure is expected to be low, provided that the minimum 12-hour REI is followed.

3.4.3 Residential Exposure and Risk Assessment

Residential risk assessment involves estimating risks to the general population, including youths and children, during or after pesticide application.

The USEPA has generated standard default assumptions for developing residential exposure assessments for both applicator and postapplication exposures when chemical- and/or site-specific field data are limited. These assumptions may be used in the absence of, or as a supplement to, chemical- and/or site-specific data and generally result in high-end estimates of exposure. These assumptions are outlined in the 2012 USEPA Standard Operating Procedures (SOP) for Residential Pesticide Exposure Assessments (PMRA# 2409268). Section 4, Gardens and Trees, of the SOP was used to assess residential exposure to cyromazine.

3.4.3.1 Residential Applicator Exposure and Risk Assessment

A residential applicator assessment was not required, since there are no registered domestic-class products containing cyromazine

3.4.3.2 Residential Postapplication Exposure and Risk Assessment

Residential postapplication exposure occurs when an individual is exposed through dermal, inhalation, and/or incidental oral (non-dietary ingestion) routes as a result of being in a residential environment that has been previously treated with a pesticide. For cyromazine, this would include treatment of outdoor ornamentals by a commercial applicator in residential areas. For potential exposures to melamine that could occur as dislodgeable residues on foliage as a result of environmental degradation of cyromazine, the human health risk assessment for cyromazine is expected to adequately protect for toxicological concerns related to melamine.

Postapplication residential exposure to cyromazine is expected to be intermittent, short-term in duration through contact with transferable residues while conducting gardening activities on outdoor ornamentals previously treated with cyromazine. For this scenario, adults (>16 years old), youth (11 < 16 years old), and children (6 < 11 years old) were chosen as the index life stages to assess, based on behavioural characteristics and the quality of the available data. Exposure is expected to be predominately dermal. Postapplication inhalation exposure is considered to be minimal, since cyromazine has a low vapour pressure and meets the criteria for an inhalation waiver based on low volatility. Since very young children are not assessed in this scenario, incidental oral exposure is not expected.

Postapplication dermal exposure was calculated using activity-specific transfer coefficients (TCs), dislodgeable foliar residue (residue transfer to skin) and exposure time. A TC is a factor that relates dermal exposure to dislodgeable foliar residues (DFR), and is based on the amount of treated surface that a person contacts while performing activities in a given period (usually expressed in units of cm^2 per hour).

It is specific to a particular population and activity/location (for example, adults conducting gardening activities on outdoor ornamentals). Calculated dermal MOEs exceeded the target MOEs for cyromazine for all populations and thus, risks were shown to be acceptable.

The results of the residential postapplication risk assessment are summarized in Appendix VIII.

3.5 Aggregate Exposure and Risk Assessment

Aggregate exposure is the total exposure to a single pesticide that may occur from dietary (food and drinking water), residential and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal and inhalation).

3.5.1 Toxicological Reference Values for Aggregate Risk Assessment

Short-term for Adults

For short-term aggregate risk assessment (dermal, oral), the toxicological endpoint selected for aggregation is malformations. The available dermal toxicity study did not assess the endpoint of concern (that is, malformations). Therefore, an oral study was used for both the oral and dermal routes of exposure. The NOAEL of 5 mg/kg bw/day from the gavage developmental toxicity study in NZW Buckshire rabbits was selected for aggregate risk assessment, based on increased incidences of malformations in the young at the LOAEL of 10 mg/kg bw/day in the absence of maternal toxicity. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As outlined in the *Pest Control Products Act* Hazard Characterization section, the 10-fold PCPA factor was retained when the endpoint of malformations from the rabbit developmental toxicity study was selected for risk assessment purposes, resulting in a target MOE of 1000 for all routes of exposure.

Short-term for Children

For short-term aggregate risk assessment (dermal, oral) for children, the common toxicological endpoint selected for aggregation was decreased viability in offspring. The available dermal toxicity study did not assess the endpoint of concern (decreased viability in the young animal). Therefore, an oral study was used for both the oral and dermal routes of exposure. An offspring NOAEL of 51 mg/kg bw/day from the rat dietary reproductive toxicity study was selected for aggregate risk assessment. Decreased viability as well as decreased body weight, organ weight changes and lung nodules were observed in the young at the LOAEL of 169 mg/kg bw/day, in the presence of maternal toxicity. As outlined in the *Pest Control Products Act* Hazard Characterization section, the PCPA factor was reduced to threefold when the endpoint of decreased viability in the young was selected for risk assessment purposes. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied, resulting in a target MOE of 300 for all routes of exposure.

3.5.2 Aggregate Exposure and Risk Assessment

In an aggregate risk assessment, the combined potential risk associated with food, drinking water and various residential exposure pathways is assessed. A major consideration is the likelihood of co-occurrence of exposures and durations of exposures.

For cyromazine, an aggregate assessment was conducted for adults, youth and children who would have residential exposure following application to outdoor ornamentals plus dietary cyromazine exposure from food and drinking water.

The results of the aggregate assessment for cyromazine are presented in Appendix VIII.

The calculated aggregate MOEs exceeded the target MOE of 1000 for youth and children. For adults the aggregate MOE was 912; however, the aggregate risks are considered to be acceptable due to conservatisms in the exposure assessment for both residential exposure and dietary exposure. The available plant metabolism studies demonstrate there is degradation of cyromazine to melamine in plants. However, there is insufficient information to estimate the distribution of melamine and cyromazine residues on the foliage of treated ornamental plants. As such, a health protective approach was taken in which it was assumed that 100% of the residues present were in the form of cyromazine.

For melamine, a quantitative aggregate risk assessment was not conducted due to the lack of information related to melamine formation on foliage which is the basis of the residential assessment from cyromazine use on ornamentals. As noted above, it was assumed that 100% of the foliar residues present were in the form of cyromazine. Aggregate risks for melamine are expected to be acceptable based on the fact that chronic dietary exposures for melamine were less than 10% of the melamine TDI and potential contribution from residential exposures would not be expected to result in exceedances of the TDI. In addition, the residential and aggregate risk assessment for cyromazine was shown to be acceptable and the human health risk assessment for cyromazine is expected to adequately protect for toxicological concerns related to melamine present as a result of the metabolism of cyromazine.

3.6 Cumulative Assessment

The *Pest Control Products Act* requires the Agency to consider the cumulative effects of pest control products that have a common mechanism of toxicity. Cyromazine and melamine belong to a group of chemicals classified as triazines. Cyromazine and melamine were not included in the USEPA triazine common mechanism of toxicity group for the purpose of cumulative risk assessment. The USEPA's triazine common mechanism of toxicity group, which includes atrazine, simazine, propazine and the metabolites 2,3-amino-6-chloro-s-triazine (DACT), des-ethyl atrazine (DEA) and des-isopropyl atrazine (DIA), was determined based on disruption of the hypothalamic-pituitary-gonadal (HPG) axis in the female rat, which resulted in decreased lutenizing hormone (LH) levels, prolonged and increased exposure to estrogen and prolactin, and subsequent development of mammary gland tumours (PMRA# 2722907, PMRA# 2993955). Other possible consequences of decreased LH levels include delayed puberty, pregnancy loss and anovulation (PMRA# 2722907). Although the MoA for hormone disruption is relevant to

humans, the MoA for mammary gland tumour development is not relevant to humans since humans respond to decreased LH levels with decreased production of estrogen and prolactin (PMRA# 2993955).

Cyromazine and melamine were excluded from the USEPA triazine common mechanism of toxicity group owing to their conclusion that cyromazine does not produce treatment-related mammary gland tumours in rodents, the presence of “moieties that have a confounding effect as to their mechanism of toxicity”, and “no known mechanism of toxicity that would support grouping them by a common mechanism with atrazine, simazine” (PMRA# 2722907). Since the PMRA concluded that cyromazine caused treatment-related mammary gland tumours in rats, albeit at an excessive dose level, the possibility exists that cyromazine may share a common mechanism of toxicity with other s-triazines, though the MoA for mammary gland tumour development may not be relevant to humans. Other toxicological effects which are associated with cyromazine and other triazine compounds include testicular tumours (for example, terbutryn) and eye malformations (for example, cyanazine and simazine).

Although findings in the database support the endocrine system as a target for cyromazine toxicity, data are currently lacking with respect to the effects of cyromazine on the HPG axis and may be required to confirm or negate the common mechanism finding. Similarly, additional toxicological data may be required to explore the common mechanisms of toxicity for the other shared toxicological effects noted above. Upon completion of the re-evaluation of the individual chemicals in the triazine group, the PMRA will determine whether a cumulative effects assessment is required, and if so, it will be performed with all relevant chemicals and scenarios of the common mechanism group.

3.7 Incident Reports

As of 23 October 2019, one human incident involving cyromazine has been reported to the PMRA. This serious incident involved multiple pesticide products including at least nine other active ingredients. A female of unknown age reported that she was exposed to multiple pesticide products over a course of 23 years of employment, and she developed cancer (leukemia). Due to the uncertainties and limited information regarding the exposures to the different pesticide products, there was insufficient information to assess an association with the pesticide products. No additional mitigation measures for cyromazine were proposed as a result of this incident.

4.0 Environmental Assessment

4.1 Fate and Behaviour in the Environment

A summary of environmental fate data for cyromazine is presented in Appendix IX, Table 1.

Cyromazine is stable to hydrolysis and soil photolysis at enviromentally relevant conditions. Indirect aqueous photolysis enhanced by photosensitizers in the environment may contribute to the dissipation of cyromazine in the photic zone of water bodies.

Cyromazine is non-persistent to slightly persistent under aerobic soil conditions and moderately persistent to persistent in aerobic water-sediment systems. Biotransformation on land and water is an important route of dissipation of cyromazine. The major transformation product produced in biotransformation studies is melamine.

Degradation occurs simultaneously with evolution of carbon dioxide (maximum of 32.5% AR) and formation of non-extractable residues (NER) (maximum of 25.8% AR), which is associated with soil organic matter. Under anaerobic conditions, cyromazine is moderately persistent in soil.

Depending on soil type, cyromazine has low to very high mobility (K_{FOC} values of 40.2 to 521 mL/g; K_{oc} values of 59.03 to 1698 mL/g), according to the classification of Cohen *et al.* 1984[3] (Appendix IX, Table 2a). Melamine (K_{FOC} values of 97 to 423 ml/g) exhibited moderate to high mobility in the soils tested (Appendix IX, Table 2b). No relationship was observed between adsorption coefficients and clay content, pH, organic carbon or cation exchange capacity. Based on the groundwater ubiquity score (GUS) of Gustafson (1989),[4] cyromazine could be a leacher depending on the soil type, while melamine is considered to be a leacher. Cyromazine and melamine are very soluble in water (13 000 and 4850 mg/L, respectively). The results of adsorption/desorption studies, water modelling, criteria of Cohen *et al*. (1984)[3] for leaching, groundwater ubiquity score (GUS) and field studies all suggest that residues of cyromazine and melamine have the potential to leach.

Available field trials indicate that cyromazine is not expected to build up in soil or be carried over in important amounts into the next growing season. Under field conditions, cyromazine remained mostly in the top 30 cm soil layer while melamine remained mainly in the top 45 cm soil layer and was occassionally measured at depths down to 120 cm. Melamine has the potential of carryover to the next growing season. Other potential sources of melamine found in the environment include adhesives, coatings and flame retardants.

Cyromazine is not expected to be volatile from moist soil and water surfaces (vapour pressure of 4.48×10^{-7} Pa at 25 °C, Henry's Law Constant of 5.956×10^{-9} Pa·m³/mol). Melamine is also not expected to be volatile from moist soil and water surfaces (vapour pressure of 7.5×10^{-9} Pa, Henry's Law Constant of 1.86×10^{-9} Pa · m³ /mol).

Cyromazine has a log K_{ow} of -0.061 which indicates that it is not expected to bioaccumulate in biota. Melamine is also not expected to bioaccumulate based on a log K_{ow} of -1.14.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects

[3] PMRA#1918520; Cohen, S.Z. et al, 1984, Potential Pesticide Contamination of Groundwater from Agricultural Uses - ACS Symposium Series, Volume 259, Pages 297 to 325, DACO: 9.9

[4] PMRA#1562809; 1989, MON 7200 Dissipation in Soil: Rates of Formation and Decline of Three Major Metabolites, DACO: 8.2.3.3.1

occur. Estimated environmental concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (in other words, protection at the community, population, or individual level).

Initially, a screening level risk assessment is performed to identify specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value [RQ = exposure/(toxicity × uncertainty factor – if applicable)], and the risk quotient is then compared to the level of concern (Appendix IX, Table 3).

If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

4.2.1 Risks to Terrestrial Organisms

A summary of terrestrial organism toxicity data for cyromazine and melamine is presented in Appendix IX, Table 4. For the assessment of risk, toxicity endpoints chosen from the most sensitive species were used as surrogates for the wide range of species that can be potentially exposed following use of cyromazine. The terrestrial risk assessment takes into account the maximum cumulative application rates registered for cyromazine on celery, outdoor ornamentals and potatoes.

Earthworms

For earthworms, the expected environmental concentration is calculated based on a direct application of cyromazine to bare soil at the maximum seasonal application rate (141 g a.i./ha × 5 applications at 7-day intervals) and takes into consideration dissipation of cyromazine between applications (half-life of 57.54 days). The associated risk quotient based on the maximum cumulative application rate (RQ = <0.01) indicates that cyromazine and melamine are not expected to pose an acute and chronic risk to earthworms (Appendix IX, Table 5).

Bees (pollinators)

Foraging bees could be exposed directly to cyromazine spray droplets during application or to cyromazine residues found on the surface of plants (contact exposure). Foraging bees could also be exposed to cyromazine through the ingestion of pollen and nectar contaminated from direct spray or through the systemic movement in the plant (oral exposure). In addition, brood may be exposed to cyromazine as foraging bees bring contaminated pollen and nectar back to the hive.

A screening level assessment indicated no risks to adult bees from acute oral and contact exposure. With the available data, a screening level assessment of chronic risk to adult bees and effects on bee brood could not be conducted. Available Tier II semi-field and Tier III field studies were reviewed to look for evidence of adult chronic and bee brood acute and chronic effects.

Effects from semi-field tunnel studies and field studies were compared with proposed foliar application rates and timing. As no measured pollen and nectar residues were available, feeding study effects were compared to default foliar spray values for tall grass residue, which provide conservative exposure estimates. Semi-field studies showed that chronic risks to adult honey bees are acceptable at exposure levels up to 400 g a.i./ha. In a colony-feeding study, chronic effects to adult bumble bee reproduction were seen, with a significant reduction in males produced by a dominant laying worker after exposure to pollen and sugar water spiked with 100 mg a.i./L. A semi-field study showed potential effects to bee brood after being exposed to *Phacelia tanacetifolia* treated with 16 or 400 g a.i./ha. These results showed no dose response among the treatments and there were limitations with the study design, resulting in uncertainty as to whether these effects were treatment related. In two colony-feeding studies, effects to both honey bee and bumble bee brood were seen after being exposed to 100–225 mg a.i./L of cyromazine in food.

The effects identified from the colony feeding studies were further considered by comparing the feeding study effects levels to default conservative Tier I exposure levels estimated for pollen and nectar. The adverse effects to adult bees and brood were observed at exposure levels of 81.32–182.99 mg/kg (which correlates to 100–225 mg a.i./L), well above the pollen and nectar exposure estimate (13.82 mg/kg). As a result, risk to pollinators is acceptable.

The available Tier III field study showed no adverse colony level effects to honey bees after a 28-day exposure to cyromazine applied at a rate of 300 g a.i./ha.

Overall, laboratory, semi-field and full-field studies indicate that the risk to pollinators from foliar application of cyromazine is acceptable when applied according to the registered use pattern.

As onions are typically harvested before bloom, onion seed treatment uses are not expected to pose a risk to pollinators.

Beneficial arthropods

The risk assessment for beneficial arthropods assumes the major route of exposure is from contact with treated plant material both on the treated area (from direct spray on the crop) and at the margins of the treated field (from spray drift). The expected concentration of cyromazine residues on foliage within the treated field is calculated using the highest labelled cumulative application rate and a value for the dissipation of cyromazine on the surface of the leaves.

In laboratory studies conducted with *Aphidius rhopalosiphi* mummies (parasitic wasp), *Coccinella septempunctata* larvae (ladybird beetles), *Poecilus cupreus* adults (ground beetle) and *Aleochara bilineata* adults (rove beetle), the level of concern was not exceeded. In extended laboratory tests carried out with freshly dried residues on plant leaves, cyromazine caused no adverse effects on life-cycles of parasitic wasps, ladybird beetles, green lacewing, and juvenile springtails. The level of concern of 1 was exceeded only for the foliar dwelling predatory mite species *Typhlodromus pyri* (in-field RQ = 3.9 to 75.6; off-field RQ = 2.3 to 56) and *Phytoseiulus persimilis* (in-field RQ = 6 to 23.8; off-field RQ = 1.4 to 17.6) for use on celery and outdoor ornamentals; and *T. pyri* (in-field RQ = 6 to 115.6; off-field RQ = 7) and *P. persimilis* (in-field RQ = 9.2 to 36.4; off-field RQ = 2.2) for use on potato. EEC values were refined to consider foliar interception (in-field) and vegetation distribution (off-field). The exposure estimates assume deposition to a 2-dimensional structure. Therefore, the values can be corrected to take into account the 3-dimensional structure where a certain fraction is intercepted by the crop (for in-field exposure) or the off-field vegetation (for off-field exposure). For the in-field EEC, crop-specific foliar interception factors are applied to the application rate. For the off-field EEC, a vegetation distribution factor is applied to the application drift rate. The refined risk assessment indicates that the level of concern for beneficial arthropods (especially the predatory mite) was still exceeded from the use of cyromazine (off-field RQ <6, in-field RQ<93) (Appendix IX, Table 5).

In field studies carried out with fresh and field-aged residues on plant leaves, cyromazine caused adverse effects on the life cycle of exposed predatory mite species *T. pyri*. Mortality and reproductive effects were observed in-field (16 to 98% mortality) and off-field (15 to 29% mortality; 100 to 44% fecundity) up to 35 days after the last application. For off-field scenarios (at applications of 3 × 3.015g a.i./ha × 7 days to 4 × 10.065 g a.i./ha × 7 days), the observed effects decreased as the residues aged (from a max of 29% to 5% mortality; and from a max of 100% to 5% fecundity), 14 days after the last application. In-field (at application rates ranging from 900 g a.i./ha to 1200 g a.i./ha), the observed effects remained persistent even as the residues aged and gradually decreased to 16 to 27% mortality, 35 days after the last application. Though some recovery was observed after 28 days, the amount of time needed by mites to recover from the effects and recolonize was uncertain.

Labelled cumulative application rates in Canada range from 419.25 g a.i./ha (on potatoes) to 846.3 g a.i./ha per crop cycle (greenhouse ornamentals). Considering the effects observed off-field at rates as low as 9 to 40 g a.i./ha (52% fecundity) the level of concern for beneficial arthropods are expected to be exceeded from exposure to cyromazine at most labelled application rates.

Label statements are proposed to warn users of potential effects to beneficial arthropods and to indicate that drift to off-field areas should be minimized.

Birds and Mammals

Foliar applications

For birds, risk quotients calculated at the screening level for cyromazine did not exceed the level of concern on an acute or reproductive basis for foliar application (Appendix IX, Table 6). For small mammals, the level of concern was exceeded for reproductive effects at the screening level (RQ up to 15.9). A refined risk assessment indicated that the level of concern was not exceeded for reproductive effects on small mammals using mean residue values and a reproductive endpoint (Appendix IX, Table 7).

Seed treatment

When pesticides are used as a seed treatment, the treated seed may be consumed as a food item by both birds and mammals. The risk assessment method for treated seed is similar to that of spray applications, except that the dietary items are treated seeds rather than dietary items sprayed with pesticide. Cyromazine is registered for use as a seed treatment on green and dry onions. A risk assessment was conducted for birds and mammals to address the consumption of treated seed.

The exposure of birds and mammals to a pesticide through consumption of treated seed is a function of the amount of pesticide on the seed, the body weight and food ingestion rate of the animal and the number of seeds available for consumption. In the screening level assessment, it is assumed that the diet consists entirely of treated seeds and all of the treated seed that is planted is available for consumption *ad libitum* over an extended period of time. Variables, such as feeding preference, availability of treated seed or potential avoidance behaviour toward treated seed are not considered at the screening level.

The risk was assessed using generic bird and mammal body weights. The toxicity endpoints selected for use in the risk assessment are presented in Appendix IX, Table 8. For each size of organism, the expected daily exposure (EDE) is calculated using the following equation: EDE (mg a.i./kg bw/day) = (FIR/BW) × EEC

FIR: Food ingestion rate, in g dry weight per day
BW: Body weight of organism, in g
EEC: Concentration of pesticide in diet, in mg a.i./kg dry weight diet

Screening level EEC values were determined for treated green and dry onion seed (50 000 mg a.i./kg seeds). The Food Ingestion Rate (FIR) is based on allometric equations from Nagy (1987).[5] These equations determine the mass of food consumed per day in dry weight, based on the body weight of the organism.

[5] PMRA# 1918529; Nagy, Kenneth A., 1987, Field Metabolic Rate and Food Requirement Scaling in

The screening level EDEs and risk quotients for each size class of birds and mammals feeding on treated seed are presented in Appendix IX, Table 8. The LOC is exceeded for acute and reproductive effects for all bird and mammal size categories for green and dry onion seeds.

The risk values for the screening level assessments assume that all planted seed is available.The risk assessment was expanded to take into consideration that not all seeds planted will be exposed and available for consumption. De Snoo and Luttik (2004)[6] suggest that the percentage of seeds remaining on the soil surface in field headlands is dependent on the seeding method and the time of year in which seeding occurs; the values reported include 0.5% for precision drilling, 3.3% for standard drilling in spring, and 9.2% for standard drilling in autumn. Green and dry onion seeds are assumed to be seeded using standard drilling in spring. This information was used along with information on the typical seeding rate to estimate the minimum and maximum area required for a bird and mammal to find enough seeds to reach the toxicity endpoint. Although this characterization does not change the RQ values determined, it puts the exposure risk into perspective.

In Appendix IX, Table 9, the number of seeds needed to be consumed per day to reach the toxicity endpoint can be compared to the foraging area required for birds and mammals to reach the toxicity endpoint. The number of seeds to reach the endpoint is expressed as a range based on known seed size range. Similarly, a range is shown for the area required for foraging based on a range of known seeding rates.

In such cases where few numbers of seeds are required from small area of forage, adverse effects to birds and mammals from consumption of treated seeds are considered plausible. For dry and green onion seeds, the number of treated seeds needing to be consumed to reach the reproductive LOC is lowest for small and medium mammals (less than 1 seed) followed by small birds (approximately 4 seeds) and then large mammals (less than 10 seeds). The area required to forage for enough seeds to reach the reproductive endpoint is also small (in other words, less than 1 m^2 for the small and medium sized mammals, approximately 2 m^2 for the large mammals and about 1 m^2 for small birds. A relatively low number of seeds need to be ingested on a small foraging area to reach the reproductive LOC for medium sized birds (approximately 21 seeds and almost 6 m^2 for birds).

In terms of acute risk, the number of seeds needing to be consumed to reach the acute LOC is low for small birds and small and medium mammals (20 seeds for small birds, and 11 and 27 seeds for small and medium mammals, respectively) and the estimated area required to forage for enough seeds is also small (5 m^2 for small birds, 3 m^2 and 7 m^2 for small and medium mammals, respectively).

Birds and small mammals are not expected to consider onion seed a palatable food source (pungent, aromatic smell which may be irritating to birds and small mammals). For medium and large sized birds and large mammals, acute intoxications are considered less likely with

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Mammals and Birds, Ecological Monographs, Volume 57, Number 2, Pages 111 to 128, DACO: 9.9

[6] PMRA# 1918521; de Snoo, Geert R. and Robert Luttik, 2004, Availability of Pesticide -Treated Seed on Arable Fields - Pest Management Science, Volume 60, Pages 501 to 506, DACO: 9.9

cyromazine treated onion seeds because of the relatively large number of seeds needing to be ingested and/or the large foraging area required to acquire enough treated seed to reach the toxicity endpoints.

Based on the results of the risk assessment, (in other words, low number of seeds and small foraging area required to find enough treated seed to reach the LOC), the level of concern for acute and reproductive risks for birds and small mammals may be exceeded from consumption of dry and green onion seeds treated with cyromazine. Hazard statements are proposed on seed treatment product labels and seed tag labels.

Non-target plants

The toxicity of cyromazine to non-target plants was determined through vegetative vigour and seedling emergence assays using standard crop species. A screening level risk assessment compared the cumulative application rate to plant toxicity endpoints. The maximum cumulative application rate (600 g a.i./ha) takes into account the maximum labelled application rate (5 × 141 g a.i./ha), the application interval (7 days) and the dissipation of the compound on the surface of the leaves or on soil (half-life of 67.64 days). The level of concern was not exceeded for vegetative vigor (RQ <0.61) but was exceeded for seedling emergence (RQ <2) (Appendix IX, Table 5).

The risk to terrestrial vascular plants was further characterized by looking at off-field exposure from drift. For ground application, using an ASAE (American Society of Agricultural Engineers) 'medium' droplet size and using ASAE fine for airblast applications (early and late), the maximum spray drift deposition at one meter downwind from the point of application is 6% for ground application and 74% and 59% for early and late airblast applications respectively. Using the EEC values determined for off-field drift, for ground application the level of concern is not exceeded (RQ < 0.12), however the level of concern is still exceeded for airblast applications (RQ <1.48) (Appendix IX, Table 5). To mitigate risks, spray buffer zones are proposed to protect non-target terrestrial vascular plants.

4.2.2 Risks to Aquatic Organisms

A summary of aquatic toxicity data for cyromazine and melamine is presented in Appendix IX, Table 10. The aquatic risk assessment is presented in Appendix IX, Tables 11 to 14.

Freshwater invertebrates

At the screening level, cyromazine did not pose an acute risks to freshwater invertebrates, but did pose potential chronic risk to chironomids (RQ =3.4). As the level of concern was exceeded at the screening level, risk from chronic exposure to cyromazine was further refined taking into account run-off and spray drift. Screening level risk quotients for acute and chronic exposure of aquatic invertebrates to the transformation product melamine did not exceed the level of concern (Appendix IX, Table 12).

For spray drift, refined EEC values were calculated for ground and early/late airblast applications using a maximum drift deposition percent at one metre downwind from the point of application. The maximum percent drift deposition for ground using an ASAE “medium” droplet size and ASAE “fine” droplet size for airblast application (as specified on the product labels) is 6%, 74% and 59% of the application rates, respectively. The EEC values were calculated for water bodies 80 cm deep. The refined risk quotients for chironomids indicate that the level of concern from exposure to cyromazine due to spray drift is exceeded for early and late airblast applications (RQ = 2.03 to 2.5), but not for ground applications (RQ = 0.2) (Appendix IX, Table 13). Spray buffer zones are proposed to mitigate risks to freshwater invertebrates.

The risk from exposure to run-off into a body of water directly adjacent to the application field was determined using the 90th percentile of the run-off EEC values predicted by PRZM-EXAMS. The risk quotient for exposure to cyromazine was calculated using toxicity endpoints and EEC values representing the 90th percentile of 21-day concentration representing the length of the chronic exposure. The risk quotient for chironomids resulting from chronic exposure to cyromazine through runoff exceeded the level of concern of 1 (RQ = 3.8) (Appendix IX, Table 14). A hazard statement is proposed for product labels along with standard runoff statements.

A search for cyromazine and melamine water monitoring data from Canada and the United States was undertaken as part of this review. Canadian surface water monitoring data was very limited (29 samples each of cyromazine and melamine). Due to the lack of data, an assessment of the potential risk to aquatic organisms using water monitoring data could not be conducted.

Freshwater fish

The screening level risk quotients for freshwater fish resulting from acute and chronic exposure to cyromazine and melamine did not exceed the level of concern (Appendix IX, Tables 11 and 12). The use of cyromazine is not expected to pose an acute or chronic risk to freshwater fish.

Amphibians

For the amphibian risk assessment, when amphibian toxicity data is not available, fish toxicity endpoints are used as surrogate data to represent aquatic life-stages of amphibians. The amphibian risk assessment is done using EECs calculated in 15 cm deep water.

The screening level risk quotients for acute and chronic exposures of amphibians to cyromazine did not exceed the level of concern (RQ = 0.006 and 0.03 for acute and chronic exposures, respectively) (Appendix IX, Table 11). The use of cyromazine is not expected to pose an acute or chronic risk to amphibians.

Freshwater algae and vascular plants

At the screening level, the risk quotients for freshwater algae resulting from acute exposure to cyromazine and melamine did not exceed the level of concern (RQ = 0.0002 and 0.006 for acute exposure only) (Appendix IX, Tables 11 and 12). Use of cyromazine is not expected to pose an acute or chronic risk to freshwater algae and vascular plants.

Marine/estuarine invertebrates

At the screening level, the risk quotients for marine invertebrates (mysid shrimp and eastern oyster) resulting from acute and chronic exposure to cyromazine did not exceed the level of concern (RQ = 0.10 and 0.34 for acute and chronic exposures, respectively) (Appendix IX, Table 11). The use of cyromazine is not expected to pose an acute or chronic risk to marine invertebrates.

4.2.3 Environmental Incident Reports

A search of the PMRA Incident Report Database found no incidents linked to cyromazine as of 15 April 2019. No environmental incidents involving cyromazine were found in the USEPA Ecological Incident Information System (EIIS) up to 5 October 2015, the last date of report in the database. As well, the USEPA published a summary on ecological incidents and reported that they have not received any reports of adverse field effects to non-target animals or plants attributed to cyromazine (PMRA# 2911919).

5.0 Value Assessment

Cyromazine is effective for targeting dipteran leafminers, as it is readily absorbed by plants and has a strong translaminar activity. This is of particular value since eggs are laid within leaves and the larvae feed (tunnel) within the leaf. As a result, the larvae cannot be targeted by foliar sprays using non-systemic insecticides. Non-systemic foliar sprays only target adult flies on the plants and are less effective at reducing leafminer (larval) populations.

Cyromazine is the only MoA group 17 insecticide registered in Canada, and therefore it is considered a valuable tool for resistance management.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

In accordance with the PMRA Regulatory Directive DIR99-03, the assessment of cyromazine against Track 1 criteria of Toxic Substances Management Policy (TSMP) under *Canadian Environmental Protection Act* was conducted. It was determined that:

- Cyromazine does not meet all Track 1 criteria, and is not considered a Track 1 substance (refer to Appendix X, Table 1),
- Cyromazine does not form any transformation products that meet all Track 1 criteria.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical grade active ingredient and formulants and contaminants in the end-use products are compared against the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*. The list is used as described in the PMRA Notice of Intent NOI2005-01 and is based on existing policies and regulations including DIR99-03; and DIR2006-02, and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

Technical grade cyromazine and its end-use products do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette.*

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02.[7]

7.0 Conclusion of Science Evaluation

7.1 Value

Cyromazine is a systemic insect growth regulator. It works by contact action, interfering with molting and pupation, so that dipteran insects do not develop. Cyromazine is valued as a tool to manage sciarid flies in mushroom houses, onion maggot in green onions, and leafminer in outdoor ornamentals.

7.2 Human Health

Based on the current use pattern of cyromazine, human health risks were not shown to be acceptable for most uses, due to occupational risks, and therefore, the following uses are proposed for cancellation:

- Planting/handling imported, treated dry bulb onion seeds
- Potatoes
- Leafy vegetables
- Leafy brassica vegetables
- Celery
- Outdoor ornamentals grown for cut flowers
- Greenhouse ornamentals
- Greenhouse lettuce

For remaining uses, human health risks are considered to be acceptable when used with the proposed risk mitigation measures.

[7] DIR2006-02, *Formulants Policy and Implementation Guidance Document*.

7.3 Environmental Risk

To mitigate potential risks to non-target organisms, spray buffer zones to protect sensitive aquatic and terrestrial habitats from spray drift and precautionary label statements to inform users of potential risks to the environment are required. With these measures in place, risks to the environment from the use of cyromazine are considered to be acceptable.

List of Abbreviations

% AR	Percent Applied Radioactivity
µg	micrograms
a.i.	active ingredient
ADI	Acceptable Daily Intake
AHETF	Agricultural Handler Exposure Task Force
appl.	application
ARfD	Acute Reference Dose
ARTF	Agricultural Re-entry Task Force
atm	atmosphere
ATPD	Area treated per day
BAF	Bioaccumulation Factor
BCF	Bioconcentration Factor
bw	Body Weight
bwg	Body Weight Gain
CAF	Composite Assessment Factor
CAS	Chemical Abstracts Service
CEC	Cation Exchange Capacity
CEPA	Canadian Environmental Protection Act
CFIA	Canadian Food Inspection Agency
CI	Confidence Interval
cm	centimetres
cm^2	Centimeters squared
cm^2/h	Centimeters squared per hour
CMC	Carboxymethylcellulose
CR	Chemical Resistant
DA	Dermal absorption
DACT	2,3-amino-6-chloro-s-triazine
DEA	des-ethyl atrazine
DEEM-FCID	Dietary Exposure Evaluation Model - Food Commodity Intake Database
DFOP	Double First Order in Parallel
DFR	Dislodgeable foliar residue
DIA	des-isopropyl atrazine
DNA	Deoxyribonucleic acid
DT_{50}	Dissipation Time 50% (the time required to observe a 50% decline in concentration)
DT_{90}	Dissipation Time 90% (the time required to observe a 90% decline in concentration)
dw	dry weight
E_bC_{50}	Effective Concentration for 50% reduction in biomass growth
E_rC_{50}	Effective Concentration for 50% reduction in growth rate
EC_{25}	Effective Concentration on 25% of the population
ECCC	Environment and Climate Change Canada
EDE	Estimated Daily Exposure
EEC	Estimated Environmental Concentration

ELS	Early Life Stage
ER_{25}	Effective Rate on 25% of the population
ER_{50}	Effective Rate on 50% of the population
F0	Parental Generation
F1	First Generation
F2	Second Generation
FIR	Food Ingestion Rate
FOB	Functional Observation Battery
g	gram
GC-NPD	Gas Chromatography – Nitrogen Phosphorus Detector
h	hour
ha	hectare(s)
HC	Health Canada
hct	Hematocrit
Hgb	Hemoglobin
HPLC-UV	High Performance Liquid Chromatography – Ultra Violet
IORE	Indeterminate Order Rate Equation
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
K_d	soil-water partition coefficient
K_{FOC}	organic carbon normalized Freundlich adsorption coefficient
K_{oc}	organic-carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	litre
LC_{50}	Lethal Concentration 50%
LC-MS/MS	Liquid Chromatography – Mass Spectrometry
LD_{50}	Lethal Dose 50%
LOAEC	Lowest Observed Adverse Effect Concentration
LOAEL	Lowest Observed Adverse Effect Level
LOC	Level of Concern
LOQ	Limits of Quantification
LR_{50}	Lethal Rate 50%
m	meter
M/L/A	Mixer/Loader/Applicator
MAS	Maximum Average Score
Max	Maximum
MCH	Mean Cell Haemoglobin
mg	milligram
Min	Minimum
mL	millilitre
MOE	Margin of exposure
MPHG	Mechanically Pressurized Hand Gun
MPHW	Manually Pressurized Hand Wand
MRL	Maximum Residue Limit
MTD	Maximum Tolerated Dose
N/A	Not Available

NAFTA	North American Free Trade Agreement
NER	Non-Extractible Residue
NOAEL	No Observed Adverse Effect Level
NOEbC	No Observed Effect Concentration on Biomass
NOEC	No Observed Effect Concentration
NOEL	No Observed Effect Level
NOER	No Observed Effect Rate
NOErC	No Observed Effect Concentration on Growth Rate
NZW	New Zealand White
OC	Organic Carbon Content
PEG	Polyethylene Glycol
PHED	Pesticide Handlers Exposure Database
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
PND	Post Natal Day
PPE	Personal Protective Equipment
ppm	parts per million
RAGS	Risk Assessment Guidance for Superfund
RBC	Red Blood Cells
REI	Restricted-Entry Interval
rel	Relative
RQ	Risk Quotient
SFO	Single First-Order
SP	Soluble Powder
$t_{1/2}$	half-life
TC	Transfer co-efficient
tR	Representative half-life of the kinetic model
TSMP	Toxic Substances Management Policy
UF	Uncertainty Factor
µg	Microgram
USDA PDP	United States Department of Agriculture's Pesticide Data Program
USEPA	United States Environmental Protection Agency
UV	ultraviolet
veg. dist.	vegetation distribution factor
VUI	Verified Use Information
wk	week
WP	Wettable Powder
WSP	Water Soluble Packaging
♂	Males
♀	Females
↑	Increased
↓	Decreased

Appendix I Registered Cyromazine Products in Canada[1]

Registrant	Registration Number	Product Name	Marketing Class	Formulation Type	Active Ingredient (%, g/L)
Syngenta Canada Inc.	24463	Cyromazine Technical	T	Dust or Powder	97
	24464	Governor 75WP Insecticide	C	Wettable Powder	75
	24465	Citation 75WP Insecticide	C	Wettable Powder	75

[1] as of 17 September 2019, excluding discontinued products or products with a submission for discontinuation.

Appendix II Registered Uses of Cyromazine as of 24 July 2019 (excluding discontinued products or products with a submission for discontinuation).

Site	Pest(s)	Formulations	Application Method and Equipment	Maximum Single Application Rate (g a.i./ha)	Maximum Cumulative Application Rate per Year	Maximum Number of Applications per year	Minimum Interval Between Applications (Days)
Use-site category 5 – Greenhouse Food Crops							
Greenhouse lettuce	Fungus gnat (*Bradysia* sp.)	Wettable powder	Ground application: foliar spray. Do not apply this product through any type of irrigation equipment.	99 g/ha {based upon a maximum spray volume of 1000 L/ha}	Per crop cycle 396 g/ha 3960 g/ha/year	4 per crop cycle 8–10 crop cycles per year	7
Mushroom house (compost)	Sciarid fly [not larvae]	Wettable powder	Ground application: coarse drenching spray at low pressure to compost material to minimize the formation of mist	Per crop cycle **5 ppm**[1] (0.005g/kg of compost -Wet weight @ 66.6 % water)	Per crop cycle **5 ppm**[1] (0.005g/kg of compost -Wet weight @ 66.6 % water)	1 per crop cycle 6.5 growth cycles per year (whole growth cycle is 8 weeks)	Not applicable
Mushroom house (casing)	Sciarid fly [not larvae]	Wettable powder	Ground application: low volume drench spray to casing material surface	Per crop cycle 14 g/100m^2 of wet casing material to a depth of 5–8 cm (Equivalent to **5 ppm**)	Per crop cycle 14 g/100m^2 of wet casing material to a depth of 5–8 cm (Equivalent to **5 ppm**) 91 g/100m^2/ year	1 per crop cycle 6.5 growth cycles per year (whole growth cycle is 8 weeks)	Not applicable
Use-site category 6 – Greenhouse Non-Food Crops							
Greenhouse ornamentals	Fungus gnat, shore fly	Wettable powder	Ground application: soil media drench and broadcast surface spray (benches, floors etc.)	100 g/ha {based upon a spray volume of 1000 L/ha}	600 g/ha per crop cycle {based upon a spray volume of 1000 L/ha} [based on 6 applications per crop cycle] 4800 g/ha/ year	[6 applications per crop cycle, up to 8 crop cycle per year # of applications per year varies greatly. For example, from 6 applications per year for orchids, up to 48 applications per year for cut flowers]	7
Greenhouse ornamentals	Leafminer (*Liromyza* genus only)	Wettable powder	Ground application: foliar spray	141 g/ha {based upon a spray volume of 1000 L/ha}	846.3 g/ha per crop cycle {based upon a spray volume of 1000 L/ha}	[6 applications per crop cycle, up to 8 crop cycle per year	7

Site	Pest(s)	Formulations	Application Method and Equipment	Maximum Single Application Rate (g a.i./ha)	Maximum Cumulative Application Rate per Year	Maximum Number of Applications per year	Minimum Interval Between Applications (Days)
					[based on 6 applications per crop cycle] 6770 g/ha/ year	# of applications per year varies greatly. For example, from 6 applications per year for orchids, up to 48 applications per year for cut flowers]	
Use-site category 10 - Seed Treatments Food and Feed							
Onion seeds (dry and green) treated prior to import for use in Eastern Canada (muck soils) only	Onion maggot	Wettable powder	Not applicable - seeds not treated in Canada	50 g/kg seed Dry onions: (225 g/ha)[2] Green onions: (350 g/ha)[2]	50 g/kg seed Dry onions: (225 g/ha)[2] Green onions: (350 g/ha)[2]	1	Not applicable
Use-site category 13 - Terrestrial Feed Crops and Use-site category 14 - Terrestrial Food Crops							
Potato (Ontario, Québec and Atlantic Provinces only)	Colorado potato beetle	Wettable powder	Ground application: foliar spray	279.75 g/ha	419.25 g/ha	2	6
Use-site category 14 - Terrestrial Food Crops							
Crop group 4 leafy vegetables (except Brassica vegetables)	Pea leafminer (*Liriomyza huidobrensis*)	Wettable powder	Ground application: foliar spray	141 g/ha	705 g/ha	5	7
Crop group 5B Leafy Brassica greens)	Pea leafminer (*Liriomyza huidobrensis*)	Wettable powder	Ground application: foliar spray	141 g/ha	705 g/ha	5	7
Celery	Leafminers (*Liromyza* genus)	Wettable powder	Ground application: foliar spray. Do not apply this product through any type of irrigation equipment.	141 g/ha	705 g/ha	5	7
Use-site category 27 - Ornamentals Outdoor							
Outdoor ornamentals	Leafminers (*Liromyza* genus)	Wettable powder	Ground application: foliar spray using airblast, horizontal boom, or handheld.	141 g/ha	705 g/ha	5	7

1. Calculation for mushroom compost; Compost at 66.6 % moisture weighing 112.3 kg/m^2 weighs 11 230 kg/100m^2. One pouch contains 56.25 g a.i. (= 0.05625 kg a.i.). Therefore, one pouch can treat 100 m^2 of compost: 0.05625 kg a.i./11 230 kg compost = 0.000005 kg a.i./kg compost (5 ppm) @ 66.6% moisture.

2. Onion rate calculations

Dry bulb onions:

50 g a.i./1 kg of seed; Seeding rate = 4–4.5 kg seed/ha; Rate per ha = 200–225 g a.i./ha

Green onions:

50 g a.i./1 kg of; Seeding rate = 7 kg seed/ha; Rate per ha = 350g a.i./ha

Appendix III Toxicity Profile and Endpoints for Health Risk Assessment

Table 1 Toxicological Reference Values for Use in the Human Health Risk Assessment for Cyromazine

Exposure Scenario	Study	Point of Departure and Endpoint	CAF or Target MOE[1]
Acute dietary females 13 – 49 years of age	Oral developmental toxicity in the Buckshire NZW rabbit	Developmental NOAEL = 5 mg/kg bw/day Increased eye/craniofacial, soft tissue and external malformations	1000
ARfD = 0.005 mg/kg bw			
Acute dietary general population excluding females 13–49 years of age	Oral developmental toxicity in Dutch Belted and Dutchland NZW rabbits	Maternal NOAEL = 10 mg/kg bw/day Early bw loss	100
ARfD = 0.1 mg/kg bw			
Repeated dietary females 13–49 years of age	Oral developmental toxicity in the Buckshire NZW rabbit	Developmental NOAEL = 5 mg/kg bw/day Increased eye/craniofacial, soft tissue and external malformations	1000
ADI = 0.005 mg/kg bw/day			
Repeated dietary general population excluding females 13–49 years of age	2-year dietary toxicity study in the rat	NOAEL = 1.4 mg/kg bw/day Decreased bw, and histopathological changes in the mammary gland and uterus	100
ADI = 0.014 mg/kg bw/day			
Short-, intermediate- and long-term dermal for adults[2]	Oral developmental toxicity in the Buckshire NZW rabbit	Developmental NOAEL = 5 mg/kg bw/day Increased eye/craniofacial, soft tissue and external malformations	1000
Short-term dermal for children[2]	2-Generation dietary reproductive toxicity study in the rat	Offspring NOAEL = 51 mg/kg bw/day Decreased viability, organ weight changes and lung nodules in the young	300
Short-, intermediate- and long-term inhalation for adults[3]	Oral developmental toxicity in the Buckshire NZW rabbit	Developmental NOAEL = 5 mg/kg bw/day Increased eye/craniofacial, soft tissue and external malformations	1000
Short-term aggregate risk for adults **Oral and Dermal[2]**	Oral developmental toxicity in the Buckshire NZW rabbit	Common endpoint: eye/craniofacial, soft tissue and external malformations Oral: Developmental NOAEL = 5 mg/kg bw/day Dermal: Developmental NOAEL = 5 mg/kg bw/day	Oral: 1000 Dermal: 1000
Short-term aggregate risk for children **Oral and Dermal[2]**	2-Generation dietary reproductive toxicity study in the rat	Common endpoint: decreased offspring viability Oral: Offspring NOAEL = 51 mg/kg bw/day Dermal: Offspring NOAEL = 51 mg/kg bw/day	Oral: 300 Dermal: 300

Exposure Scenario	Study	Point of Departure and Endpoint	CAF or Target MOE[1]
Cancer Risk Assessment	Increase in the combined incidence of mammary gland adenomas and adenocarcinomas in female rats, and equivocal increase in mammary gland and testicular tumours in male rats at a dose which exceeded the maximum tolerated dose. These tumours are not considered relevant to human health risk assessment. Equivocal evidence of carcinogenicity (mammary gland tumours) in male rats and female mice at non-excessive doses. No cancer unit risk estimate (q_1^*) is required. Cancer risk is addressed through the selected toxicological reference values for cyromazine.		

[1] CAF (Composite assessment factor) refers to the total uncertainty and PCPA factors for dietary and residential risk assessment; MOE refers to the target margin of exposure for occupational or residential assessment.
[2] Since an oral NOAEL was selected, a dermal absorption factor (27%) was used for route-to-route extrapolation.
[3] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used for route-to-route extrapolation.

Table 2 Toxicology Profile for Cyromazine – Toxicokinetic and Metabolism Studies

Note: Effects noted below are known or assumed to occur in both sexes unless otherwise noted: in such cases, sex-specific effects are separated by semi-colons. Effects on organ weights are known or assumed to reflect changes in both absolute weight and relative (to body weight) weight, unless otherwise noted.

Toxicokinetic and Metabolism Studies	
Study/Species	**Results/Effects**
Absorption, Distribution, Metabolism, Elimination - Oral Gavage CD Rat PMRA# 1198578	Single oral dose of 0.5 mg/kg bw [^{14}C] triazine ring-labelled cyromazine. **Absorption:** Cyromazine was extensively absorbed (recovery of radioactivity was 97.8%) in both sexes within 72 hrs. **Distribution:** There were no sex-related differences in distribution. Cyromazine was detected in liver (0.007 ppm) while all other tissue levels were below the limit of detection 72 hrs after exposure. **Metabolism:** There were no apparent sex-related differences in metabolism. The unchanged parent compound (82.5% of the administered dose) and three unidentified metabolites were detected in urine after 24 hrs; these metabolites accounted for 3% to 5% of the radioactivity in urine. After 24 hrs, three unidentified metabolites were also detected in feces, and accounted for 0.1% to 4.1% of the administered dose; the unchanged parent in feces corresponded to <0.1% of the administered dose. **Elimination:** There were no significant sex-related differences in elimination; ♂ eliminated slightly more radioactivity in the feces than ♀. The majority of the administered radioactivity (94.7%) was eliminated in the urine within 24 hrs. The majority of the radioactivity in urine was identified as unchanged parent compound (80%); small amounts of three unidentified metabolites (3% to 5%) were also present in urine. In the first 24 hrs, a small amount of the administered dose was eliminated in the feces (0.6% in ♀ and 3.7% in ♂) and expired air (<0.1%) in both sexes.
Absorption, Distribution, Metabolism, Elimination - Oral Gavage	Repeated oral dose of 0 or 3 mg/kg bw/day [^{14}C] triazine ring-labelled cyromazine for 14 days. **Absorption:** Blood levels increased to a plateau of 0.016 µg/g within 9 days of exposure.

Toxicokinetic and Metabolism Studies	
Study/Species	**Results/Effects**
Hanlbm:WIST (SPF) Rat PMRA# 2337322	Twenty four hrs following the last exposure, blood levels declined with a $t_{1/2}$ in blood of 6.4 days. **Distribution:** The highest mean tissue residue levels during dosing and after the last exposure were detected in liver ($t_{1/2}$ = 3 days) and kidney ($t_{1/2}$ = 2.2) days, followed by whole blood, adrenal and thyroid. Levels in testes ($t_{1/2}$ = 2 days) and brain ($t_{1/2}$ = 2.2 days) were low during dosing and after the last exposure; levels in fat were generally below the limit of quantitation. All selected tissues and organs showed ↑ residue values during the dosing period, reaching peak levels 24 hrs after the last dose (with the exception of liver which reached a peak level of 0.08 ppm during the dosing period). At 24 hrs post-exposure, only 0.01% of the administered dose remained in tissues. **Metabolism:** The unchanged parent compound and smaller amounts of eight (unidentified) metabolites were detected in urine and feces. The metabolite patterns in urine and feces (investigated at three time intervals during dosing) were not qualitatively or quantitatively influenced by duration of dosing. **Elimination:** A steady-state for elimination was achieved within 24 hrs of the first exposure. Thereafter, the daily elimination remained constant until the end of dosing, accounting for ~90% and ~4% of the administered daily dose for urine and feces, respectively. The majority of the administered test substance was eliminated in urine (92.9%) as the unchanged parent, with small amounts eliminated in feces (4.2%).
Absorption, Distribution, Metabolism, Elimination - Oral Gavage Sprague Dawley Rat PMRA# 1161017	Single oral dose of 0, 3 or 300 mg/kg bw [^{14}C] triazine ring-labelled cyromazine, or repeated doses (0 or 3 mg/kg bw/day) of unlabelled cyromazine followed by a single dose of [^{14}C] triazine ring-labelled cyromazine at 3 mg/kg bw. **Absorption:** Extensive absorption was noted with all dosing regimens. Total eliminated radioactivity ranged from ~82% to 94% within seven days after the last dose. **Distribution:** Seven days after the last dose, tissue levels of radioactivity were generally low in both sexes. Measurable levels were recorded in carcass, liver and blood (RBC), with higher tissue levels noted in both sexes following a single high dose, compared to those noted following a single low dose or a preconditioned low dose. **Metabolism:** No sex- or dose-related differences in metabolic profiles were noted. Cyromazine (64% to 83% of radiolabel in urine; mean = 72%), melamine (4% to 10%; mean = 7%), hydroxycyromazine (6% to 14%; mean = 9%) and methylcyromazine (ND to 3%; mean = 2%) were identified in urine in both sexes. Similarly, cyromazine (65% to 77% of radiolabel in feces; mean = 71%) melamine (5% to 7%; mean = 6%), hydroxycyromazine and methylcyromazine and other minor metabolites (mean = 8%) were identified in feces. **Elimination:** No significant sex- or dose-related differences were noted in the elimination profiles. The majority of the administered radioactivity was elimination via urine within the first 24 hrs (78% to 90%). Peak fecal elimination was recorded at 24 hrs; total fecal elimination ranged from 2.7% to 7.5%, seven days after the last dose for all dosing regimens.

Toxicokinetic and Metabolism Studies	
Study/Species	**Results/Effects**
Metabolism, Elimination - Capsule Monkey PMRA# 1206558	Single oral dose of 0.05 or 0.5 mg/kg bw [^{14}C] triazine ring-labelled cyromazine. **Low Dose:** **Metabolism/Elimination:** The total mean recovery of radioactivity (urine and feces) was 75.8% and 78.8% in both sexes after 24 hrs and 96 hrs, respectively. There were no significant sex-related differences in metabolism or elimination. The majority of the recovered radioactivity was eliminated in urine (75.3%) within 24 hrs. In urine, more than 93% of the radioactivity was characterized as unchanged parent, and ~6% was melamine After 24 hrs, fecal elimination accounted for <1% of the recovered dose in both sexes. **High-Dose:** **Metabolism/Elimination:** The total mean recovery of radioactivity (urine and feces) was 66.1% and 69.5% in both sexes after 24 hrs and 96 hrs, respectively. There were no significant sex-related differences in metabolism or elimination. The majority of the recovered radioactivity was eliminated in urine (~97%) within 24 hrs. In urine, more than 93% of the radioactivity was characterized as unchanged parent and ~6% was melamine. After 24 hrs, fecal elimination accounted for ~3% of the recovered dose in both sexes.
Metabolism, Elimination - Capsule Monkey PMRA# 2337324	Single oral dose of 0.05 or 0.5 mg/kg bw [^{14}C] triazine ring-labelled cyromazine. **Supplemental** **Low Dose:** **Metabolism/Elimination:** Recovery was variable (based on the total recovery of administered radioactivity in urine and feces of 43% in ♂ and 77% in ♀) after 24 hrs. There were no significant sex-related differences in metabolism or elimination. In both sexes, the majority of the recovered radioactivity was eliminated in urine (32% to 49%) within 24 hrs. Fecal elimination accounted for ≤14% of the administered dose after 24 hrs in both sexes. In the urine of both sexes, 96% to 100% of the radioactivity was characterized as parent compound, and 0 to 4% was identified as melamine. **High-Dose:** **Metabolism/Elimination:** Recovery was variable (based on the total recovery in urine and feces of 77% in ♂ and 59% in ♀) after 24 hrs. There were no significant sex-related differences in metabolism or elimination. In both sexes, the majority of the recovered radioactivity was eliminated in urine (51% to 65%) within 24 hrs. Fecal elimination accounted for ≤0.2% of the administered dose after 24 hrs. In the urine of both sexes, 95% to 97% of the radioactivity was characterized as unchanged parent, and ~3% to 4% was identified as melamine.

Table 3 Toxicology Profile for Cyromazine – Acute Toxicity Studies

Note: Effects noted below are known or assumed to occur in both sexes unless otherwise noted: in such cases, sex-specific effects are separated by semi-colons. Effects on organ weights are known or assumed to reflect changes in both absolute weight and relative (to body weight) weight, unless otherwise noted

Acute Toxicity Studies	
Study/Species	**Results/Effects**
Acute Oral Toxicity - Gavage Tif:MAG Mouse PMRA# 1249111	LD_{50} = 2029 mg/kg bw (♂/♀) (in PEG) LD_{50} = 1348 mg/kg bw (♂) (in PEG) LD_{50} = 2924 mg/kg bw (♀) (in PEG) Clinical signs of toxicity (within 2 hrs) included sedation, dyspnea, curved position and ruffled fur. **Low acute oral toxicity**
Acute Oral Toxicity - Gavage Sprague-Dawley Rat PMRA# 2337312	LD_{50} = 3920 mg/kg bw (♂/♀) (in CMC) LD_{50} = 4050 mg/kg bw (♂) (in CMC) LD_{50} = 3530 mg/kg bw (♀) (in CMC) Clinical signs of toxicity included decreased activity, ataxia, constricted pupils, diarrhea, lacrimation, piloerection, polyuria, ptosis, salivation, sensitivity to touch and chromodacryorrhea. **Low acute oral toxicity**
Acute Oral Toxicity - Gavage Sprague-Dawley Rat PMRA# 2337313	LD_{50} > 2000 mg/kg bw (♀) (in CMC) Clinical signs of toxicity included hypoactivity, ano-genital staining and soft feces. Discoloration of the intestines was noted following gross necropsy. **Low acute oral toxicity**
Acute Oral Toxicity - Gavage Tif:RAIf Rat PMRA# 1249112	**Supplemental** LD_{50} = 3387 mg/kg bw (in PEG) Clinical signs of toxicity included sedation, dyspnoea, exophthalmos, curved position and ruffled fur. **Low acute oral toxicity**
Acute Oral Toxicity - Gavage Himalayan Rabbit PMRA# 1249113	LD_{50} = 1467 mg/kg bw (♂/♀) (in CMC) Clinical signs of toxicity included tremors, ataxia, salivation, ventral position, sedation, dyspnoea, exophthalmos, curved position and ruffled fur. **Low acute oral toxicity**
Acute Dermal Toxicity	LD_{50} > 3170 mg/kg bw (♂/♀) (in PEG)

Acute Toxicity Studies	
Study/Species	**Results/Effects**
Tif:RAIf Rat PMRA# 1249116	Clinical signs of toxicity included dyspnoea, curved position and ruffled fur. **Low acute dermal toxicity**
Acute Dermal Toxicity Sprague-Dawley Rat PMRA# 2337314	LD_{50} > 2000 mg/kg bw (♂/♀) (in distilled water) No adverse clinical signs. **Low acute dermal toxicity**
Acute Inhalation Toxicity - Nose-Only Sprague-Dawley Rat PMRA# 2337315	LC_{50} > 3.6 mg/L (♂/♀) **≥ 0.74 mg/L** (♂/♀)**:** ↓ activity, piloerection; discoloration of lungs (♂) **3.6 mg/L** (♂/♀): nasal discharge; ↓ bw (♀) **Low acute inhalation toxicity**
Eye Irritation New Zealand White Rabbit PMRA# 1249118	MAS (unwashed) = 14.7 MAS (washed) = 16.0 **Mildly irritating to the eye**
Dermal Irritation Himalayan Rabbit PMRA# 1249119	Very slight to well-defined erythema, and very slight to moderate oedema were noted at 24 hrs on abraded skin. No reaction to very slight erythema and oedema were noted at 24 hrs on intact skin. Mean Irritation Score = 1.1 **Mildly irritating to the skin**
Dermal Irritation New Zealand White Rabbit PMRA# 2337317	Very slight erythema was noted 1 h after patch removal. All animals were free from dermal irritation within 24 hrs. Mean Irritation Score = 0.3 **Non-irritating to the skin**

Acute Toxicity Studies	
Study/Species	**Results/Effects**
Dermal Sensitization - Maximization Test Himalayan Spotted Guinea-Pig PMRA# 2337318	Negative **Not a dermal sensitizer**

Table 4 Toxicology Profile for Cyromazine – Subchronic Toxicity Studies

Note: Effects noted below are known or assumed to occur in both sexes unless otherwise noted: in such cases, sex-specific effects are separated by semi-colons. Effects on organ weights are known or assumed to reflect changes in both absolute weight and relative (to body weight) weight, unless otherwise noted.

Subchronic Toxicity Studies	
Study/Species	**Results/Effects**
7-Week Oral Toxicity - Diet CD-1 Mouse PMRA# 1198576	**Supplemental (range-finding study)** **≥ 56 mg/kg bw/day (♂):** ↓ fc, ↓ bw at wk 7 **≥ 200 mg/kg bw/day (♀):** ↓ fc **1358/2442 mg/kg bw/ (♂/♀):** mortality; clinical signs of toxicity (tremors, cold to touch, yellow material in anogenital region and ventral abdomen "bluish") (♂); ↓ bw at wk 7 (♀)
13-Week Oral Toxicity - Diet Sprague-Dawley Rat PMRA# 1249123 PMRA# 1157647	**NOAEL = 79/88 mg/kg bw/day (♂/♀)** **LOAEL = 232/264 mg/kg bw/day (♂/♀)** based on ↓ bw throughout treatment, ↑ ALT; ↓ kidney wt, ↑ brain wt (♂); mortality in 1♀ (wk 3), ↓ ovary wt, ↓ erythrocytes, ↓ Hgb, ↓ Hct (♀) 4-Wk Recovery**:** **264 mg/kg bw/day** (♀): ↓ bw in ♀
13-Week Oral Toxicity - Diet Beagle Dog PMRA# 1198216	**NOAEL = 36 mg/kg bw/day (♂/♀)** **LOAEL = 99.7/95.5 mg/kg bw/day (♂/♀)** based on ↓ fc, ↓ Hct, ↓ Hgb, ↓ leucocytes, ↓ erythrocytes, ↓ cholesterol; ↑ liver wt, ↓ testes wt, diffuse degeneration of the testes (♂) 4-Wk Recovery **99.7 mg/kg bw/day (♂):** ↓ bw, ↓ testes wt
6-Month Oral Toxicity - Diet Beagle Dog PMRA# 1198217	**NOAEL = 0.9 mg/kg bw/day (♀); 9.3 mg/kg bw/day (♂)** **LOAEL = 8.9 mg/kg bw/day (♀)** based on marginal ↓ bw, ↓ bwg, swollen mammary gland (wk 12) and swollen nipples (wk 13) in 1♀**,** ↓ Hct **92.3/91 mg/kg bw/day (♂/♀)**: ↓ RBC count, ↓ Ca; ↓ Hgb, ↓ serum cholesterol, ↑ AST, ↓ bw throughout treatment, ↓ fc, ↑ brain wt, ↓ thyroid wt, ↓ testes wt, mortality in 1♂ (septicemia), ataxia in ♂, ↑ platelet counts, ↓ Hct (♂); ↓ RBC, ↓ Hgb, ↑ liver wt, ↑ kidney

Subchronic Toxicity Studies	
Study/Species	**Results/Effects**
	wt, ↑ heart wt, ↑ ovary wt, nodules on nipple in 1♀**,** tremors in 1♀**,** ectopic adrenal tissue (♀) 4-Wk Recovery **92.3/91 mg/kg bw/day (**♂/♀**):** ↓ testes wt; ↑ ovary wt
1-Year Oral Toxicity - Diet Beagle Dog PMRA# 2337319	**NOAEL = 5.7/6.0 mg/kg bw/day (**♂/♀) based on ↑ plasma protein, ↑ globulin, ↓ albumin:globulin ratio (♂); dose-related ↑ ovary wt (♀); not considered adverse **LOAEL = 22.8 mg/kg bw/day (**♂**)** based on ↑ abs kidney wt, microcytic anemia, ↑ platelet counts, ↑ rel heart wt (♂); ↑ heart wt, ↑ liver wt, ↑ plasma protein, ↑ globulin, ↓albumin:globulin ratio, ↑ rel brain wt, ↑ rel kidney wt (♀) **93.7/110 mg/kg bw/day (**♂/♀**):** vomiting, hypochromic and microcytic anemia (↓ Hgb,↓ Hct, ↓ MCV, ↓ MCH, ↓ RBC), hard myocardium, severe chronic myocarditis of right atrium, focal chronic tubular lesions in kidney, hypercellularity of bone marrow; ↓ testes wt, ↑ abs heart wt, ↑ liver wt, ↓ triglycerides, ↓ creatine kinase activity, foci of cartilaginous metaplasia in right atrium of the heart (♂); mortality in 1 animal (with degeneration and necrosis in kidney and liver), microcytic anemia, ↓ fc, ↓ bwg, moderate ovarian atrophy in 1♀, ↑ plasma chloride, ↑ ALP, ↑ ALT, ↑ γ-glutamyl transpeptidase (GGT) in 1♀, ↑ abs kidney wt (♀) Note: non-dose related ↑ mammary secretory activity (minimal to slight) was noted in ♀ at ≥1.5 mg/kg bw/day
21-Day Dermal Toxicity New Zealand White Rabbit PMRA# 1141037	**NOAEL ≥ 2000 mg/kg bw/day (**♂/♀**)** based on lack of treatment-related effects at the limit dose

Subchronic Toxicity Studies	
Study/Species	**Results/Effects**
28-Day Inhalation Toxicity - Nose Only Tif:RAIf Rat PMRA# 1141038	**NOAEC not established** **LOAEC = 0.055 mg/L (11 mg/kg bw/day) (♂/♀)** based on piloerection, dyspnea, hunched posture, ↓ spontaneous activity (moderate and severe at mid- and high-dose, respectively); ↓ bw (starting wk 3), ↓ bwg, ↓fc, ↓ abs prostate wt, ↓ abs pituitary wt (♂); ↓ abs thymus wt (♀) **≥ 0.21 mg/L** (♀): ↑ liver wt **0.71 mg/L** (♂/♀): ↑ cholesterol; ↑ RBC count, ↑ Hgb, ↑ Hct, ↑ leucocyte count (♂); lymphocyte infiltration of adrenal cortex, ↑ ALP (♀) 3-Wk Recovery: **710 mg/m^3** (♂/♀): piloerection, dyspnea and hunched posture in all animals; lymphocyte infiltration of adrenal cortex, ↑ abs adrenal wt, ↓ abs uterine wt (♀)

Table 5 Toxicology Profile for Cyromazine – Neurotoxicity Studies

Note: Effects noted below are known or assumed to occur in both sexes unless otherwise noted: in such cases, sex-specific effects are separated by semi-colons. Effects on organ weights are known or assumed to reflect changes in both absolute weight and relative (to body weight) weight, unless otherwise noted.

Neurotoxicity Studies	
Study/Species	**Results/Effects**
Acute Oral Neurotoxicity - Gavage Sprague-Dawley Rat PMRA# 2337328	**Supplemental (range-finding study)** **≥ 500 mg/kg bw** (♂/♀)**:** ↓ mean bwg, ↓ fc **≥ 1000 mg/kg bw** (♂)**:** ↓ bw **2000 mg/kg bw** (♀)**:** ↓ bw
Acute Oral Neurotoxicity - Gavage Sprague-Dawley Rat FOB Locomotor Activity (LMA) PMRA# 2337327	**NOAEL not established (♂); 250 mg/kg bw (♀)** **LOAEL = 250 mg/kg bw (♂)** based on ↓ fc, dose-related ↓ cumulative ambulatory LMA counts at 3 hrs post-dosing on day 0 **≥ 1000 mg/kg bw** (♂/♀)**:** ↓ bw, ↓ cumulative total LMA counts 3 hrs post-dosing (♂); ↓ bwg (days 0 to 1), ↓ fc, dose-related ↓ mean cumulative ambulatory LMA counts 3 hrs post-dosing on day 0 (♀) **2000 mg/kg bw** (♂/♀)**:** bw loss, ↓ body temperature, red staining around nose, ↓ hind limb footsplay (♂); ↓ defecation, small feces, bw loss (♀)

Table 6 Toxicology Profile for Cyromazine – Chronic Toxicity/Carcinogenicity Studies

Note: Effects noted below are known or assumed to occur in both sexes unless otherwise noted: in such cases, sex-specific effects are separated by semi-colons. Effects on organ weights are known or assumed to reflect changes in both absolute weight and relative (to body weight) weight, unless otherwise noted.

Chronic Toxicity/Carcinogenicity Studies	
Study/Species	**Results/Effects**
2-Year Chronic Toxicity/Carcinogenicity - Diet CD-1 Mouse PMRA# 1198577 PMRA# 1157656 PMRA# 1141042 PMRA# 1158528 PMRA# 2722216 PMRA# 2722219	**NOAEL = 6.5 mg/kg bw/day (♂); 164 mg/kg bw/day (♀)** **LOAEL = 126 mg/kg bw/day (♂)** based on ↓ bw, ↑ incidence of testicular atrophy at termination **384/476 mg/kg bw/day (♂/♀):** ↑ rel liver wt, ↑ incidence of focal adenomatous hyperplasia of the lungs at termination; ↑ rel heart wt (♂); ↓ survival in last 4 wks of study, enlarged lymph nodes at termination, ↓ abs kidney wt, ↑ incidence of cystic ovarian follicle at termination, ↑ incidence of cystic hyperplasia of the mammary gland at termination (♀) **Neoplastic Effects** **Mammary Gland Adenocarcinoma (Re-read)** Incidence in ♀ (decedents and terminal sacrifice) at 0, 8.2, 164 or 476 mg/kg bw/day was 2/49 (4%), 4/48 (8%), 3/53 (6%) or 6/50 (12%). [HC mean = 1.3%; range = 0 to 5%] **Combined Mammary Gland Adenocarcinoma/Adenoacanthomas (Re-read)** Incidence in ♀ (decedents and terminal sacrifice) at 0, 8.2, 164 or 476 mg/kg bw/day was 4/49 (8%), 5/48 (10%), 3/53 (6%) or 7/50 (14%). [Historical control data were NA]. **Equivocal evidence of mammary gland tumours in ♀ mice**
2-Year Chronic Toxicity/Carcinogenicity Study - Diet Charles River CD Rat PMRA# 1198218 PMRA# 1141040 PMRA# 1141039 PMRA# 1158528 PMRA# 2722228 PMRA# 2722229	**The MTD was exceeded at the high-dose in both sexes.** **NOAEL = 1.4 mg/kg bw/day (♀); 14.7 mg/kg bw/day (♂)** **LOAEL = 18.8 mg/kg bw/day (♀)** based on ↓ bw, ↑ incidence of cystic hyperplasia of mammary gland, ↑ incidence of cystic uterine endometrium **≥ 157/210 mg/kg bw/day (♂/♀):** ↓ fc, ↓ bw throughout treatment, ↓ abs heart wt at termination and recovery, ↑ rel brain wt at interim, termination and recovery (♂ only), ↑ liver wt, ↓ abs kidney wt at termination and recovery (♀ only), bronchiectasis; ↑ incidence of pigment in spleen, ↑ renal pyelitis, ↑ rel testes wt at interim, termination and recovery (♂); ↑ incidence of distended uterus, ↑ incidence of mammary galactocele (milk cysts), ↑ incidence of renal pelvic epithelial hyperplasia, ↑ lung congestion, ↑ incidence of thymic cysts, ↑ incidence of bile duct proliferation, ↑ rel kidney wt (♀) **Neoplastic Effects:** **Mammary Gland Adenoma (Re-read data for ♀ only)** The incidence in ♀ (decedents and terminal sacrifice) receiving 0, 1.8, 18.8 or 210 mg/kg bw/day was: 3/53 (6%), 4/58 (7%), 1/58 (2%) or 5/59 (8%), respectively (USEPA, 1995). [HC mean (♀) = 4.9%; range = 0 to 21.7%] The incidence in ♂ (decedents and terminal) receiving 0, 1.4, 14.7 or 157 mg/kg bw/day was: 0/56 (0), 0/46 (0), 0/43 (0) or 1/55 (2%), respectively.

Chronic Toxicity/Carcinogenicity Studies	
Study/Species	**Results/Effects**
	[HC mean (♂) = 0.3%; range = 0 to 3.3%] **Mammary Gland Adenocarcinoma (Re-read data)** The incidence in ♀ (decedents and terminal sacrifice) receiving 0, 1.8, 18.8 or 210 mg/kg bw/day was: 6/53 (11%), 8/58 (14%), 6/58 (10%) or 12/59 (20%); marginally-positive trend test (p= 0.057) [HC "mammary carcinoma" mean (♀) = 9.5%; range = 1.5% to 21.4%] **Combined Mammary Gland Adenoma/Adenocarcinoma (Original data)** The incidence (decedents and terminal sacrifice) in ♀ at 0, 1.8, 18.8 or 210 mg/kg bw/day was 6/53 (11%), 10/58 (17%), 7/58 (12%) or 17/59 (28.8%, p = 0.019); positive trend test (p= 0.005) [HC mean (♀) = 15.3%; range = 0 to 21.7%] The incidence (decedents and terminal sacrifice) in ♂ receiving 0, 1.4, 14.7 or 157 mg/kg bw/day was: 0/56 (0), 0/46 (0), 2/43 (5%) or 1/55 (2%). [HC data for combined tumours in ♂ NA] **Testicular Interstitial Cell Tumours (Original data)** The incidence in ♂ (decedents and terminal sacrifice) receiving 0, 1.4, 14.7 or 157 mg/kg bw/day was 1/60 (2%), 2/59 (3%), 1/58 (2%) or 6/57 (10.5%, p = 0.049); positive test for trend (p= 0.004) [HC mean = 7.7%; range = 0 to 22%] **Evidence of mammary gland tumours in ♀ rats at dose exceeding MTD.** **Equivocal evidence of mammary gland and testicular tumours in ♂ rats at dose exceeding the MTD.**

Table 7 Toxicology Profile for Cyromazine – Developmental/Reproductive Toxicity Studies

Note: Effects noted below are known or assumed to occur in both sexes unless otherwise noted: in such cases, sex-specific effects are separated by semi-colons. Effects on organ weights are known or assumed to reflect changes in both absolute weight and relative (to body weight) weight, unless otherwise noted.

Developmental/Reproductive Toxicity Studies	
Study/Species	**Results/Effects**
2-Generation Reproductive Toxicity Study - Diet Sprague-Dawley Rat (one litter/generation) PMRA# 1198220 PMRA# 1198575	Parental Toxicity **Parental NOAEL = 1.6 mg/kg bw/day (♂/♀)** **Parental LOAEL = 51 mg/kg bw/day (♂/♀)** based on ↓ fc in F0, ↓ bw in F0; ↓ abs liver wt in F0 (♂); ↓ liver wt in F1 (♀) **169 mg/kg bw/day (♂):** ↓ bw in F1♂, ↑ F0/F1 rel testes wt, ↓ abs liver wt in F1 (♂) Reproductive Toxicity **Reproductive NOAEL = 51 mg/kg bw/day (♂/♀)**

Developmental/Reproductive Toxicity Studies	
Study/Species	**Results/Effects**
PMRA# 1157649	**Reproductive LOAEL = 169 mg/kg bw/day (♂/♀)** based on ↓ fertility in F0♂, ↓ copulation in F1♂, slight ↓ F2 pup survival index at birth, ↓ mean F1/F2 pup bw at birth Offspring Toxicity **Offspring NOAEL not established** **Offspring LOAEL = 1.6 mg/kg bw/day (♂/♀):** only 1 eye present in F1/F2 pups [0 in controls, 2 F1 pups ♂/♀ at low-dose, 1 F2♂ pup at mid-dose, 1 F2♂ pup at high-dose (assumed to be anophthalmia or cyclopia)] **≥ 51 mg/kg bw/day (♂/♀):** marginal ↓ F1 bw on PND 21, marginal ↓ F2 bw on PND 4 and PND 7; ↑ F1 rel testes wt (♂) **169 mg/kg bw/day (♂/♀):** ↓ abs kidney wt in F1/F2, ↓ F1 pup survival index on PND 4, ↓ mean pup bw in F1/F2 up to PND 21, lung nodules in F1**,** ↓ F2 abs brain wt; ↓ abs brain wt in F1♀, ↑ rel heart wt in F1♀ (♀) **Equivocal evidence of malformations in the absence of maternal toxicity.**
Developmental Toxicity - Gavage Sprague-Dawley Rat PMRA# 1198586	**Supplemental (range-finding study)** Maternal Toxicity: **≥ 600 mg/kg bw/day:** ↓ bw, oral discharge, matting of haircoat around mouth **≥ 1000 mg/kg bw/day**: matting and staining of abdominal/anogenital haircoat **≥ 1500 mg/kg bw/day:** mortality **2500 mg/kg bw/day:** 100% mortality Developmental Toxicity: **≥ 1500 mg/kg bw/day:** ↓ viable fetuses (note: 1 animal with low number of implants skewed the data for number of viable fetuses), ↑ late resorptions, ↑ post-implantation loss/dam
Developmental Toxicity - Gavage Sprague-Dawley Rat PMRA# 1198597 PMRA# 1157650	Maternal Toxicity **Maternal NOAEL = 100 mg/kg bw/day** **Maternal LOAEL = 300 mg/kg bw/day** based on bw loss GD 6 to 9, ↓ bw on GD 20, red nasal discharge, matting and staining of anogenital haircoat **600 mg/kg bw/day:** ↓ bw, ↑ activity Developmental Toxicity **Developmental NOAEL = 300 mg/kg bw/day** **Developmental LOAEL = 600 mg/kg bw/day** based on ↓ mean fetal bw, ↑ fetal and litter incidences of total malformations, ↑ fetal and litter incidences of omphalocele, ↑ litter incidence of ↓ skull ossification, ↑ fetal and litter incidences of unossified sternebrae #5 and/or sternebrae #6, ↑ fetal and litter incidences of "other sternebrae unossified"

Developmental/Reproductive Toxicity Studies	
Study/Species	**Results/Effects**
	Evidence of malformations in the presence of maternal toxicity.
Developmental Toxicity - Gavage Dutch Belted Rabbit (Langshaw colony) PMRA# 1198608	**Supplemental (range-finding study)** Maternal Toxicity **≥ 50 mg/kg bw/day:** ↓ bw throughout gestation **≥ 150 mg/kg bw/day:** bw loss, mortality **≥ 300 mg/kg bw/day:** matting of haircoat in anogenital and nose areas Developmental Toxicity **≥ 50 mg/kg bw/day:** ↓ implantations **≥ 150 mg/kg bw/day:** ↓ viable fetuses (due to excessive maternal mortality) and ↓ implantations **≥ 300 mg/kg bw/day:** no viable fetuses (due to mortality in 4/5 dams, and resorption of entire litter in 1 dam)
Developmental Toxicity - Gavage Dutch Belted Rabbit (Langshaw colony) PMRA# 1198619 PMRA# 1157651 PMRA# 1157652 PMRA# 1157654	**Experiment 1 (Supplemental):** Maternal Toxicity **≥ 25 mg/kg bw/day:** ↑ pre-implantation loss, pitted kidney, lung congestion **≥ 50 mg/kg bw/day:** ↓ bw GD 18 to 28, ↑ abortions **75 mg/kg bw/day:** ↑ mortality, slight ↓ number of dams with viable fetuses, ↓ number of viable fetuses/dam, ↑ post-implantation loss/dam, "ovary replaced by firm black to tan masses" in 1 dam Developmental Toxicity **≥ 50 mg/kg bw/day:** ↑ fetal and litter incidences of unossified sternebrae #5 and/or sternebrae #6 **75 mg/kg bw/day**: ↑ fetal and litter incidences of total malformations, ↑ fetal and litter incidences of external malformations, ↑ fetal and litter incidences of ↓ skeletal ossification, fetal anasarca (massive edema of the head and neck) in 2 fetuses from 1 litter **Experiment 2**: Maternal Toxicity **Maternal NOAEL = 10 mg/kg bw/day** **Maternal LOAEL = 30 mg mg/kg bw/day** based on bw loss GD 6 to 28, ↓ bw GD 18-28, ↑ abortions **60 mg/kg bw/day:** mortality, lung congestion/foci, ↑ number of early resorptions, ↑ post-implantation loss/dam Developmental Toxicity **Developmental NOAEL not established**

Developmental/Reproductive Toxicity Studies	
Study/Species	**Results/Effects**
	Developmental LOAEL = 10 mg/kg bw/day based on ↓ mean fetal bw, ↑ fetal and litter incidences of total malformations **≥ 30 mg/kg bw/day:** fetal anasarca in 1 fetus (not observed at 60 mg/kg bw/day) **60 mg/kg bw/day:** ↑ fetal and litter incidences of hydrocephaly with dome-shaped head, ↑ fetal and litter incidences of fused sternebrae, ↑ fetal and litter incidences of skull anomaly (premaxillae, nasals and jugals malformed/small, bilateral), ↑ fetal and litter incidences of omphalocele **Evidence of malformations in the absence of maternal toxicity.** **Evidence of sensitivity of the young.**
Developmental Toxicity - Gavage Dutch Belted Rabbit (Langshaw colony) PMRA# 1203328	**Supplemental (enteric disease)** Maternal Toxicity **≥ 10 mg/kg bw/day:** mortality (suspected enteric disease), lung congestion, abortion **≥ 30 mg/kg bw/day:** wt loss, ocular discharge, ↑ post-implantation loss, ↑ post-implantation loss/dam, premature delivery **60 mg/kg bw/day:** diarrhea, soft stools, ↓ feces, ↓ bw, ↓ fc throughout gestation Developmental Toxicity **60 mg/kg bw/day:** ↑ litter incidence of variations, ↑ fetal and litter incidences of Hyoid arches bent, 1 fetus with thoracogastroschisis, malpositioned heart and sternoschisis (cleft sternum)
Developmental Toxicity - Gavage New Zealand White Rabbit (Buckshire colony) BUK(CRL)NZWfBR PMRA# 1247972 PMRA# 1203326 PMRA# 1247973 PMRA# 2722230 PMRA# 2723045 PMRA# 2722768	Maternal Toxicity **Maternal NOAEL = 30 mg/kg bw/day** **≥ 30 mg/kg bw/day:** ↓ bwg GD 7 to 20, ↓ fc GD 7 to 20, ↓ defecation and urination; not toxicologically significant **Maternal LOAEL = 60 mg/kg bw/day** based on ↓ bw (GD 14 to 20), ↑ mean number of late resorptions, abortion, ↑ mean number of early resorptions, ↑ mean number of post-implantation losses Developmental Toxicity **Developmental NOAEL = 5 mg/kg bw/day** **Developmental LOAEL = 10 mg/kg bw/day** based on ↑ fetal and litter incidences of external malformations, ↑ fetal and litter incidences of soft tissue malformations, ↑ fetal and litter incidences of cyclopia with multiple head malformations [including cyclopia with proboscis, otocephaly (agnathia/no oral opening with pinnae malpositioned/located more ventrally than normal) and exencephaly]; ↑ fetal and litter incidences of hydrocephaly, ↑ fetal and litter incidences of diaphragmatic hernia **≥ 30 mg/kg bw/day:** ↑ fetal and litter incidences of umbilical hernia, ↑ fetal and litter incidences of total malformations; malformations were noted in 6 litters including: litter 1 (1 fetus with skull anomaly and hydrocephaly and another fetus with spina bifida, umbilical hernia, cyclopia and multiple head anomalies comprised of eyes fused and located in a single socket, proboscis, exencephaly and nares absent), litter 2 (1 fetus with micrognathia/maxilla and hydrocephaly), litter 3 (1 fetus with rib anomaly and

Developmental/Reproductive Toxicity Studies	
Study/Species	**Results/Effects**
	diaphragmatic hernia, and another fetus with diaphragmatic hernia), litter 4 (separate incidences of vertebral anomaly, diaphragmatic hernia, kidney and ureter anomaly), litters 5 and 6 (each with 1 fetus with vertebral anomaly) **60 mg/kg bw/day:** ↑ fetal and litter incidences of open eyelid, ↑ fetal and litter incidences of fused sternebrae, ↑ fetal and litter incidences of vertebral anomaly, ↑ fetal and litter incidences of rib anomaly**,** ↑ fetal and litter incidences of externally apparent skull anomaly (small nostrils and cleft palate), ↑ fetal and litter incidences of accessory skull bones in the parietal or nasal sutures, ↑ fetal and litter incidences of 13th rudimentary rib(s) **Evidence of malformations in the absence of maternal toxicity.** **Evidence of sensitivity of the young.**
Teratology/ Post-Natal Toxicity Study - Gavage New Zealand White Rabbit (Dutchland colony) Hra(NZW)SPF PMRA# 1203327 PMRA# 1146409 PMRA# 2723045	Maternal Toxicity **Maternal NOAEL = 10 mg/kg bw/day** **Maternal LOAEL = 30 mg/kg bw/day** based on ↓ fc during treatment**,** slight ↓ bw (GD 20 only), bw loss during treatment (primarily GD 7 to 10 and GD 10 to 14), ↓ urination and ↓ defecation during treatment Reproductive Toxicity No treatment-related effects. Developmental Toxicity **Developmental NOAEL not established** **Developmental LOAEL = 5 mg/kg bw/day** based on ↑ fetal and litter incidences of external malformations, microphthalmia/anophthalmia in 1 fetus **≥ 10 mg/kg bw/day:** ↑ fetal and litter incidences of soft tissue malformations, ↑ fetal and litter incidences of diaphragmatic hernia, agnathia and macroglossia in 1 fetus **30 mg/kg bw/day:** pinnae misplaced/small or absent in 1 fetus Offspring Toxicity **Offspring NOAEL = 10 mg/kg bw/day** **Offspring LOAEL = 30 mg/kg bw/day** based on ↑ kit and litter incidences of external malformations PND 0 to 4, ↑ kit and litter incidences of soft tissue malformations, 1 kit found dead PND 0 to 4 had cyclopia, cleft palate and omphalocele **Evidence of malformations in the absence of maternal toxicity.** **Evidence of sensitivity of the young.**
Study of Malformations in the NZW Rabbit Buckshire Colony Control Population BUK: (CRL)NZWfBR Rabbit Special investigation of: 1) the possible genetic origin of severe craniofacial malformations	**Supplemental (Special Study)** There were no differences in the incidences of variations or malformations between groups sired by Buck #2749, and those sired by other bucks. Even when only craniofacial defects were considered, the incidences in groups sired by Buck #2749 were similar to all comparison groups. No fetuses with cyclopia or diaphragmatic hernia were observed in control fetuses sired by Buck #2749 in this study. Although 1 control fetus in Group 2 sired by an alternate buck (not gavaged) revealed diaphragmatic hernia [resulting in a fetal incidence of 1/233 (0.4%)

Developmental/Reproductive Toxicity Studies	
Study/Species	**Results/Effects**
involving Buck 2749; 2) the background incidence of spontaneous malformations in the NZW rabbit Buckshire colony and; 3) effects of gavage-induced stress on fetal malformations. PMRA# 1203325	and litter incidence of 1/39 (2.6%)], these incidences are considerably lower than those noted in the cyromazine Buckshire study (PMRA# 1247972), in which rabbits were treated with up to 30 mg/kg bw/day cyromazine (in other words, 2.2% to 4.2% fetal incidence; 14.3% to 20% litter incidence). The data do not suggest a relationship between buck #2749 and the occurrence of fetuses with more than 1 malformation in previous studies. In addition, the data suggest that gavage treatment has no significant effect on the spontaneous malformation rate in this strain.

Table 8 Toxicology Profile for Cyromazine – In Vitro Genotoxicity Studies

Note: Effects noted below are known or assumed to occur in both sexes unless otherwise noted: in such cases, sex-specific effects are separated by semi-colons. Effects on organ weights are known or assumed to reflect changes in both absolute weight and relative (to body weight) weight, unless otherwise noted.

In Vitro Genotoxicity Studies	
Study/Species	**Results/Effects**
Reverse Mutation Salmonella typhimurium strains: TA98, TA100, TA1535, TA1537, TA1538 E. coli WP2 uvrA PMRA# 2337320 PMRA# 1165104	Negative, with or without metabolic activation
Reverse Mutation Salmonella typhimurium strains: TA98, TA100, TA1535 and TA1537 PMRA# 1198630	Negative, with or without metabolic activation
Gene Mutation, Mitotic Gene Conversion and Recombination S. cerevisiae D7 PMRA # 1165105	Negative, with or without metabolic activation
Forward Mutation L5178Y $TK^{+/-}$ Mouse Lymphoma Cells PMRA# 2337321	Negative, with or without metabolic activation

In Vitro Genotoxicity Studies	
Study/Species	**Results/Effects**
Forward Mutation L5178Y TK$^{+/-}$ Mouse Lymphoma Cells PMRA # 1165102	Negative, with or without metabolic activation
Point Mutation Assay V79 Chinese Hamster Embryonic Lung Cells PMRA # 1165101	Negative, with or without metabolic activation
DNA Damage CD-1 Mouse Hepatocytes (Adult ♂) PMRA# 1198633	Negative
Unscheduled DNA Synthesis CD-1 Mouse Hepatocytes PMRA# 1198633	Negative
Unscheduled DNA Synthesis F344 Rat Hepatocytes (♂) PMRA# 1165098	**Supplemental** Negative
Chromosomal Aberrations Human Peripheral Lymphocytes PMRA# 1165103	**Supplemental** Negative, with or without metabolic activation

Table 9 Toxicology Profile for Cyromazine – In Vivo Genotoxicity Studies

Note: Effects noted below are known or assumed to occur in both sexes unless otherwise noted: in such cases, sex-specific effects are separated by semi-colons. Effects on organ weights are known or assumed to reflect changes in both absolute weight and relative (to body weight) weight, unless otherwise noted.

In Vivo Genotoxicity Studies	
Study/Species	**Results/Effects**
Dominant Lethal Assay - Gavage Tif:MAGF (SPF) Mouse	**Supplemental** Negative

In Vivo Genotoxicity Studies	
Study/Species	**Results/Effects**
PMRA# 1198631	**678 mg/kg bw:** mortality in 3/20 ♂ within 24 hrs of dosing
Micronucleus Test - Gavage Tif:MAGF (SPF) Mouse Bone Marrow Cells PMRA # 1165097	Negative **1080 mg/kg bw:** mortality in 1♂ within 72 hrs (time of death was not specified)
Nucleus Anomalies - Gavage Chinese Hamster Bone Marrow Cells PMRA# 1198632	**Supplemental** Negative
Spot Test - Intraperitoneal Injection C57B1/6 ♀ Mouse T-Stock ♂ Mouse PMRA # 1165100	**Supplemental** Inconclusive Dose-related statistically-significant ↑ frequency of recessive spots, relative to concurrent controls, but not historical controls. The data were considered inconclusive since interpretation was confounded by the lack of positive controls, and reduced reproductive performance at the highest dose level resulting in a smaller number of observations. **≥ 300 mg/kg bw:** marked ↓ pup survival, ↑ incidence of pigmented and white recessive spots, ↑ white mid-ventral spots **600 mg/kg bw**: ↓ number of pregnant ♀, ↓ number of litters, ↓ mean litter size, ↑ pigmented and white recessive spots, ↑ white mid-ventral spots

Appendix IV Dietary Exposure and Risk Estimates for Cyromazine

Table 1 Acute Dietary Exposure and Risk from Cyromazine

Population Group	Cyromazine Acute Food Only		Cyromazine Acute Food and Water	
	Exposure (mg/kg bw/day)[1]	% ARfD[2]	Exposure (mg/kg bw/day)[1]	% ARfD[2]
General Population	-	-	-	-
All Infants	0.0034	3%	0.0069	7%
Children 1–2 Years	0.0071	7%	0.0081	8%
Children 3–5 Years	0.0063	6%	0.0071	7%
Children 6–12 Years	0.0036	4%	0.0043	4%
Male 13–19 years	0.0025	3%	0.0032	3%
Male 20–49 Years	0.0036	4%	0.0043	4%
Adults 50–99 Years	0.0029	3%	0.0037	4%
Female 13–49 Years	0.0030	59%	0.0039	78%

[1] Acute exposure reported at the 95th percentile.

[2] ARfD = 0.1 mg/kg bw (population groups excluding females 13–49); ARfD = 0.005 mg/kg bw for females 13–49.

Table 2 Acute Dietary Exposure and Risk from Melamine via Cyromazine Use

Population Group	Melamine Acute Food Only		Melamine Acute Food and Water	
	Exposure (mg/kg bw/day)[1]	% TDI[2]	Exposure (mg/kg bw/day)[1]	% TDI[2]
General Population	0.024	12%	0.027	14%
All Infants	0.020	10%	0.030	15%
Children 1–2 Years	0.031	15%	0.035	18%
Children 3–5 Years	0.031	15%	0.034	17%
Children 6–12 Years	0.022	11%	0.025	12%
Youth 13–19 years	0.019	10%	0.022	11%
Adults 20–49 Years	0.024	12%	0.027	13%
Adults 50–99 Years	0.024	12%	0.027	14%
Female 13–49 Years	0.025	12%	0.028	14%

[1] Acute exposure reported at the 95th percentile.

[2] TDI = 0.2 mg/kg bw (All population groups).

Table 3 Chronic Dietary Exposure and Risk from Cyromazine

Population Group	Cyromazine Chronic Food Only		Cyromazine Chronic Food and Water	
	Exposure (mg/kg bw/day)	% ADI[1]	Exposure (mg/kg bw/day)	% ADI[1]
General Population	-	-	-	-
All Infants	0.0007	5%	0.0025	18%
Children 1–2 Years	0.0019	14%	0.0026	19%
Children 3–5 Years	0.0015	10%	0.0020	14%
Children 6–12 Years	0.0012	9%	0.0016	12%
Male 13–19 years	0.0008	6%	0.0011	8%
Male 20–49 Years	0.0011	8%	0.0015	11%
Adults 50–99 Years	0.0014	10%	0.0019	13%
Female 13–49 Years	0.0010	20%	0.0015	30%

[1] ADI = 0.014 mg/kg bw/day (population groups excluding females 13–49); ADI = 0.005 mg/kg bw/day for females 13–49

Table 4 Chronic Dietary Exposure and Risk from Melamine via Cyromazine Use

Population Group	Melamine Chronic Food Only		Melamine Chronic Food and Water	
	Exposure (mg/kg bw/day)	% TDI	Exposure (mg/kg bw/day)	%TDI
General Population	0.0070	4%	0.0095	4%
All Infants	0.0045	2%	0.0137	7%
Children 1–2 Years	0.0104	5%	0.0138	7%
Children 3–5 Years	0.0096	5%	0.0124	6%
Children 6–12 Years	0.0068	3%	0.0089	5%
Adults 13–19 years	0.0052	3%	0.0070	4%
Adults 20–49 Years	0.0068	3%	0.0093	5%
Adults 50–99 Years	0.0074	4%	0.0098	5%
Female 13–49 Years	0.0069	3%	0.0093	5%

[1] TDI = 0.2 mg/kg bw/day (All population groups).

Appendix V Food Residue Chemistry Summary

Cyromazine is an insecticide and larvicide that interferes with the moulting and pupation stage of insects. It is currently registered for ground application on various vegetables and ornamentals in Canada. Onion seeds treated with cyromazine outside of Canada can also be imported for use in Eastern Canada.

The nature of the residue in plant commodities is understood based on metabolism studies for celery, head lettuce, and tomatoes. The major metabolic pathway observed in test crops is the conversion of cyromazine to melamine via cleavage of the cyclopropyl group. The residue definition in plant commodities for enforcement and risk assessment purposes is cyromazine and melamine.

The nature of the residue in animal commodities is understood based on metabolism and magnitude of residue studies for goats, sheep, and hens. Cyromazine equivalent residues were mostly excreted in the test animals when fed with ^{14}C-cyromazine in the diet. Of the remaining residues: the highest concentrations were found in the liver, kidney, and eggs (of hens) with lower concentrations observed in other tissues and milk. Cyromazine was the major residue found in excrements and most tissues. Melamine was found intermittently at significant levels (>10% of the total radio-labelled residue) in excrements and tissues. N-methyl-cyromazine was also found at high levels in the liver and excrements of goats but was not observed in other test species. The residue definition for risk assessment purposes is the parent cyromazine. The definition is based on data from both metabolism and magnitude of residue studies (refer to details below). The residue definition for enforcement purposes is not required at this time as there are no established Canadian MRLs for animal commodities.

A number of analytical methods (LC-MS/MS, GC-NPD, and HPLC-UV) have been developed to analyze cyromazine and melamine residues in plant and animal commodities. The methods are adequate for residue data collection and enforcement. The LOQs vary but is most commonly set at 0.05 ppm for cyromazine and 0.05 ppm for melamine (when adjusted for the molecular weight of cyromazine). An HPLC-UV method was also developed to analyze N-methyl-cyromazine in animal and plant matrices with a LOQ of 0.05 ppm for most matrices.

Freezer storage stability data were adequate for plant matrices. Cyromazine and melamine residues were observed to be stable for up to 24 months in frozen potato, tomato, bean, sunflower seed, and mango samples. Adequate freezer storage stability data were not available for animal commodities. It is recommended that any future livestock magnitude of residue studies be submitted with accompanying or concurrent freezer storage stability data.

Supervised field trial studies were available for celery, leafy and head/stem brassicas, leafy vegetables, cucumber, melons, mushrooms, onions, peppers, and potato. The studies are adequate to support current registrations and MRLs. Combined residues of cyromazine and melamine are not expected to exceed established Canadian MRLs in/on test crops when cyromazine is used according to label directions. Residue data were also available for tomato and potato processed forms. Cyromazine and melamine specific processing factors were derived from the data and incorporated into the dietary assessment. Crop residue estimates were based on various sources depending on the availability and suitability of the data. The sources included monitoring data

from the Canadian Food Inspection Agency (CFIA) or United States Department of Agriculture's Pesticide Data Program (USDA PDP), Canadian MRLs, American Tolerances, and Codex MRLs.

Livestock feeding, topical application, and manure application (magnitude of residue) studies were available. The studies were conducted in accordance with livestock-related cyromazine uses in other countries, such as in the United States where cyromazine is used as a poultry feed additive, or in Australia and New Zealand where cyromazine can be applied topically to sheep. There are no livestock and feed crop uses for cyromazine in Canada. Based on the data available, the only residues expected to be present in animal commodities is cyromazine residues in imported sheep and poultry commodities. Melamine and N-methyl-cyromazine are not expected to be present at significant levels in animal commodities as a result of cyromazine use. For the risk assessment, the USEPA Tolerance was used to estimate cyromazine residues in poultry and the Codex MRL was used to estimates cyromazine residues for sheep. There are no Canadian MRLs currently established for animal commodities.

Confined and field crop rotation studies were available on file. There is indication that cyromazine and melamine residues could potentially accumulate in rotational crops planted back into cyromazine-treated fields. Plant back interval restrictions are specified on current cyromazine labels to reduce the potential for indirect residues and no further changes are proposed.

Overall, the residue chemistry database is adequate to support the current registered uses for cyromazine in Canada.

Appendix VI Occupational Handler Exposure Risk Assessment for Cyromazine

Table 1 Mixer, Loader, Applicator Occupational Exposure and Risk Assessment, Vegetables and Ornamentals

Crop	Formulation	Scenario	Application Equipment	Max Rate (kg a.i./ha)	ATPD (ha/day)	Dermal Exposure[a] (mg/kg bw/day)	Inhalation Exposure[b] (mg/kg bw/day)	Dermal MOE[c]	Inhalation MOE[c]	Combined MOE[d]
Potatoes	WSP	Closed M/L Baseline PPE, Open A Baseline PPE	Groundboom Farmer	0.27975	107	4.75E-03	6.96E-04	1053	7184	918
		Closed M/L Baseline PPE, Open A Baseline PPE	Groundboom Custom	0.27975	360	1.60E-02	2.34E-03	313	2135	273
		Closed M/L **Mid-level** PPE, **Closed A Mid-level** PPE			360	4.19E-03	3.02E-04	1192	16549	1112
Leafy Vegetables/Leafy Brassica/ Celery	WSP	Closed M/L Mid-level PPE, Open A Mid-level PPE	Groundboom	0.141	26	2.74E-04	8.52E-05	18300	58700	13900
Outdoor Ornamentals	WSP	Closed M/L Mid-level PPE, Open A Mid-level PPE	Groundboom	0.141	26	2.74E-04	8.52E-05	18300	58700	13900
		Closed M/L/A, Mid-level PPE	MPHW	0.141	150 L/day	5.25E-05	1.19E-05	95300	418000	77600
		Closed M/L/A, Mid-level PPE	Backpack		150 L/day	1.85E-04	1.64E-05	27000	305000	24800
		Closed M/L/A, Mid-level PPE	MPHG		3800 L/day	4.44E-03	1.01E-03	1130	4940	917
		Closed M/L Mid-level PPE, Open A, Mid-level PPE without CR hat	Airblast	0.141	20	3.24E-02	3.26E-04	154	15318	153
		Closed M/L Mid-level PPE, Open A, Mid-level PPE **with CR hat**				1.58E-03	3.26E-04	3167	15318	2624
		Closed M/L, Baseline PPE, **Closed A**, Baseline PPE				2.11E-04	1.76E-05	23696	283688	21870
Greenhouse Lettuce	WSP	Closed M/L/A, Mid-level PPE	MPHW	0.099	150 L/day	3.68E-05	8.39E-06	136000	596000	111000
			Backpack		150 L/day	1.30E-04	1.15E-05	38400	434000	35300
			MPHG		3800 L/day	3.12E-03	7.10E-04	1600	7040	1310

Crop	Formulation	Scenario	Application Equipment	Max Rate (kg a.i./ha)	ATPD (ha/day)	Dermal Exposure[a] (mg/kg bw/day)	Inhalation Exposure[b] (mg/kg bw/day)	Dermal MOE[c]	Inhalation MOE[c]	Combined MOE[d]
Greenhouse Ornamentals	WSP	Closed M/L/A, Mid-level PPE	MPHW	0.141	150 L/day	5.25E-05	1.19E-05	95300	418000	77600
			Backpack		150 L/day	1.85E-04	1.64E-05	27000	305000	24800
			MPHG		3800 L/day	4.44E-03	1.01E-03	1130	4940	917

Shaded cells indicate those calculated MOEs that are below the target MOE of 1000
ATPD = Area Treated Per Day, MOE = Margin of Exposure, WSP = Water Soluble Packaging, M/L =Mix/Load, M/L/A = Mix/Load/Apply, A = Apply, PPE = Personal Protective Equipment, MPHW = Manually-Pressurized Handwand, MPHG = Mechanically-Pressurized Hand Gun, CR = Chemical-resistant
Label PPE: Citation 75 WP Single layer, long-sleeved shirt, chemical-resistant gloves and coveralls, Governor 75 WP Single layer, long sleeved shirt and chemical-resistant gloves
[a] Dermal exposure (mg/kg bw/day) = (dermal unit exposure × ATPD × maximum application rate × 27% dermal absorption)/80 kg body weight
[b] Inhalation exposure (mg/kg bw/day) = (inhalation unit exposure × ATPD × maximum application rate)/80 kg body weight
[c] Short-, Intermediate-term: Based on a NOAEL of 5 mg/kg bw/day from an oral developmental toxicity study in rabbits. Target MOE=1000.
[d] Combined MOE = NOAEL/(EXP_{derm}+EXP_{inh}). Target MOE = 1000

Table 2 Mixer, Loader, Applicator Exposure and Risk Assessment of Cyromazine, Mushroom Houses – Compost and Casing Layer

Crop	Formulation	Scenario	Application	Max Rate (g a.i./100 m^2)	Dermal Exposure[a] (mg/kg bw/day)	Inhalation Exposure[b] (mg/kg bw/day)	Dermal MOE[c]	Inhalation MOE[c]	Combined MOE[d]
Compost	WSP	PHED, Open M/L/A MPHW, Baseline PPE	Coarse drench, low pressure spray	56.25	1.33E-03	6.37E-05	3759	78458	3587
Casing	WSP	PHED, Open M/L/A MPHW, Baseline PPE	MPHW	14	4.91E-03	2.31E-04	1018	21671	972

MOE = Margin of Exposure, WSP = Water Soluble Packaging, M/L/A = Mix/Load/Apply, PPE = Personal Protective Equipment, MPHW = Manually-Pressurized Handwand
Baseline PPE: Single layer, long-sleeved shirt and chemical-resistant gloves
[a] Dermal exposure (mg/kg bw/day) = (dermal unit exposure (µg/kg a.i) × 0.001 (µg → mg) × 744 m^2/day (compost: amount of compost needed for 744 m^2 of mushroom beds, casing: area of mushroom house beds a worker will treat per day) × maximum application rate (g a.i./ 100 m^2) × 0.001 (g → kg) × 27% dermal absorption)/80 kg body weight
[b] Inhalation exposure (mg/kg bw/day) = (inhalation unit exposure (µg/kg a.i) × 0.001 (µg → mg) × 744 m^2/day (compost: amount of compost needed for 744 m^2 of mushroom beds, casing: area of mushroom house beds a worker will treat per day) × maximum application rate (g a.i./ 100 m^2) × 0.001 (g → kg))/80 kg body weight
[c] Short-, Intermediate-term: Based on a NOAEL of 5 mg/kg bw/day from an oral developmental toxicity study in rabbits. Target MOE = 1000
[d] Combined MOE = NOAEL/(EXP_{derm}+EXP_{inh}), Short-, Intermediate-, Long-Term Target MOE = 1000

Table 3 Mixer/Loader/Applicator Exposure and Risk Assessment of Cyromazine, Planting Treated Seeds, Onions

Crop	Formulation	Study	Scenario	Application Rate (g a.i./kg seed)	Seeding Rate (kg seed/ha)	ATPD (ha/day)	Max Rate (kg a.i./ha)	Dermal MOE[a]	Inhalation MOE[a]	Combined MOE[b]
Onion Seeds, Dry bulb onions	WSP	PMRA# 1571553[c], Corn	Loading/Planting	50	4	12.9[d]	0.2	379	1872	315
Onion Seeds, Green	WSP	PMRA# 1571553[c], Corn	Loading/Planting	50	7	0.4[e]	0.35	6985	34494	5809

Shaded cells indicate those calculated MOEs that are below the target MOE of 1000

ATPD = Area Treated Per Day, MOE = Margin of Exposure, WSP = Water Soluble Packaging, PPE = Personal Protective Equipment, CR = Chemical Resistant

Baseline PPE: Single layer, long-sleeved shirt and chemical-resistant gloves

[a]Short-, Intermediate-term: Based on a NOAEL of 5 mg/kg bw/day from an oral developmental toxicity study in rabbits. Target MOE = 1000

[b]Combined MOE = NOAEL/(EXP_{derm}+EXP_{inh}), Target MOE = 1000

[c]PPE: single layer and chemical-resistant gloves

[d]95th percentile of dry onion farm size, STATS CAN Percentile Farm Size – 2016 Census of Agriculture

[e]95th percentile of green onion farm size, STATS CAN Percentile Farm Size – 2016 Census of Agriculture

Appendix VII Occupational Postapplication Risk Assessment for Cyromazine

Table I Postapplication Occupational Exposure and Risk Assessment

Crop	Rate (kg/ha)	NAPS	Int (days)	Activity	TC (cm^2/h)[a]	DFR Inputs			Day 0 Estimates		REI (days)[e]
						Peak	Disp	DFR_0[b]	Exp[c]	MOE[d] (Target = 1000)	
Potato	0.27975	2	6	Irrigation (hand set involving foliar contact)	1750	25%	10%	1.07	50.6	99	22
				Roguing	1100				31.8	157	18
				Scouting	210				6.07	823	2
				Hand Weeding	70				2.02	2470	0.5
Leafy Vegetables/Leafy Brassica	0.141	5	7	Irrigation (hand set)	1750	25%	10%	0.66	31.1	161	18
				Hand Harvesting	1100				19.6	256	13
				Transplanting	230				4.09	1220	0.5
				Scouting	210				3.74	1340	0.5
				Thinning, Hand Weeding	70				1.25	4020	0.5
Celery	0.141	5	7	Irrigation (hand set)	1750	25%	10%	0.66	31.1	161	18
				Hand Harvesting	1100				19.6	256	13
				Transplanting	230				4.09	1220	0.5
				Scouting	210				3.74	1340	0.5
				Thinning, Hand Weeding	70				1.25	4020	0.5
Outdoor Ornamentals grown for cut flower production	0.141	5	7	Disbudding, Hand Harvesting, Hand Pruning	4000	25%	10%	0.66	71.15	70	26
				Irrigation (hand set)	1750				31.13	161	18
				Container Moving, Pinching, Plant support/staking, Scouting, Transplanting, Hand Weeding,	230				4.09	1220	0.5
Outdoor Ornamentals not grown for cut flower production	0.141	5	7	Irrigation	1750	25%	10%	0.66	31.13	161	18
				All other activities	230				4.09	1220	0.5
Greenhouse Lettuce	0.099	4	7	All Activities	230	25%	0%	0.99	6.15	813	NA
Greenhouse Ornamentals, grown for cut flower production	0.141	6	7	Disbudding, Hand Harvesting, Hand Pruning	4000	25%	2.3%	1.46	158	32	149
				Irrigation (hand set)	1750				69.11	72	113

Crop	Rate (kg/ha)	NAPS	Int (days)	Activity	TC (cm^2/h)[a]	DFR Inputs			Day 0 Estimates		REI (days)[e]
						Peak	Disp	DFR_0[b]	Exp[c]	MOE[d] (Target = 1000)	
				Container Moving, Pinching, Plant support/staking, Scouting, Transplanting, Hand Weeding,	230				9.08	550	26
Greenhouse Ornamentals, not grown for cut flower production	0.141	6	7	All activities	230	25%	2.3%	1.46	9.08	550	26

Shaded cells indicate those calculated MOEs that are below the target MOE of 1000

NAPS = Number of Applications per Season, Int = Application Interval, TC = Transfer Coefficient, DFR = Dislodgeable Foliar Residue, Peak = Peak DFR as Percent of Rate, Disp = Percent Dissipation per Day, DFR_0 = Day 0 DFR ($\mu g/cm^2$), Exp = Exposure (µg/kg bw/day), MOE = Margin of Exposure, REI = Restricted-Entry Interval

[a] ARTF Transfer Coefficients (PMRA# 2115788)

[b] DFR_0 ($\mu g/cm^2$) = Peak dislodgeable residue (25%) × maximum application rate (kg a.i./ha) × 10 (kg a.i./ha → $\mu g/cm^2$). DFR (multiple applications) = DFR_{n-1} – (DFR_{n-1} × Dissipation rate) + DFR_0, where n= NAPS

[c] Dermal exposure (mg a.i./kg bw/day) = (DFR ($\mu g/cm^2$) × TC (cm^2/h) × work duration (8 h) × Dermal Absorption (27%) × 0.001 (convertion factor))/ Body weight (80 kg)

[d] Based on the short-, intermediate-, long-term, dermal NOAEL of 5 mg/kg bw/day from an oral developmental toxicity study in rabbits. Target MOE of 1000.

[e] Day at which Target MOE of 1000 is reached.

Table 2 Postapplication Dermal Exposure from Treated Soil

Max App Rate (kg a.i./ha)	Soil Concentration (mg a.i./kg soil)	Adherence Factor[a] (mg soil/cm^2)	Surface Area[b] (cm^2)	Dermal Exposure[c] (mg/kg bw/day)	Dermal MOE[d] Target = 1000
Commercial Worker in a Mushroom House – Compost Layer					
5.67	5	0.60	3300	3.34E-05	149645

[a] From the USEPA Superfund guidance document (USEPA, 2004). Value from exposure scenario Staged Activity: Pipe Layers (wet soil), geometric mean.

[b] Surface area of exposed skin (head, hands, forearms). Value from the USEPA Superfund guidance document (USEPA, 2004)

[c] Dermal exposure (µg/kg bw/day) = soil concentration × adherence factor × conversion factor ($1x10^{-6}$ kg soil to mg soil) × surface area × 1 event/day × dermal absorption factor (0.27) /body weight (80kg).

[d] Based on the short-term, dermal NOAEL of 5 mg/kg bw/day from an oral developmental toxicity study in rabbits. Target MOE of 1000.

Appendix VIII Residential and Aggregate Risk Assessment for Cyromazine

Table 1 Residential Postapplication Exposure to Cyromazine on Outdoor Ornamentals

Scenario	Lifestage	DFR (µg/cm^2)[a]	Transfer Coefficient (cm^2/h)[b]	Exposure Time (h)	Body Weight (kg)	Dermal Exposure (mg/kg/bw/day)[c]	Dermal MOE[d]
Trees	Adult	0.659	1700	1	80	0.0038	1322
	Youth 11 < 16 yrs		1400	0.5	57	0.0022	2288
	Children 6 < 11 yrs		930	0.5	32	0.0026	19725

DFR = dislodgeable foliar residue, MOE = Margin of Exposure

[a] Maximum DFR after 5 applications with 7 days between applications for outdoor ornamentals.

[b] TC = transfer coefficient. TCs from the USEPA Residential SOP, Section 4: Gardens and Trees (2012b)

[c] Exposure = DFR (µg/cm^2) × 0.001 (mg/µg) × DA (27%) × TC × exposure time/Body Weight.

[d] Adults/Youth: NOAEL of 5 mg/kg bw/day from an oral rabbit developmental toxicity study, target MOE of 1000. Children: NOAEL of 51 mg/kg bw/day from a dietary rat reproductive toxicity study, target MOE of 300.

Table 2 Aggregate Exposure and Risk Assessment

Sub-population	Scenario	Residential Exposure[a] (mg/kg bw/day)	Dietary Exposure (mg/kg bw/day)	Total Exposure[b] (mg/kg bw/day)	Aggregate MOE[c] Target = 1000 (300 for children)
Adults > 16 yrs	Trees	0.0038	0.0017	0.0053	912
Youth 11 < 16 yrs		0.0022	0.0015	0.0037	1357
Children 6 < 11 yrs		0.0026	0.0018	0.0044	11629

MOE = margin of exposure

[a] Total exposure from residential postapplication activities. See Appendix VIII, Table 1.

[b] Total exposure from residential dermal and chronic dietary exposure.

[c] MOE = NOAEL/ Total Exposure. Based on the aggregate endpoints. For adults/youth: a NOAEL of 5 mg/kg bw/day from an oral rabbit developmental toxicity study, target MOE of 1000. For children a NOAEL of 51 mg/kg bw/day from a dietary rat reproductive toxicity study, target MOE of 300.

Appendix IX Environmental Assessment

Table 1 Fate and Behaviour of Cyromazine and Melamine in the Environment.

Property	Test substance	Value	Transformation products	Comments	Reference PMRA
Abiotic transformation					
Hydrolysis	Cyromazine	Acidic condition 50 ºC, DT_{50}: 103 d; 70 ºC, DT_{50}: 8.04 d; Basic condition 70 ºC, DT_{50}: 81.5 d;	Major: 70 ºC: 2-amino-4-cyclopropylamino-6-hydroxy-s-triazine 76% AR Minor: 70 ºC: 2-amino-4-cyclopropylamino-6-hydroxy-s-triazine formed 9% AR; and 2-cyclopropylamino-4, 6-dihydroxy-s-triazine formed 4%	Cyromazine is stable to hydrolysis in environmentally relevant conditions.	1198611
Phototransfor-mation in soil	Cyromazine	Phototransformation was similar in the dark control and irradiated samples.	Major, Irradiated: Moist soil: NER:23% AR Dry soil: NER:18% AR Major, Dark: Moist soil: NER: 26% AR Dry soil: NER: 20% AR	Not expected to be a route of dissipation for cyromazine	1198612
		Moist Irradiated: DT_{50}: 28 d without NER DT_{50}: 99.6 d with NER	Major, Irradiated: **Moist soil**: Melamine: 54% AR NER: 32.9% AR **Dry soil**: Melamine: 14.7% AR NER: 14.2 % AR Minor, Dark: **Moist soil**: Melamine: 1.3 % AR NER: 8.7 % AR	Soil photolysis is not a significant route of dissipation for cyromazine.	2861358

Property	Test substance	Value	Transformation products	Comments	Reference PMRA
Phototransfor-mation in water	CGA 72662	**Irradiated** sensitized DT_{50}: 9.8 hrs tR_{IORE} [1] = 80.8 hrs (corresponding to 3.4 d) **Non-sensitized**: No dissipation observed. **Dark Control** No dissipation observed.	Irradiated: sensitized with 1% acetone Major: Melamine: 54 ppm	Aqueous photolysis is not a significant route but may contribute to the dissipation of cyromazine in the photic zone	1198613
Soil Biotransformation					
Biotransfor-mation in aerobic soil	^{14}C-cyromazine	25 ºC sandy loam soil: DT_{50}: 25.5 d DT_{90}: 142 d (IORE)[1] tR_{IORE} = 42.6 d	Major: Melamine: 62.3% AR NOA 435343: 14.7% AR NER: 10% AR CO_2: 14.3% AR	Cyromazine is slightly persistent. Melamine remained at more than 60% AR at the end of the study.	2767394
	^{14}C-cyromazine	Marsillargues soil silty clay loam: DT_{50}: 38 d DT_{90}: 146 d (IORE)[1] tR_{IORE} [1]= 43.8 d	Major: Melamine: 74.5% AR Minor: NER: 7.4% AR CO_2: 7.2% AR	Cyromazine is slightly persistent. Melamine remained at 74.5% AR at the end of the study	2767390
		18 Acres sandy clay loam: DT_{50}: 42.6 d DT_{90}: 222 d (DFOP)[1] slow $t_{1/2}$ = 78.4 d	Major: Melamine: 46.6%AR NER: 25.0% AR Minor: CO_2: 7.3% AR	Cyromazine is slightly persistent. Melamine remianed at more than 40% AR at the end of the study	
	^{14}C-cyromazine	20 ºC Gartenacker soil: loam/silt loam: DT_{50}:2.25 d DT_{90}:21.3 d (IORE) [1] tR_{IORE} [1] = 6.41 d	Major: Melamine: 73.1% AR NER: 18.8% AR CO_2: 32.5% AR	Cyromazine is non-persistent. Melamine remained at more than 40% AR at the end of the study	2767393
	^{14}C-cyromazine	10 ºC Gartenacker soil: loam/silt loam: DT_{50}: 5.33 d DT_{90}: 17.7 d (SFO)[1] The result for	Major: Melamine: 81.5% AR NER: 13.7% AR CO_2: 12.6% AR		

Property	Test substance	Value	Transformation products	Comments	Reference PMRA
		incubation at 10 ºC will not be used in fate characterization.			
Biotransformation in anaerobic soil	^{14}C-cyromazine	25 ºC Sandy loam soil: Hanford, (%sand/silt/clay) 73/22/50; pH 6.7; 0.32% OC; CEC 4.8 DT_{50}: 104d DT_{90}: 345d (SFO)[1]	Major Melamine:35.8% AR Minor CO_2: 1.6% AR NER: 6.7% AR Unknown: 2.2% AR	Cyromazine is moderately persistent in anaerobic soil Melamine was still increasing at the end of the study.	2767397
Aquatic Biotransformation					
Biotransformation in aerobic water-sediment systems	[^{14}C-triazine] cyromazine	Rhine river water and silty clay soil system(4.2% clay, 45.5% silt, 50.3% sand, pH 7.4, 0.9% OC) Aerobic 25 ºC Whole system DT_{50}: 258 d DT_{90}: 857 d (SFO)[1]	Major Products Melamine: 20.6% AR	Cyromazine is persistent in the whole system	2767391
		Pond water and pond sediment system(2.5% clay, 25.3% silt, 72.2% sand, pH 7.2, 5.4% OC) Aerobic 25 ºC Whole system DT_{50}: 105 d DT_{90}: 348 d (SFO)[1]	Major Products Melamine: 38.0% AR	Cyromazine is moderately persistent in the whole system	
	^{14}C-cyromazine	Switzerland; Rhine river water /sediment system (9.45% clay, 31.82% silt, 58.73% sand, pH 7.7) Water phase DT_{50}: 15.9 d DT_{90}: 234 d (DFOP)[1] Slow t½ = 112days Whole System DT_{50}: 253 d DT_{90}: 841 d (SFO)[1]	Major: NER: 12.1% AR Minor: Melamine: 3.46 % AR CO_2: 7.6% AR	Cyromazine is slightly persistent in water phase Cyromazine is persistent in the whole river system	2767398
		Switzerland; Pond water /sediment system (25.29% clay, 58.18% silt, 16.53% sand, pH 7.24)	Major: NER: 12.86% AR Minor: Melamine: 3.43 % AR CO_2: 5.25% AR	Cyromazine is Non- persistent in water phase Cyromazine is persistent in the	

Property	Test substance	Value	Transformation products	Comments	Reference PMRA
		Water phase DT_{50}: 12.8 d DT_{90}: 477 d (IORE)[1] tR_{IORE} [1]= 143 d Whole System DT_{50}: 462 d DT_{90}: 1799 d (SFO)[1] Slow t½ = 576 d		whole river system	
Biotransformation in anaerobic water-sediment systems		No biotransformation study conducted in anaerobic water/sediment systems with cyromazine was available for review.			
Mobility					
Adsorption / desorption in soil	^{14}C-cyromazine	Cyromazine Four soil types: K_d: 0.47–47.56 mL/g; K_{oc}: 59.03–1698 mL/g	Cyromazine is classified as having low to very high mobility in the soils tested.		1148762
	^{14}C-cyromazine	Cyromazine Four soil types: K_d: 0.52–17 mL/g; K_{FOC}: 40.2–183 mL/g	Cyromazine is classified as having moderate to very high mobility in the soils tested.		1198614
	^{14}C-cyromazine	Cyromazine Three soil types: K_d: 1.44–6.77 mL/g; K_{FOC}: 96–521 mL/g	Cyromazine is classified as having low to high mobility in the soils tested		2861358
	^{14}C-melamine	Melamine Three soil types: K_d: 1.45–5.50 mL/g; K_{FOC}: 97–423 mL/g	Melamine is classified as having moderate to high mobility in the soils tested		
	NOA 435343	NOA435343 Three soil types: K_d: 0.35–3.35 mL/g; K_{oc}: 24.83–116.2 mL/g	NOA435343 is classified as having moderate to very high mobility in the soils tested		2767402
Soil Column Leaching	^{14}C-cyromazine applied as a 50 SP formulation at a rate corresponding to 5 kg/ha cyromazine.	Soil columns with four soils: Collombey, Switzerland – (sand) Lakeland, FL, United States- (sand) Les Evouettes, Switzerland- (silty loam) Vetroz, Switzerland- (sandy loam) Leachate Collombey - 32.7% AR Lakeland - <0.5% AR Les Evouettes - <0.5% AR	 >30 cm 16 cm 14 cm 18 cm		1198616

Property	Test substance	Value	Transformation products	Comments	Reference PMRA
		Vetroz - <0.5% AR			
	Aged ^{14}C-cyromazine applied at 5 mg/kg, incubated for 28 days under aerobic, dark 75% field moisture capacity at 25±1 °C	28-day aged residue, leached for 16 days with 200 mm water on two soils: Collombey, Switzerland – (sand) Les Evouettes, Switzerland – (silty loam) Leachate Collombey – 0.37% AR Les Evouettes – 0.06% AR	cyromazine 0–2 cm–19.1 % AR 18–20 cm–9.4% AR 0–2 cm - 23.3 % AR. NER Collombey – 34.6% AR Les Evouettes – 51.9% AR	Melamine Collombey-65.6% AR Les Evouettes – 55.2% AR	1206424
	Aged ^{14}C-cyromazine applied at 2.8 and 4.2 mg/kg, incubated for 30 days under aerobic, dark 75% field moisture capacity at 25±1ºC	30-day aged residue, leached for 45 days with 571.5 mm water on two soils: Collombey, Switzerland – (sand) Les Evouettes, Switzerland- (silty loam) Leachate Collombey – 51.0% AR Cyromazine = 18% AR Melamine = 29% AR Les Evouettes – <0.1% AR	cyromazine 44.4% AR in soil 0–6 cm – 15.3% AR 94.6 % AR in soil 0–6 cm – 58.7% NER Collombey – 23.9% AR Les Evouettes – 55.9% AR		1198615
	Cyromazine in the form of Trigard 75WP applied by ground boom on tomatoes at 6 × 140 g a.i./ha.	2-acre tomato field in Hillsborough County, Florida with constant irrigation from August to November. **Groundwater** Cyromazine = zero detection Melamine = 0.1–0.21 µg/L (4 of 290	Soil Cyromazine 0-15 cm = 10.6 to 47.2 µg/kg Melamine 0–15 cm = 10.7 to 76.1 µg/kg 15–30 cm = 10.9 to 27.8 µg/kg	Cyromazine and melamine have a potential to leach in sandy soil.	2767403

Property	Test substance	Value	Transformation products	Comments	Reference PMRA
		samples)			
Volatilization	Not required based on the low vapour pressure (3.19 × 10-6 Pa at 25 °C) and Henry's law constant (2.8 × 10-4 Pa · m³ / mol at 20 °C).				
Terrestrial Field studies					
Field dissipation in four sites in Canada: Plattsville, ON Cambridge, ON Truro, NS Kentville, NS	Cyromazine applied as Trigard (Governor) 75 WP formulation at a first application rate of 280 g a.i/ha and 476 g a.i./ha and a second application at 280 g a.i./ha.	Several bare plots at 4 sites in potato growing areas of Southern Ontario and Maritime region of Nova Scotia, Canada Cyromazine DT_{50} = 58, 68.9, 81.2 and 90.1 days (SFO)[1] at the four sites, respectively. Carryover was low (range of 15 to 25% of initial cyromazine concentrations).	Major: Cyromazine was found mainly in the top 30 cm core depth with occasional detection in 90 cm Melamine was detected in the whole soil profile (down to 120 cm), but most of the residues were found in the top 45 cm.	Cyromazine is moderately persistent under the terrestrial field conditions tested.	782355, 782356, 1158191
Field dissipation in the United States with ecoregions relevant to Canadian conditions.	Trigard 75 WP at exagerrated rate of 5.6 kg/ha at single year application and double applications (superimposed at year 2)	Soil plots in York, Nebraska (silty clay), United States No Significant carryover expected. Cyromazine Half-life: Single application = 244 days. Double applications = 204 days.	Cyromazine did not move below the 15 cm soil core depth Residues of melamine were detected down to 45 cm, the deepest soil depth tested		1159661
Field dissipation in Thessaloniki, Greece.	Trigard 75 WP at 300 g a.i./ha in 400 L/ha water.	Application on bare plots of sandy loam soil for 2 years (2001 to 2003) Half-life for first season: Cyromazine = 61 days Melamine = 31 days	Trace residues of cyromazine and melamine were found in the 50–70 cm soil depth.	Cyromazine is moderately persistent while melamine is slightly persistent under field conditions.	2861358
Field dissipation in Massalaves, Valencia, Spain.		Yearly application over four subsequent early summers. Dissipation for first year: DT_{50} = 51 days DT_{90} = 169 days.	Residues of cyromazine were detected down to 30 cm soil depth and melamine to 100 cm soil depth	Cyromazine is moderately persistent	

Property	Test substance	Value	Transformation products	Comments	Reference PMRA
Aquatic Field studies					
Aquatic field dissipation	No aquatic field dissipation study with cyromazine was submitted, and data on the aquatic field disspiation of cyromazine are not required.				
Bioconcentration/bioaccumulation					
Bioconcentration in fish	^{14}C-CGA 72662 at 1 mg/L under flow-through and static conditions.	Whole body steady state BCF: was <1 for fillet, viscera, and whole fish, respectively under flow- through and static test conditions.	Melamine with a log K_{ow} of -0.4, the bioconcentration potential was not investigated	No potential for bioaccumulation in biota.	1198715
[1] Kinetics models: SFO = single first-order; IORE = indeterminate order rate equation; DFOP = double first order in parallel.					

Table 2a Leachability assessment of cyromazine based on classification system of Cohen et al. (1984)

Property	Criteria of Cohen et al (1984) indicating a potential for leaching	Value	Meets criterion for leaching
Solubility in water	>30 mg/L	1300mg/L	Yes
K_d	<5 and usually <1 or 2	K_d: 0.47–47.52 mL/g	No
K_{oc}	<300	K_{oc}: 40.2–1698mL/g	No
Henry's law constant	$<10^{-2}$ atm m^3/mol	5.956×10^{-9} Pa · m³ / mol	Yes
pK_a	Negatively charged (either fully or partially) at ambient pH	5.22 at 20 °C	No
Hydrolysis half-life	>20 weeks (>140 days)	Stable	Yes
Soil phototransformation half-life	>1 week (>7 days)	Stable	Yes
Half-life in soil	>2 to 3 weeks (>14 to 21 days)	73 days	Yes

Table 2b Leachability assessment of melamine based on classification system of Cohen et al. (1984)

Property	Criteria of Cohen et al (1984) indicating a potential for leaching	Value[1]	Meets criterion for leaching
Solubility in water	>30 mg/L	4850mg/L	Yes
K_d	<5 and usually <1 or 2	K_d: 1.45–5.50 mL/g	Yes
K_{oc}	<300	K_{FOC}: 97–423 mL/g	Yes/No
Henry's law constant	$<10^{-2}$ atm m^3/mol	5.956×10^{-9} Pa · m³ / mol	Yes
pK_a	Negatively charged (either fully or partially) at ambient pH	5 at 25 °C	No

Property	Criteria of Cohen et al (1984) indicating a potential for leaching	Value[1]	Meets criterion for leaching
Hydrolysis half-life	>20 weeks (>140 days)	Stable	Yes
Soil phototransformation half-life	>1 week (>7 days)	N/A[2]	N/A
Half-life in soil	>2 to 3 weeks (>14 to 21 days)	135, 194 and 214 days	Yes

[1] Melamine: Draft Screening Asssessment. Environment and Climate Change Canada, Health Canada, 2016.
[2] N/A not available

Table 3 PMRA Uncertainty Factors and Levels of Concern

Organism Group	Exposure	Endpoint	Uncertainty Factor when using LD_{50}, LC_{50} or EC_{50}	Level of concern
Earthworm	Acute	LC_{50}	0.5	1
Bees	Acute	LD_{50} or LC_{50}	none	0.4
Beneficial Insects	Acute	LR_{50}	none	2
Birds/Mammals	Acute oral	LD_{50}	0.1	1
	Acute dietary	5-day LD_{50} (LC_{50} converted to dose)	0.1	1
	Chronic	NOEL (NOEC converted to dose)	none	1
Vascular Plants	Acute	EC_{25}	none	1
Aquatic plants/pelagic invertebrates/benthic invertebrates	Acute	EC_{50}	0.5	1
	Chronic	NOEC	none	1
Fish	Acute	LC_{50}	0.1	1
	Chronic	NOEC	none	1
Amphibians	Acute	fish LC_{50}	0.1	1
	Chronic	fish NOEC	none	1

Table 4 Toxicity of cyromazine and melamine to Non-Target Terrestrial Species

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	Reference
Invertebrates					
Earthworm, *Eisenia fetida*	14-d Acute	Cyromazine (92.6% purity)	LC_{50}: >1000 mga i./kg soil	No classification	1047923
		Melamine (99.0% purity)	LC_{50}: >1000 mg /kg soil	No classification	2861359
		Melamine (99.8% purity)	LC_{50}: >19.68 mg kg soil (the highest	No classification	1148709

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	Reference
			concentration tested)		
	Chronic	Cyromazine (purity 78%)	28-d NOEC = 1000 mg a.i./kg (based on mortality and biomass of adults) 56-d NOEC = 333 mg a.i./kg (based on number of offspring)	No classification	2767404
		Melamine (99.0% purity)	28-d NOEC = 1875 mg /kg (based on survival, condition and fecundity)	No classification	2767405
Bees					
Honeybee, *Apis mellifera*	48-h Oral	Trigard 75 WP (purity = 75.1%)	LD_{50}: 186 µg a.i./bee	Relatively non-toxic	2861359
	48-h Contact		LD_{50}: >200 µg a.i./bee	Relatively non-toxic	2861359
TIER II					
COLONY FEEDING STUDIES					
Honeybee, *Apis mellifera* Colony feeding test with 3 colonies/treatment; colonies were fed syrup spiked with cyromazine for 24 hours that was then removed and the colonies were monitored for 21 days after exposure; colonies were located in Odenwald low mountain range near Rossdorf, Germany	24 hours	Trigard 75 WP (containing 75.1% cyromazine) at 0.225 g a.i./L added to one litre of a ready-to-use sugar solution, compared to an untreated sugar solution control and a toxic reference	The results of this study indicate no effect of cyromazine on the total size of the colonies relative to the control but showed adverse effects of cyromazine on the development of eggs and larvae for up to 1 week after exposure and to worker honey bees who emerged two weeks after exposure. The colonies recovered 2–3 weeks after exposure based on the queen resuming egg laying and no changes to the total colony size. **Study Limitations:** Amount of syrup consumed was not quantified. It is unknown if pests and diseases were assessed. Exposure to other pesticides in the area was unknown since a plant survey surrounding the hive location was not provided.		2346280
Bumble bee *Bombus terrestris* (bumble bee) Queenless micro-colonies (4 nests with 5 workers each) in a greenhouse were exposed to cyromazine 3 ways: 1. Contact: 50µL topically applied 2. Fed *ad libitum*	11 weeks	Trigard EC (containing 75% a.i.) tested 100 mg a.i./L	**Males produced:** In queenless micro-colonies, the dominant female who begins laying eggs has not been fertilized and will only produce male offspring. After feeding on sugar/water and pollen treated with cyromazine, the mean number of males produced after 11 weeks was significantly reduced when compared to the control. **Number of dead 1st and 2nd instar larvae:** After 11 weeks the mean number of dead 1st and 2nd instar larvae was significantly higher in the micro-colonies		2941332

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	Reference
500 mL sugar/water feeders under the nest were spiked 3. Fed *ad libitum* pollen that was sprayed (amount of pollen and spray not noted)			fed cyromazine treated pollen when compared to the control. The mean number of dead larvae was numerically but not statistically higher in the micro-colonies fed treated sugar/water. **Study Limitations:** The amount of cyromazine in pollen was not verified after spray applications were applied. The amount of spiked sugar/water or spiked pollen was not quantified.		
SEMI-FIELD STUDY					
Honeybee, *Apis mellifera* Semi field (Tunnel Test) Application to flowering *Phacelia tanacetifolia* in a tunnel during bee flight; 3 colonies/treatment (small 5-framed colonies used) were placed in the tunnels 3 days before application	11 Days	Trigard 75 WP (containing 75.6% a.i.) applied at 16 or 400 g a.i./ha compared to untreated control (deoinized water) and a toxic reference. NOTE: this is lower than the max single application of potato (279.75 g a.i./ha for foliar)	Exposure of bees to cyromazine 75 WP applied during bee flight at a one-time application rate of 16g a.i./haor 400g a.i./ha to flowering *Phacelia* in tunnel tests resulted in no increases in adult mortality. At the higher cyromazine treatment level, foraging levels were reduced and foraging behaviour affected but only for a short period after application before recovery. The successful development of eggs into adults was slightly affected in both treatments (with a lot of variation) but the development of larval pupae into adults was unaffected. These development results suggest that cyromazine may have a greater effect on eggs and early instar larvae than on later instar or pupae stages. **Study Limitations:** There was a high level of variability between the replicate hives for the egg development data.		2821213
TIER III FIELD STUDIES					
Honeybee, *Apis mellifera* Field Test with application to flowering sweet melon crops in fields 2000 m^2 in size in Spain; 6 colonies/treatment were placed at the edge of the treated blooming fields	28 Days	Trigard 75 WP (containing 74.8% a.i.) at 300 g a.i./ha NOTE: this is very similar to the max single application of potato (279.75 g a.i./ha for foliar)and green onion (350 g a.i./ha for seed treatment)	This study can be used as a line of evidence in the pollinator risk assessment. However, the limitations outlined below indicate that the amount of cyromazine that the test hives were exposed to is unclear. **Study Limitations:** Some colonies may have swarmed and produced replacement queen cells but it was not clear if the replacement queens had ever emerged and begun to lay eggs within the experimental period. High temperatures affected the level of foraging, which affected the level of exposure and reliability of this study. Pollen was collected in traps but the level of melon pollen in relation to other pollen as a measure of exposure was not		2821212

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	Reference
			reported.		
Beneficial Arthropods					
Larvae of ladybird beetle, *Coccinella septempunctata*	22-day exposure to dried residues on glass plates	Cyromazine 75 WP (75.6% a.i.)	$LR_{50:}$ >900 g a.i./ha (the highest concentration tested) NOER: 900 g a.i./ha (hatching) NOER: 450 g a.i./ha (egg/female)	No classification	2767406
Eggs of ladybird beetle, *Coccinella septempunctata*	Direct application with 10-day exposure to dried residues on bean leaves under extended laboratory conditions	Cyromazine 75 WP (75.6% a.i.)	$LR_{50:}$ >891 g a.i./ha (the highest concentration tested) NOER: 222.8 g a.i./ha (mortality)	No classification	2767409
4-day old 2nd instar larvae of ladybird beetle, *Coccinella septempunctata*	41-day exposure to dried residues on bean leaves under extended laboratory conditions	Cyromazine 75 WP (75.1% a.i.)	$LR_{50:}$ >891 g a.i./ha (the highest concentration tested) NOER: 222.8 g a.i./ha (reproduction)	No classification	2767417
Eggs (0–1 day old) of the green lacewing *Chrysoperla camea*	Direct application followed by 11-day exposure of hatched larve to dried residues on bean leaves under extended laboratory conditions	Cyromazine 75 WP (75.6% a.i.) at 4 applications × 330 g a.i./ha × 7 day interval.	$LR_{50:}$ >330 g a.i./ha NOER: 22.14 g a.i./ha (reproduction) **Based on high mortality in the control, end point will not be used in risk assessment but will be used in weight of evidence aproach.	No classification	2767414
Larvae (2–3 days old) of the green lacewing *Chrysoperla camea*	Exposure to residues on excised bean leaves under extended laboratory conditions	Cyromazine 75 WP (75.6% a.i.) at 4 applications × 330 g a.i./ha × 7 day interval.	$LR_{50:}$ >330 g a.i./ha NOER: 330 g a.i./ha	No classification	2767415
Pupae (2–3 days old) of the green lacewing *Chrysoperla camea*	Direct application followed by 11-day exposure to dried residues on bean leaves under extended laboratory conditions	Cyromazine 75 WP (75.6% a.i.) at 4 applications × 330 g a.i./ha × 7 day interval.	$LR_{50:}$ >330 g a.i./ha NOER: 330 g a.i./ha **Based on low mortality in the toxic reference treatment, end point will not be used in risk assessment but will be used in weight of evidence aproach.	No classification	2767416

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	Reference
Adult (2–10 wks old) Carabid Beetle, *Poecilus cupreus*	14-d Laboratory study. Direct application to beetles and exposure to treated sand	Cyromazine 75 WP (75.6% a.i.) at 450 and 900 g a.i./ha	LR_{50}: >900 g a.i./ha (the highest rate tested) NOER = 900 g a.i./ha	No classification	2767410
Adult female (10–14 day olds) Rove Beetle, *Aleochara bilineata*	14-d Laboratory study. Exposure to fresh residues on quartz san	Cyromazine 75 WP (75.6% a.i.) at 450 and 900 g a.i./ha	LR_{50}: >900 g a.i./ha (the highest rate tested) NOER = 900 g a.i./ha	No classification	2767411
Juvenile springtails (10–12 days old) of Collembola, *Folsomia candida*	28- day exposure on treated soil	Cyromazine 75 WP (75.1% a.i.)	LR_{50}: >60 mg a.i./kg (mortality) EC_{50} = 54.4 mg a.i./kg (total young produced) NOER = 9.6 mga.i./kg	No classification	2861359
Proto nymphs of Predatory mite, *Typhlodromus pyri*	14-d extended laboratory test with exposure to dry residues on bean leaves	Cyromazine 75 WP (75.1% a.i.)	$LR_{50:}$ 47 g a.i./ha NOER: 1.36 g a.i./ha	No classification	2767412
Eggs (<24 hrs old) of Predatory mite, *Typhlodromus pyri*	Direct application to eggs and exposure of hatched proto nymphs to residues on bean leaves under extended laboratory conditions	Cyromazine 75 WP (75.1% a.i.)	$LR_{50:}$ 2.42 g a.i./ha (total mortality) $LR_{50:}$ >30 g a.i./ha (egg hatch)	No classification	2861359
Proto nymphs (<24 hrs old) of Predatory mite, *Typhlodromus pyri*	Exposure (0 days, 7 days, 14 days, 28 days 35 days to freshly applied and aged residues on bean leaves under extended laboratory conditions.	Cyromazine 75 WP (75% a.i.) at: 4 × 10.065 g a.i./ha × 7 day interval (Drift Scenario 1)	0–14d LR_{50}: >10.065 g a.i./ha (mortality and fecundity) 7-d $ER_{50} \geq$10.065 g a.i./ha (mortality and fecundity)	No classification	2767412
		3 × 3.015 g a.i./ha × 7 day interval (Drift Scenario 2)	7-d NOER: 3.015 g a.i./ha (mortality) 14-d NOER: 3.015 g a.i./ha (fecundity)		
		4 × 300 g a.i./ha × 7 day interval (Max 4)	35-d $LR_{50:} \geq$ 300 g a.i./ha.(mortality)		
		3 × 300 g a.i./ha × 7 day interval (Max 3)	28-35d $LR_{50:} \geq$ 300 g a.i./ha.(mortality)		

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	Reference
Proto nymphs (<24 h old) of *Phytoseiulus persimilis*	8-d exposure to dried residues on bean leaves under extended laboratory conditions	Cyromazine 75 WP (75.1% a.i.)	$LR_{50:}$ 7.690g a.i./ha (mortality) NOER: 2.50 g a.i./ha	No classification	2861359
Proto nymphs (<24 h old) of *Phytoseiulus persimilis*	8-d exposure to fresh and aged residues (0, 7,14, 28 and 35 days) on sweet pepper leaves under extended laboratory conditions.	Cyromazine 75 WP (75.1% a.i.) at 3 × 100 g a.i./ha	0-35d $LR_{50:}$ >100g a.i./ha 0-35d NOER: 100g a.i./ha **Based on high mortality in the control, end point will not be used in risk assessment but will be used in weight of evidence aproach.		
Proto nymphs (<24 h old) of *Phytoseiulus persimilis*	7-d Exposure to residues on bean leaves under extended laboratory conditions	Cyromazine 75 WP (75.1% a.i.)	7-d LR_{50}: 30.49 g a.i./ha (post-hatch and pre-imaginal mortality) 7-d NOER: 9.8 g a.i./ha	No classification	2861359
Pupae (mummies) of Parasitoid wasp, *Aphidius rhopalosiphi*	Direct application to mummies and 8-d exposure of emerged wasps to barley seedlings infested with aphids	Cyromazine 75 WP (75.1% a.i.)	8-d $LR_{50:}$ >891 g a.i./ha NOER: 891 g a.i./ha (the highest concentration tested)	No classification	2767418
Adult Parasitoid wasp, *Aphidius rhopalosiphi*	48h-exposure to residues on barley seedlings	Cyromazine 75 WP (75.1% a.i.)	48h $LR_{50:}$ >891 g a.i./ha 48h NOER: 891 g a.i./ha	No classification	2767419
Adult Parasitoid wasp, *Encarsia formosa*	7-d exposure dried residues on tomato plants under extended laboratory condition	Cyromazine 75 WP (75.6% a.i.) at: 4 × 22.1 g a.i./ha × 7-d interval; 4 × 330 g a.i./ha × 7-d interval	LR_{50}: >330g a.i./ha NOER = 330 g a.i./ha (mortality and fecundity)	No classification	2767420
Early stage larvae of Parasitoid wasp, *Encarsia formosa*	Direct application to parasitised whitefly on tomato plants under extended laboratory condition.	Cyromazine 75 WP (75.6% a.i.) at: 3 × 22.8 g a.i./ha × 7-d interval; 3 × 330 g a.i./ha × 7-d interval	LR_{50}: >330 g a.i./ha LR_{50}: >22.8 g a.i./ha for pupal development from pre-imaginal development and fecundity with LR_{50}: >330 g a.i./ha for adult emergence	No classification	2861359

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	Reference
Pupae of Parasitoid wasp, *Encarsia formosa*	Direct application to parasitised whitefly pupae (11 days after parasitisation) on tomato plants under extended laboratory condition	Cyromazine 75 WP (75.6% a.i.) at: 2 × 23.9 g a.i./ha × 7-d interval; 2 × 330 g a.i./ha × 7-d interval	LR_{50}: >330 g a.i./ha for pupal development and fecundity of emerged adult.	No classification	2861359
Birds					
Mallard duck, *Anas platyrhynchos*	Acute	cyromazine (purity 95.6% a.i.)	14-dLD_{50}: >2510 mg a.i./kg bw NOEC: 631 mg a.i./kg bw	Practically non-toxic	1198681
	8-d Dietary	cyromazine (purity 95.6% a.i.)	LC_{50}: >5620 mg a.i./kg diet (>526 mg/kg bw/d) NOEC: 562 mg a.i./kg bw/d	Practically non-toxic	1198692
	19-w Reproduction	cyromazine (purity 96.3%).	NOEC: 300 mg a.i./kg diet (highest concentration tested) (NOEL: 38.3 mg a.i./kg bw/d)	No classification	1148703
Northern bobwhite quail, *Colinus virginianus*	Acute	cyromazine (purity 95.6%)	14-dLD_{50}: 1785 mg a.i./kg bw NOEC: 398 mg a.i./kg bw	Practically non-toxic	1198644
	8-d Dietary	cyromazine (purity 95.6%)	LC_{50}: >5620 mg a.i./kg diet (>1370 mg/kg bw/d) NOEC: 562 mg a.i./kg bw/d	Practically non-toxic	1198670
	24-w Reproduction	cyromazine (purity 96.3%)	NOEC: 1200 mg aikg diet (mean measured concentration) (NOEL: 110 mg a.i./kg bw/d)	No classification	1148702
Japanese quail, *Coturnix japonica*	Acute	cyromazine (purity not reported)	14-dLD_{50}: 2338 mg a.i./kg bw NOEC: 600 mg a.i./kg bw	Practically non-toxic	1198625
	8-d Dietary	cyromazine (purity not reported)	LC_{50}: >10 000 mg a.i./kg diet (>683 mg/kg bw/d) NOEC: 1000 mg a.i./kg diet	Practically non-toxic	1198627
Peking duck *Anas domestica*	Acute	cyromazine (purity not reported)	7-dLD_{50}: >1000 mg a.i./kg bw NOEC: 1000 mg a.i./kg bw	Practically non-toxic	1198628

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	Reference
	8-d Dietary	cyromazine (purity not reported)	LC_{50}: >10 000 mg a.i./kg diet (>1115mg/kg bw/d) NOEC: 600 mg a.i./kg diet	Practically non-toxic	1198629
Mammals					
Rat	Acute Oral Toxicity – Gavage	cyromazine	LD_{50} = 2029 mg/kg bw (♂/♀) (in PEG) LD_{50} = 1348 mg/kg bw (♂) (in PEG) LD_{50} = 2924 mg/kg bw (♀) (in PEG) Clinical signs of toxicity (within two hrs) included sedation, dyspnoea, curved position and ruffled fur. Low acute oral toxicity	Practically non-toxic	1249111
		cyromazine	LD50 = 3920 mg/kg bw (♂/♀) (in CMC) LD50 = 4050 mg/kg bw (♂) (in CMC) LD50 = 3530 mg/kg bw (♀) (in CMC) Clinical signs of toxicity included decreased activity, ataxia, constricted pupils, diarrhea, lacrimation, piloerection, polyuria, ptosis, salivation, sensitivity to touch, chromodacryorrhea. Low acute oral toxicity	Practically non-toxic	2337312

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	Reference
	2-Generation Reproductive Toxicity Study - Diet Sprague-Dawley Rat (one litter/ generation)	cyromazine	Parental Toxicity NOAEL = 1.6 mg/kg bw/day (♂/♀) (reduced bodyweights and food consumption in the male and female parental rats at doses of 1000 and 3000 mg/kg and decreased pup weight at the highest concentration tested). Reproductive toxicity NOAEL = 51 mg/kg bw/day (♂/♀) Offspring Toxicity Offspring NOAEL not established	No classification	1198220 1198575 1157649
Vascular plants					
Monocot and dicot crop species corn, *Zea* mays, soybean, *Glycine max*, wild oat, *Avena fatua*), onion, *Allium cepa*, sugar beet, *Beta vulgaris*, oilseed rape, *Brassica napus.*	21-d Seedling emergence	Trigard 75 WP	Most sensitive of 6 species: ER_{25}: >300 ga.i./ha NOER:18.75 g a.i./ha (based on phytotoxic signs soybean, *Glycine max*	No classification	2861359
	17-d Vegetative vigor	Trigard 75 WP	Most senstive of 6 species: ER_{25}: >300 g a.i./ha NOER: 75 g a.i./ha (based on phytotoxic signs on corn, *Zea mays* (8.5 on a rating scale of 1-9, with 9 being no visual damage, normal growth)	No classification	2861359

[1] Atkins *et al*. (1981) for bees and USEPA classification for others, where applicable

Table 5 Screening Level and Refined Risk Assessment of cyromazine for Non-Target Species other than Birds and Mammals.

Organism	Exposure	Endpoint Value	EEC	RQ	Level of Concern (LOC) (1) except for bees LOC (0.4)
Invertebrates					
Earthworm	Acute	LC_{50}/2: >500 mg a.i./kg soil	0.27 mg a.i./kg soil	<0.0005	Not exceeded
	Chronic	NOEC: 333 mg a.i./kg soil	0.27 mg a.i./kg soil	0.0008	Not exceeded
Bee	Contact	LD_{50}: >200 µg a.i./bee	0.279 kg a.i./ha × 2.4 µg a.i./bee per kg/ha = 0.672 µg a.i./bee	0.0003	Not exceeded
	Oral	LD_{50}: 186 µg a.i./bee	0.279 kg a.i./ha × 29 µg a.i./bee per kg/ha = 8.12 µg a.i./bee	0.04	Not exceeded
	Brood / hive	Data was not available on chronic risk to adult bees and bee brood.			
Adult Parasitoid wasp, *Aphidius rhopalosiphi*	48h-exposure on barley seedlings	48h-LR_{50}: >891 g a.i./ha	In-field: Cumulative foliar rate of 183 g a.i./ha	<0.21	Not Exceeded
Pupae (mummies) of Parasitoid wasp, *Aphidius rhopalosiphi*	8-d exposure of emerged wasps to barley seedlings infested with aphids	8-d LR_{50}: >891 g a.i./ha	In-field: Cumulative foliar rate of 183 g a.i./ha	<0.21	Not exceeded
Larvae of ladybird beetle, *Coccinella septempunctata*	22-day exposure to dried residues on glass plates	LR_{50}: >900 g a.i./ha (the highest concentration tested)	In-field: Cumulative foliar rate of 183 g a.i./ha	<0.20	Not exceeded
Adult (2–10 wks old) Carabid Beetle, *Poecilus cupreus*	14-d Laboratory study. Direct application to beetles and exposure to treated sand	LR_{50}: >900 g a.i./ha (the highest rate tested) NOER = 900 g a.i./ha	In-field: Cumulative soil rate of 600 g a.i./ha	<0.7	Not exceeded
Adult female (10-14 day olds) Rove Beetle, *Aleochara bilineata*	14-d Laboratory study. Exposure to fresh residues on quartz sand	LR_{50}: >900 g a.i./ha (the highest rate tested) NOER = 900 g a.i./ha	In-field: Cumulative soil rate of 600 g a.i./ha	<0.7	Not exceeded
Juvenile springtails (10–12 days old) of	28- day exposure on	ER_{50} = 54.4 mg a.i./kg (total	0.27 mg a.i./kg soil	0.005	Not Exceeded

Organism	Exposure	Endpoint Value	EEC	RQ	Level of Concern (LOC) (1) except for bees LOC (0.4)
Collembola, *Folsomia candida*	treated soil	young produced)			
4-day old 2nd instar larvae of ladybird beetle, *Coccinella septempunctata*	41-day exposure to dried residues on bean leaves under extended laboratory conditions	LR_{50}: >891 g a.i./ha (the highest concentration tested)	In-field: Cumulative foliar rate of 183 g a.i./ha	<0.21	Not exceeded
Larvae (2–3 days old) of the green lacewing *Chrysoperla camea*	Exposure to residues on excised bean leaves under extended laboratory conditions	LR_{50}: >330 g a.i./ha	In-field: Cumulative foliar rate of 183 g a.i./ha	<0.6	Not exceeded
Early stage larvae of Parasitoid wasp, *Encarsia formosa*	Direct application to parasitised whitefly on tomato plants under extended laboratory condition.	LR_{50}: >330 g a.i./ha	In-field: Cumulative foliar rate of 183 g a.i./ha	<0.6	Not exceeded
Risk Refinement for celery and outdoor ornamentals use					
Eggs (<24 hrs old) of Predatory mite, *Typhlodromus pyri*	Direct application to eggs and exposure of hatched proto nymphs to residues on bean leaves under extended laboratory conditions	LR_{50}: 2.42 g a.i./ha (total mortality)	In-field: Cumulative foliar rate of 183 g a.i./ha	**75.6**	**Exceeded**
			In-field crop interception factor (80%): 146.4 g a.i./ha	**60.5**	**Exceeded**
			Off-field (ground appl., 6% drift): 10.98 g a.i./ha	**4.5**	**Exceeded**
			Off-field (ground appl., 6% drift) × 10% veg. dist. factor: 1.1 g a.i./ha	0.5	Not Exceeded
			Off-field (early airblast appl., 74% drift): 135.42 g a.i./ha	**56**	**Exceeded**
			Off-field (early airblast appl., 74% drift) × 10% veg. dist. factor: 13.5 g a.i./ha	**5.6**	**Exceeded**
			Off-field (late airblast appl., 59% drift): 107.97 g a.i./ha	**44.6**	**Exceeded**

Organism	Exposure	Endpoint Value	EEC	RQ	Level of Concern (LOC) (1) except for bees LOC (0.4)
			Off-field (late airblast appl., 59% drift) × 10% veg. dist. factor: 10.8 g a.i./ha	**4.5**	**Exceeded**
Proto nymphs of Predatory mite, *Typhlodromus pyri*	14-d extended laboratory test with exposure to dry residues on bean leaves	$LR_{50:}$ 47 g a.i./ha	In-field: Cumulative foliar rate of 183 g a.i./ha	**3.9**	**Exceeded**
			In-field crop interception factor (80%): 146.4 g a.i./ha	**3.1**	**Exceeded**
			Off-field (ground appl., 6% drift): 10.98 g a.i./ha	0.2	Not Exceeded
			Off-field (ground appl., 6% drift) × 10% veg. dist. factor: 1.1 g a.i./ha	0.02	Not Exceeded
			Off-field (early airblast appl., 74% drift): 135.42 g a.i./ha	**2.9**	**Exceeded**
			Off-field (early airblast appl., 74% drift) × 10% veg. dist. factor: 13.5 g a.i./ha	0.3	Not Exceeded
			Off-field (late airblast appl., 59% drift): 107.97 ga.i./ha	**2.3**	**Exceeded**
			Off-field (late airblast appl., 59% drift) × 10% veg. dist. factor: 10.8 g a.i./ha	0.23	Not Exceeded
Proto nymphs (<24 h old) of *Phytoseiulus persimilis*	8-d exposure to dried residues on bean leaves under extended laboratory conditions	$LR_{50:}$ 7.690g a.i./ha (mortality)	In-field: Cumulative foliar rate of 183 g a.i./ha	**23.8**	**Exceeded**
			In-field crop interception factor (80%): 146.4 g a.i./ha	**19**	**Exceeded**
			Off-field (ground appl., 6% drift): 10.98 g a.i./ha	**1.4**	**Exceeded**
			Off-field (ground appl., 6% drift × 10% veg. dist. factor: 1.1 g a.i./ha	0.14	Not Exceeded
			Off-field (early airblast appl., 74% drift): 135.42 g a.i./ha	**17.6**	**Exceeded**
			Off-field (early airblast appl., 74% drift) × 10% veg. dist. factor: 13.5 g a.i./ha	**1.76**	**Exceeded**
			Off-field (late airblast appl., 59% drift): 107.97 ga.i./ha	**14**	**Exceeded**
			Off-field (late airblast appl., 59% drift) × 10% veg. dist. factor: 10.8 g	**1.4**	**Exceeded**

Organism	Exposure	Endpoint Value	EEC	RQ	Level of Concern (LOC) (1) except for bees LOC (0.4)
			a.i./ha		
Proto nymphs (<24 h old) of *Phytoseiulus persimilis*	7-d Exposure to residues on bean leaves under extended laboratory conditions	7-d LR_{50}:30.49 g a.i./ha (post-hatch and pre-imaginal mortality)	In-field: Cumulative foliar rate of 183 g a.i./ha	**6.0**	**Exceeded**
			In-field crop interception factor (80%): 146.4 g a.i./ha	**4.8**	**Exceeded**
			Off-field (ground appl., 6% drift): 10.98 g a.i./ha	0.4	Not Exceeded
			Off-field (ground appl., 6% drift) × 10% veg. dist. factor: 1.1 g a.i./ha	0.04	Not Exceeded
			Off-field (early airblast appl., 74% drift): 135.42 g a.i./ha	**4.4**	**Exceeded**
			Off-field (early airblast appl., 74% drift) × 10% veg. dist. factor: 13.5 g a.i./ha	0.44	Not Exceeded
			Off-field (late airblast appl., 59% drift): 107.97 ga.i./ha	**3.5**	**Exceeded**
			Off-field (late airblast appl., 59% drift) × 10% veg. dist. factor: 10.8 g a.i./ha	0.35	Not Exceeded
Risk Refinement for potato use					
Eggs (<24 hrs old) of Predatory mite, *Typhlodromus pyri*	Direct application to eggs and exposure of hatched proto nymphs to residues on bean leaves under extended laboratory conditions	$LR_{50:}$ 2.42 g a.i./ha (total mortality)	In-field: Cumulative foliar rate of 279.75 g a.i./ha	**115.6**	**Exceeded**
			In-field crop interception factor (80%): 223.8 g a.i./ha	**92.5**	**Exceeded**
			Off-field (ground appl., 6% drift): 16.79 g a.i./ha	**7.0**	**Exceeded**
			Off-field (ground appl., 6% drift) × 10% veg. dist. factor: 1.68 g a.i./ha	0.7	Not Exceeded
Proto nymphs of Predatory mite, *Typhlodromus pyri*	14-d extended laboratory test with exposure to dry residues on bean leaves	$LR_{50:}$ 47 g a.i./ha	In-field: Cumulative foliar rate of 279.75 g a.i./ha	**6.0**	**Exceeded**
			In-field crop interception factor (80%): 223.8 g a.i./ha	**4.8**	**Exceeded**
			Off-field (ground appl., 6% drift): 16.79 g a.i./ha	0.4	Not Exceeded
			Off-field (ground appl., 6% drift) × 10% veg. dist. factor: 1.67 g a.i./ha	0.04	Not Exceeded

Organism	Exposure	Endpoint Value	EEC	RQ	Level of Concern (LOC) (1) except for bees LOC (0.4)
Proto nymphs (<24 h old) of *Phytoseiulus persimilis*	8-d exposure to dried residues on bean leaves under extended laboratory conditions	$LR_{50:}$ 7.690g a.i./ha (mortality)	In-field: Cumulative foliar rate of 279.75 g a.i./ha	**36.4**	**Exceeded**
			Crop interception factor (80%): 223.8 g a.i./ha	**29.1**	**Exceeded**
			Off-field (ground appl., 6% drift): 16.79 g a.i./ha	**2.2**	**Exceeded**
			Off-field (ground appl., 6% drift) × 10% veg. dist. factor: 1.67 g a.i./ha	0.2	Not Exceeded
Proto nymphs (<24 h old) of *Phytoseiulus persimilis*	7-d Exposure to residues on bean leaves under extended laboratory conditions	7-d LR_{50}:30.49 g a.i./ha (post-hatch and pre-imaginal mortality)	In-field: Cumulative foliar rate of 279.75 g a.i./ha	**9.2**	**Exceeded**
			Crop interception factor (80%): 223.8 g a.i./ha	**7.3**	**Exceeded**
			Off-field (ground appl., 6% drift): 16.79 g a.i./ha	0.6	Not Exceeded
			10% veg. dist. factor: 1.67 g a.i./ha	0.06	Not Exceeded
Vascular plants					
Vascular plant	Seedling emergence	ER_{25}>300 g a.i./ha	In-field: Cumulative soil rate of 600 g a.i./ha	**<2**	**Exceeded**
			Off-field (ground appl., 6% drift): 36 g a.i./ha	<0.12	Not Exceeded
			Off-field (early airblast appl., 74% drift): 444 g a.i./ha	**<1.48**	**Exceeded**
			Off-field (late airblast appl., 59% drift): 354 ga.i./ha	**<1.18**	**Exceeded**
	Vegetative vigour	ER_{25} > 300 g a.i./ha	In-field: Cumulative foliar rate of 183 g a.i./ha	<0.61	Not Exceeded

Table 6 Screening Level Risk Assessment of Foliar Application of Cyromazine for Birds and Mammals

	Toxicity (mg a.i./kg bw/d)	Feeding Guild (food item)	EDE* (mg a.i./kg bw)	RQ	Level of Concern (1) exceeded
For use on celery and outdoor ornamentals					
Small Bird (0.02 kg)					
Acute	178.50	Insectivore	14.89	0.08	Not Exceeded
Reproduction	38.30	Insectivore	14.89	0.39	Not Exceeded
Medium Sized Bird (0.1 kg)					
Acute	178.50	Insectivore	11.62	0.07	Not Exceeded
Reproduction	38.30	Insectivore	11.62	0.3	Not Exceeded

	Toxicity (mg a.i./kg bw/d)	Feeding Guild (food item)	EDE* (mg a.i./kg bw)	RQ	Level of Concern (1) exceeded
Large Sized Bird (1 kg)					
Acute	178.50	Herbivore (short grass)	7.51	0.04	Not Exceeded
Reproduction	38.30	Herbivore (short grass)	7.51	0.2	Not Exceeded
Small Mammal (0.015 kg)					
Acute	134.80	Insectivore	8.57	0.06	Not Exceeded
Reproduction	1.6	Insectivore	8.57	**5.35**	**Exceeded**
Medium Sized Mammal (0.035 kg)					
Acute	134.80	Herbivore (short grass)	16.61	0.12	Not Exceeded
Reproduction	1.6	Herbivore (short grass)	16.61	**10.38**	**Exceeded**
Large Sized Mammal (1 kg)					
Acute	134.80	Herbivore (short grass)	8.88	0.07	Not Exceeded
Reproduction	1.6	Herbivore (short grass)	8.88	**5.55**	**Exceeded**
For use on potatoes					
Small Bird (0.02 kg)					
Acute	178.50	Insectivore	22.77	0.13	Not Exceeded
Reproduction	38.30	Insectivore	22.77	0.59	Not Exceeded
Medium Sized Bird (0.1 kg)					
Acute	178.50	Insectivore	17.77	0.10	Not Exceeded
Reproduction	38.30	Insectivore	17.77	0.46	Not Exceeded
Large Sized Bird (1 kg)					
Acute	178.50	Herbivore (short grass)	11.48	0.06	Not Exceeded
Reproduction	38.30	Herbivore (short grass)	11.48	0.3	Not Exceeded
Small Mammal (0.015 kg)					
Acute	134.80	Insectivore	13.10	0.10	Not Exceeded
Reproduction	1.6	Insectivore	13.10	**8.19**	**Exceeded**
Medium Sized Mammal (0.035 kg)					
Acute	134.80	Herbivore (short grass)	25.40	0.19	Not Exceeded
Reproduction	1.6	Herbivore (short grass)	25.40	**15.88**	**Exceeded**
Large Sized Mammal (1 kg)					
Acute	134.80	Herbivore (short grass)	13.57	0.10	Not Exceeded
Reproduction	1.6	Herbivore (short grass)	132.57	**8.48**	**Exceeded**

*EDE = Estimated dietary exposure; is calculated using the following formula: (FIR/bw) × EEC, where:
FIR = Food Ingestion Rate. For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used:
Passerine Equation (body weight < or = 200 g): FIR (g dry weight/day) = $0.398(\text{bw in g})^{0.850}$
All birds Equation (body weight >200 g): FIR (g dry weight/day) = 0.648 (bw in g) 0.651
For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = $0.235(\text{bw in g})^{0.822}$
bw: Generic Body Weight
EEC: Concentration of pesticide on food item. At the screening level, relevant food items representing the most conservative EEC for each feeding guild are used.

Table 7 Mammalian Risk Assessment Using Maximum And Mean Cyromazine Residue Values Based On The Maximum Foliar Cumulative Application Rate (Celery and Outdoor Ornamentals – 183 g a.i./ha × 5 at 7 day Intervals) and the Maximum Foliar Cumulative Rate – 279.75 g a.i./ha for Potato Use (279.75 g a.i./ha + 139.50 g a.i./ha at 6 day Interval).

	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	Maximum nomogram residues				Mean nomogram residues			
			On-field		Off Field		On-field		Off Field	
			EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ
For use on celery and outdoor ornamentals										
Small Mammal (0.015 kg)										
Reproduction	51.00	Insectivore	8.57	0.17	6.34	0.12	5.91	0.12	4.38	0.09
	51.00	Granivore (grain and seeds)	1.33	0.03	0.98	0.02	0.63	0.01	0.47	0.01
	51.00	Frugivore (fruit)	2.65	0.05	1.96	0.04	1.26	0.02	0.94	0.02
Medium Sized Mammal (0.035 kg)										
Reproduction	51.00	Insectivore	7.51	0.15	5.56	0.11	5.19	0.10	3.84	0.08
	51.00	Granivore (grain and seeds)	1.16	0.02	0.86	0.02	0.55	0.01	0.41	0.01
	51.00	Frugivore (fruit)	2.32	0.05	1.72	0.03	1.11	0.02	0.82	0.02
	51.00	Herbivore (short grass)	16.61	0.33	12.29	0.24	5.90	0.12	4.37	0.09
	51.00	Herbivore (long grass)	10.14	0.20	7.51	0.15	3.31	0.06	2.45	0.05
	51.00	Herbivore (forage crops)	15.37	0.30	11.38	0.22	5.08	0.10	3.76	0.07
Large Sized Mammal (1 kg)										
Reproduction	51.00	Insectivore	4.01	0.08	2.97	0.06	2.77	0.05	2.05	0.04
	51.00	Granivore (grain and seeds)	0.62	0.01	0.46	0.01	0.30	0.01	0.22	0.00
	51.00	Frugivore (fruit)	1.24	0.02	0.92	0.02	0.59	0.01	0.44	0.01
	51.00	Herbivore (short grass)	8.88	0.17	6.57	0.13	3.15	0.06	2.33	0.05
	51.00	Herbivore (long grass)	5.42	0.11	4.01	0.08	1.77	0.03	1.31	0.03
	51.00	Herbivore (forage crops)	8.21	0.16	6.08	0.12	2.72	0.05	2.01	0.04
For use on potatoes										
Small Mammal (0.015 kg)										
Reproduction	51.00	Insectivore	13.10	0.26	0.79	0.02	9.04	0.18	0.54	0.01
	51.00	Granivore (grain and seeds)	2.03	0.04	0.12	0.00	0.97	0.02	0.06	0.00
	51.00	Frugivore (fruit)	4.05	0.08	0.24	0.00	1.93	0.04	0.12	0.00
Medium Sized Mammal (0.035 kg)										
Reproduction	51.00	Insectivore	11.48	0.23	0.69	0.01	7.93	0.16	0.48	0.01
	51.00	Granivore (grain and seeds)	1.78	0.03	0.11	0.00	0.85	0.02	0.05	0.00

	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	Maximum nomogram residues				Mean nomogram residues			
			On-field		Off Field		On-field		Off Field	
			EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ
	51.00	Frugivore (fruit)	3.55	0.07	0.21	0.00	1.69	0.03	0.10	0.00
	51.00	Herbivore (short grass)	25.40	0.50	1.52	0.03	9.02	0.18	0.54	0.01
	51.00	Herbivore (long grass)	15.51	0.30	0.93	0.02	5.06	0.10	0.30	0.01
	51.00	Herbivore (forage crops)	23.50	0.46	1.41	0.03	7.77	0.15	0.47	0.01
Large Sized Mammal (1 kg)										
Reproduction	51.00	Insectivore	6.13	0.12	0.37	0.01	4.24	0.08	0.25	0.00
	51.00	Granivore (grain and seeds)	0.95	0.02	0.06	0.00	0.45	0.01	0.03	0.00
	51.00	Frugivore (fruit)	1.90	0.04	0.11	0.00	0.91	0.02	0.05	0.00
	51.00	Herbivore (short grass)	13.57	0.27	0.81	0.02	4.82	0.09	0.29	0.01
	51.00	Herbivore (long grass)	8.29	0.16	0.50	0.01	2.71	0.05	0.16	0.00
	51.00	Herbivore (forage crops)	12.56	0.25	0.75	0.01	4.15	0.08	0.25	0.00

Table 8 Screening Level Assessment of Seed Treatment with Cyromazine for Birds and Mammals (green and dry onion seeds – 50 000 mg a.i./kg seed).

	Study Endpoint (mg a.i./kg bw/day / UF)	EDE (mg a.i./kg bw/day)	RQ	Level of Concern (1) exceeded
Small bird (0.02 kg)				
Acute	178.50	12696.926	**71.1**	**Exceeded**
Reproduction	38.30	12696.926	**331.5**	**Exceeded**
Medium bird (0.10 kg)				
Acute	178.50	9973.626	**55.9**	**Exceeded**
Reproduction	38.30	9973.626	**260.4**	**Exceeded**
Large bird (1.00 kg)				
Acute	178.50	2907.669	**16.3**	**Exceeded**
Reproduction	38.30	2907.669	**75.9**	**Exceeded**
Small mammals (0.015 kg)				
Acute	134.80	7255.939	**53.8**	**Exceeded**
Reproduction	1.6	7255.939	**4535.0**	**Exceeded**
Medium mammals (0.035 kg)				
Acute	134.80	6240.132	**46.3**	**Exceeded**
Reproduction	1.6	6240.132	**3900.1**	**Exceeded**
Large mammals (1.00 kg)				
Acute	134.80	3435.879	**25.5**	**Exceeded**
Reproduction	1.6	3435.879	**2147.4**	**Exceeded**

Table 9 Toxicity Assessment of Cyromazine Treated Seed to Birds and Mammals by Determining the Number of Seeds Required to Reach Endpoint and the Foraging Area Required.

Study Endpoint (mg a.i./kg bw/day / UF)		EDE (mg a.i./kg bw/day)	RQ	Number of seeds needed to reach endpoint		Area required (m^2)	
						Standard drilling - spring	
				min	max	min	max
Small bird (0.02 kg)							
Acute	178.50	12696.926	**71.1**	19.99	19.99	4.81	5.41
Reproduction	38.30	12696.926	**331.5**	4.29	4.29	1.03	1.16
Medium bird (0.10 kg)							
Acute	178.50	9973.626	**55.9**	99.96	99.96	24.04	27.05
Reproduction	38.30	9973.626	**260.4**	21.45	21.45	5.16	5.80
Large bird (1.00 kg)							
Acute	178.50	2907.669	**16.3**	999.60	999.60	240.40	270.45
Reproduction	38.30	2907.669	**75.9**	214.48	214.48	51.58	58.03
Small mammals (0.015 kg)							
Acute	134.80	7255.939	**53.8**	11.32	11.32	2.72	3.06
Reproduction	1.60	7255.939	**4535.0**	0.13	0.13	0.03	0.04
Medium mammals (0.035 kg)							
Acute	134.80	6240.132	**46.3**	26.42	26.42	6.35	7.15
Reproduction	1.60	6240.132	**3900.1**	0.31	0.31	0.08	0.08
Large mammals (1.00 kg)							
Acute	134.80	3435.879	**25.5**	754.88	754.88	181.55	204.24
Reproduction	1.60	3435.879	**2147.4**	8.96	8.96	2.15	2.42

[1] – Minimum and maximum area required based on minimum and maximum seeding rate (seeding rates based on VUI table - PMRA 2729803). UF= uncertainty factor.

Table 10 Toxicity of Cyromazine and Transformation Product, Melamine to Non-Target Aquatic Species

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	PMRA#
Freshwater species					
Daphnia magna	48-h Acute	Cyromazine (95.6% purity)	EC_{50}: >92.8 mg a.i./L (measured concentration) NOEC: 91 mg a.i./L	Could not be classified because of non-definitive endpoint	1206477
	48- h Acute (static)	Cyromazine (97.5% purity)	EC_{50}: >100 mg/L NOEC = 4.6 mg/L	Could not be classified because of non-definitive endpoint	2861359
	48-h Acute	Trigard 75 WP	EC_{50}: 90 mg/L	Slightly toxic	

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	PMRA#
	Static test	(purity 75.6%)	(equivalent to 68.94 mg a.i./L)		
	48-h Acute	Melamine (99% purity)	EC_{50}**:** 60 mg/L (95%C I = 44–96 mg/L) NOEC: 6.25 mg/L	Slightly toxic	
	48-h Acute Static	Melamine	EC_{50}: >2000 mg/L NOEC: 1000 mg/L	Could not be classified because of non-definitive endpoint	1185816
	21-d Chronic		NOEC: 32 mg /L (mortality and reproduction)	No classification	
	21-d Chronic	Cyromazine (93.4% purity)	NOEC: 0.31mg a.i./L (based on reproduction and length of surviving adults)	No classification	1148704
Sediment dwelling invertebrate, Larvae of *Chironomus riparius*	48-h Acute Semi-Static	Cyromazine (97.4% purity)	EC_{50}: >120 mg a.i./L (the highest concentration tested)	Could not be classified because of non-definitive endpoint	2767421
	26-d Chronic, spiked water		NOEC: 0.025 mg/L in overlying water (based on toxicity symptoms, emergence ratios and rates of development).	No classification	2767422
Rainbow trout, *Oncorhynchus mykiss*	96-h Acute	Cyromazine Technical	LC_{50}: >100 mg a.i./L NOEC: 1mg a.i./L	Could not be classified because of non-definitive endpoint	1198703
			LC_{50}: >87.9 mg a.i./L (measured concentration) NOEC: 50.8mg a.i./L	Could not be classified because of non-definitive endpoint	1206429
		Melamine (purity 99%)	LC_{50}: >120 mg/L (nominal concentration) NOEC: 120mg /L	Could not be classified because of non-definitive endpoint	2861359
	96-h Acute	Cyromazine 75 WP (75.6% a.i.)	LC_{50}: >100 mg a.i./L (based on nominal	Could not be classified because of	2861359

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	PMRA#
			concentration) NOEC: 32 mg/L	non-definitive endpoint	
Common carp, *Cyprinus carpio*	96-h Acute	Cyromazine Technical	LC_{50}: >100 mg a.i./L NOEC: 10mg a.i./L	Could not be classified because of non-definitive endpoint	1198703
		Cyromazine Technical (97.5% a.i.)	LC_{50}: >100 mg a.i./L (only concentration tested)	Could not be classified because of non-definitive endpoint	2861359
Bluegill sunfish, *Lepomis macrochirus*	96-h Acute	Cyromazine Technical	LC_{50}: >87.9 mg a.i./L (measured concentration) NOEC: 87.9 mg a.i./L	Could not be classified because of non-definitive endpoint	1206427
Channel catfish, *Ictalurus punctatus*	96-h Acute	Cyromazine Technical (95.6% purity)	LC_{50}: >91.6 mg a.i./L (measured concentration) NOEC: 91.6 mg a.i./L	Could not be classified because of non-definitive endpoint	1206428
Fathead minow *Pimephales promelas*	96-h Acute	Cyromazine Technical (93.4% purity)	LC_{50}: 715 mg a.i./L (95% CI: 629-816 mg a.i./L) measured concentration. NOEC: 190 mg a.i./L	Practically non-toxic	1148706
	Chronic (ELS)	Cyromazine (purity 93.4%)	NOEC: 14 mg a.i./L (mean measured concentration) based on effects on body weight at 36 mg a.i. /L and above. Other effects observed in the study were curvature of the spine at the two highest treatment levels.	No classification	
Green algae, *Selenastrum capricornutum*	72-h Acute (Static)	Melamine (99% purity)	E_bC_{50}: >100 mg /L (the highest concentration tested) ErC_{50}: >100 mg L	No classification	2861359
	72-h Acute (static)	Trigard 75 WP (75.6% a.i.)	ErC_{50}: >100 mg a.i./L EbC50: 30 mg	No classification	

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	PMRA#
			a.i./L Most sensitive endpoint = area under curve (biomas) (nominal concentration) NOE_rC & NOE_bC: 13.6 mg a.i./L		
Green algae, *Scenedesmus subspicatus*	96-h Acute	Cyromazine	EC_{50}: 124 mg a.i. /L (growth inhibition)	No classification	1198661
	96-h Acute (static)	Melamine	EC_{50}: 940 mg a.i. /L (growth inhibition) NOEC 320 mg/L	No classification	782358
Marine/estuarine species					
Mollusk, Eastern oyster, *Crassostrea virginica*	96-h Acute (flow-through)	Cyromazine (97.2% purity)	LC_{50}: >100 mg a.i./L (the highest concentration tested)	Could not be classified because of non-definitive endpoint	2337333
Crustacean, mysid shrimp, *Americamysis bahia*	28-day chronic (flow-through)		NOEC: 0.25 mg a.i./L (based on male body length at 14 days) (nominal concentration)	No classification	2337334
[1] USEPA classification, where applicable.					

Table 11 Screening Level Risk Assessment of Cyromazine to Aquatic Organisms

Organism	Exposure	Endpoint Value (mg a.i./L)	EEC (mg a.i./L)	RQ	Level of Concern (1)
Freshwater species					
Invertebrates (*Daphnia magna*)	Acute	$EC_{50}/2$ = 34.47	0.086	0.003	Not exceeded
	Chronic	NOEC = 0.31	0.086	0.28	Not exceeded
Chironomus riparius	Acute	$EC_{50}/2$ = 60	0.086	0.001	Not exceeded
	Chronic	NOEC = 0.025	0.086	**3.44**	**Exceeded**
Fish	Acute	$LC_{50}/10$ = 71.5	0.086	0.001	Not exceeded
	Early-life stage	NOEC = 14	0.086	0.006	Not exceeded
Amphibians (fish end-points)	Acute	$LC_{50}/10$ = 71.5	0.46	0.006	Not exceeded
	chronic	NOEC = 14	0.46	0.033	Not exceeded
Algae	Acute	$EC_{50}/2$ = 62	0.086	0.001	Not exceeded

Organism	Exposure	Endpoint Value (mg a.i./L)	EEC (mg a.i./L)	RQ	Level of Concern (1)
Marine species					
Crustacean	Acute	$LC_{50}/2 = 50$	0.086	0.002	Not exceeded
Mollusk	chronic	NOEC = 0.25	0.086	0.344	Not exceeded

Table 12 Screening Level Risk Assessment of Transformation Product, Melamine for Terrestrial and Aquatic Organisms

Organism	Exposure	Endpoint Value (mg/L)	EEC (mg/L)	RQ	Level of Concern (1)
Terrestrial					
Earthworm	Acute	LC50/2: >9.84 mg/kg soil	0.21 mg/kg soil	<0.021	Not exceeded
	Chronic	NOEC:1875 mg/kg soil		0.00011	Not exceeded
Aquatic					
Invertebrates (*Daphnia magna*)	Acute	$EC_{50}/2 = 30$	0.065	0.002	Not exceeded
	Chronic	NOEC = 32	0.065	0.002	Not exceeded
Fish	Acute	$LC_{50}/10 > 12$	0.065	<0.005	Not exceeded
Algae	Acute	$EC_{50}/2 = 470$	0.065	0.00014	Not exceeded

Table 13 Refined Risk Assessment of Potential Risk from Drift of Cyromazine to Aquatic Organisms

Organism	Exposure	Endpoint value	Refined EEC	RQ	Level of Concern (1)
Chironomus riparius	Chronic	NOEC = 0.025 mg a.i./L	Ground appl. (6% drift): 0.0052 mg a.i./L	0.20	Not Exceeded
			Early airblast. (74% drift): 0.064 mg a.i./L	**2.5**	**Exceeded**
			Late airblast. (59% drift): 0.051 mg a.i./L	**2.03**	**Exceeded**

Table 14 Risk Quotients for Aquatic Organisms Determined for Runoff of Cyromazine in Water Bodies.

Organism	Exposure	Endpoint value (mg/L)	Refined EEC (mg a.i./L)	RQ	Level of Concern (1)
Chironomus riparius	Chronic (runoff)	NOEC = 0.025 mg a.i./L	0.094	**3.8**	**Exceeded**
	Chronic (pore water)		0.079	**3.2**	**Exceeded**

Appendix X Toxic Substances Management Policy

Table 1 Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Cyromazine Endpoints
CEPA toxic or CEPA toxic equivalent[1]	Yes		Yes
Predominantly anthropogenic[2]	Yes		Yes
Persistence[3]:	Soil	Half-life ≥ 182 days	No. Laboratory studies: DT_{50} of 2.25, 25.5, 38 and 42.6 days in aerobic soil.
	Water	Half-life ≥ 182 days	No. DT_{50} of 12.8 to 15.9 days in aquatic aerobic water and total water-sediment system.
	Sediment	Half-life ≥ 365 days	Total system DT_{50} values range from 105, 253, 258 and 462 days in aerobic water-sediment systems.
	Air	Half-life ≥ 2 days or evidence of long range transport	Volatilisation is not an important route of dissipation and long-range atmospheric transport is unlikely to occur based on the vapour pressure (4.48×10^{-7} Pa at 25°C) and Henry's law constant (5.956×10^{-9} $Pa.m^3/mol$ at 25°C).
Bioaccumulation[4]	Log $K_{ow} \geq 5$		No 0.061 at 25°C
	BCF ≥ 5000		No <1
	BAF ≥ 5000		Not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet TSMP Track 1 criteria.

[1]All pesticides will be considered CEPA-toxic or CEPA toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (in other words, all other TSMP criteria are met).
[2]The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.
[3] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.
[4]Field data (for example, BAFs) are preferred over laboratory data (for example, BCFs) which, in turn, are preferred over chemical properties (for example, log K_{ow}).

Appendix XI Expected Environmental Concentrations (EECs)

Soil

EECs in soil were calculated based on the maximum, labelled single application rate of 141 g a.i./ha × 5 times with DT_{50} of 57.54 days to take into consideration dissipation between applications. Application is made to bare soil using ground application (medium spray; 6% drift) and airblast application (medium spray; early airblast 74% drift and late airblast 59% drift) with a soil bulk density of 1.5 g/cm^3 and that it is mixed evenly to a depth of 15 cm.

Table 1 Initial EECs of Cyromazine in Soil Following a Single Application on Potato and Outdoor Ornamentals Using Ground and Airblast Application Methods.

Crop	Cyromazine Cumulative Using Ground Application And Airblast (g a.i./ha)	Cyromazine EEC in soil Direct Overspray (mg a.i./kg soil)
Potato	399.75	0.178
Celery and Outdoor Ornamentals	600.012	0.27

Vegetation and other food sources

EECs for cyromazine on wildlife food sources were estimated based on correlations in Hoerger and Kenaga (1972) and Kenaga (1973), and modified according to Fletcher et al. (1994). The EECs were determined for both in-field and off-field exposure. The highest cyromazine application rate was chosen to calculate screening level EECs (celery and outdoor ornamentals: 141 g a.i./ha × 5 × 7) and potatoes at a maximum foliar cumulative seasonal rate of 279.75 g a.i./ha (based on 2 applications of cyromazine at (279.75 +139.50 g a.i./ha) at a 6 d interval. A cyromazine 3.3 d foliar half-life was applied to the EEC for all food items. At the screening level, the EECs on food sources were based on the maximum Kenaga values at the maximum, single application rate.

Table 2 Screening Level EECs (mg a.i./kg dw) in Vegetation (Foliar Half-Life = 3.3 d) and Insects After a Direct Over-Spray at 183 g a.i./ha) of Cyromazine on Field

Short range grass	Long grass	Forage crops	Pods with seeds	Insects	Grain and seeds	Fruit
129.22	78.90	119.56	9.28	58.41	9.04	18.08

Table 3 Screening Level EECs (mg a.i./kg dw) in Vegetation (Foliar Half-Life = 3.3 d) and Insects After a Direct Over-Spray at 279.75 g a.i./ha) of Cyromazine on Field

Short range grass	Long grass	Forage crops	Pods with seeds	Insects	Grain and seeds	Fruit
197.56	120.63	182.79	89.30	14.18	13.82	27.64

Water

EECs as a result of overspray into a body of water were calculated using the assumption that the water body has received a direct application of cyromazine and it has mixed evenly in a 80 cm or 15-cm depth of water (Table 4). An initial EEC immediately following a single application was calculated as a conservative measure.

Table 4 Initial EECs of cyromazine in Water – Direct application and due to drift

Crop	Cyromazine Appl. Rate at 141 g a.i./ha × 5 × 7 days	Water Depth (cm)	cyromazine EEC in water Direct Overspray (mg a.i./L)	EEC in water Spray Drift of 6% for medium spray ground boom[a] (mg a.i./L)	EEC in water Spray Drift of 74% for medium spray early airblast[b] (mg a.i./L)	EEC in water Spray Drift of 74% for medium spray early airblast[c] (mg a.i./L)
Celery & Outdoor Ornamentals	687.57	15	0.46	0.028	0.34	0.59
		80	0.086	0.005	0.06	0.05

[a] Based on ground boom sprayer application with medium spray quality (ASAE) spray drift is calculated at 6% of the application rate;
[b] Based on early airblast application with medium spray quality (ASAE) spray drift is calculated at 74% of the application rate.
[c] Based on late airblast application with medium spray quality (ASAE) spray drift is calculated at 59% of the application.

Appendix XII Proposed Label Amendments for Products Containing Cyromazine

Information on labels of currently registered products should not be removed unless it contradicts the label statements provided below.

1.0 Label Amendments for Cyromazine Technical Products

Before the STORAGE section, **Add** the title "ENVIRONMENTAL PRECAUTIONS" and the following statements:

"TOXIC to aquatic organisms"

"DO NOT discharge effluent containing this product into sewer systems, lakes, streams, ponds, estuaries, oceans or other waters."

2.0 Label Amendments for Cyromazine Commercial End-Use Products

All Commercial End-use Products

Cancelled Uses

Use instructions for the following crops/uses must be **removed** from the product labels:

- Onion seeds, dry bulb (imported treated seed)
- Potatoes
- Leafy Vegetables
- Celery
- Leafy Brassica Vegetables
- Cut Flowers (Outdoor and Greenhouse)
- Greenhouse Ornamentals
- Greenhouse Lettuce

After the PRECAUTIONS section, **Add** the title "ENVIRONMENTAL PRECAUTIONS" and the following statements:

"**TOXIC** to non-target terrestrial plants. Observe buffer zones specified under DIRECTIONS FOR USE."

"**TOXIC** to aquatic organisms. Observe buffer zones specified under DIRECTIONS FOR USE."

"Toxic to certain beneficial insects. Minimize spray drift to reduce harmful effects on beneficial insects in habitats next to the application site such as hedgerows and woodland."

"Not acutely toxic to adult bees but may affect reproduction and development of bees. However, when this product is applied and used according to label directions, risk to bees is expected to be negligible. As a best practice, avoid application when bees are present in the treatment area and minimize spray drift."

"To reduce runoff from treated areas into aquatic habitats, avoid application to areas with a moderate to steep slope, compacted soil or clay."

"Avoid application when heavy rain is forecast."

"Contamination of aquatic areas as a result of runoff may be reduced by including a vegetative strip between the treated area and the edge of the water body."

"The residues of cyromazine (melamine) are persistent and may carryover. It is recommended that any products containing cyromazine not be used in areas treated with this product during the previous season."

"This product demonstrates the properties and characteristics associated with chemicals detected in groundwater. The use of this product in areas where soils are permeable, particularly where the water table is shallow, may result in groundwater contamination."

Under PRECAUTIONS, **remove** the following statements:

"Avoid application when heavy rain is forecast."

"Contamination of aquatic areas as a result of runoff may be reduced by including a vegetative strip between the treated area and the edge of the water body."

"To reduce runoff from treated areas into aquatic habitats, consider the characteristics and conditions of the site before treatment. Site characteristics and conditions that may lead to runoff include, but are not limited to: heavy rainfall, moderate to steep slope, bare soil, poorly draining soil (e.g. soils that are compacted, fine textured, or low in organic matter such as clay)."

"DO NOT contaminate irrigation or drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes."

"Avoid contamination of food and feed, domestic or irrigation water supplies, lakes, streams and ponds. Do not reuse bag; destroy when empty."

Under DIRECTIONS FOR USE:

The following statements are required for all agricultural and commercial pesticide products, **Add**:

"As this product is not registered for the control of pests in aquatic systems, DO NOT use to control aquatic pests."

"DO NOT contaminate irrigation or drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes."

Replace:

"Do not apply by aircraft." or "DO NOT APPLY BY AIR."

With:

"DO NOT apply using aerial application equipment."

Remove:

"This product demonstrates the properties and characteristics associated with chemicals detected in groundwater. The use of this product in areas where soils are permeable, particularly where the water table is shallow, may result in groundwater contamination. Do not apply within 15 metres of well-heads or aquatic systems, including marshes, ponds, ditches, streams, rivers and lakes. Do not mix, load or clean spray equipment within 30 metres of well-heads or aquatic systems."

Add the title STORAGE, and the following statement:

"To prevent contamination store this product away from food or feed."

Delete the entire "DECONTAMINATION AND DISPOSAL" section

Delete the entire "CONTAINER DISPOSAL" section

Add:

DISPOSAL

1. Empty bag thoroughly into spray tank.
2. Make the empty bag unsuitable for further use.

3. For information on disposal of unused, unwanted product, contact the manufacturer or the provincial regulatory agency. Contact the manufacturer and the provincial regulatory agency in case of a spill, and for clean-up of spills.

Buffer Zone Related Label Statements Required For All End-use Products with Uses Other Than Seed Treatment:

Add to ENVIRONMENTAL PRECAUTIONS:

TOXIC to aquatic organisms and non-target terrestrial plants. Observe buffer zones specified under DIRECTIONS FOR USE.

Add to DIRECTIONS FOR USE:

Field sprayer application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE S572.1) medium classification. Boom height must be 60 cm or less above the crop or ground.

Airblast application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** direct spray above plants to be treated. Turn off outward pointing nozzles at row ends and outer rows. **DO NOT** apply when wind speed is greater than 16 km/h at the application site as measured outside of the treatment area on the upwind side.

Buffer zones:

Spot treatments using hand-held equipment do not require a buffer zone.

The buffer zones specified in the table below are required between the point of direct application and the closest downwind edge of sensitive terrestrial habitats (such as grasslands, forested areas, shelter belts, woodlots, hedgerows, riparian areas and shrublands), and sensitive freshwater habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs and wetlands.

Method of application	Crop		Buffer Zones (metres) Required for the Protection of:		
			Freshwater Habitat of Depths:		Terrestrial Habitat:
			Less than 1 m	Greater than 1 m	
Field sprayer	All crops		1	1	1
		Early growth Stage	3	1	2

Method of application	Crop		Buffer Zones (metres) Required for the Protection of:		
			Freshwater Habitat of Depths:		Terrestrial Habitat:
			Less than 1 m	Greater than 1 m	
Airblast	Outdoor ornamentals	Late growth stage	2	1	1

For tank mixes, consult the labels of the tank-mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture and apply using the coarsest spray (ASAE) category indicated on the labels for those tank mix partners.

The buffer zones for this product can be modified based on weather conditions and spray equipment configuration by accessing the Buffer Zone Calculator on the Pest Management Regulatory Agency web site.

Label amendments specific to Governor 75WP (24464):

Under PRECAUTIONS:

Replace:

"When handling or planting treated seed wear long sleeved shirt, long pants and boots."

With:

"When handling or planting treated seed wear long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes. Planting must be done using a closed cab system."

Under ENVIRONMENTAL PRECAUTIONS include the following:

"Treated seed is toxic to birds and small mammals. Any spilled or exposed seeds must be incorporated into the soil or otherwise cleaned-up from the soil surface."

Add the title USE RESTRICTIONS above the following statement (currently under DIRECTIONS FOR USE):

"All Seed Packaging Labels containing seed treated with GOVERNOR 75WP must contain the following statements:"

Under USE RESTRICTIONS, **add** the following statement:

"All containers or packages containing treated seed for sale or use in Canada must be labelled or tagged as follows: Toxic to birds. Any spilled or exposed seeds must be incorporated into the soil or otherwise cleaned-up from the soil surface".

Label amendments specific to Citation 75WP (24465):

Under PRECAUTIONS:

Replace:

"When mixing, loading or applying the product wear water-tolerant coveralls (e.g. TYVEK) over long-sleeve shirt and long pants, boots and chemical-resistant gloves. Greenhouse growers should wear gloves when handling treated crops."

With:

"Wear coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes during mixing, loading, application, clean-up and repair. In addition, wear chemical-resistant head gear during open cab airblast application. Chemical Resistant headgear includes sou'wester hat, chemical resistant rain hat or large brimmed waterproof hat and hood with sufficient neck protection."

Add:

"DO NOT use on ornamentals being grown for cut flower production."

Add:

"DO NOT use in greenhouses."

Add:

"When treating mushroom house compost and casing, wear long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes during mixing, loading, application, clean-up and repair."

Add:

"To be applied only to compost and casing when mushrooms are not present. **DO NOT APPLY** directly to mushrooms."

Under ENVIRONMENTAL PRECAUTIONS include the following:

> "DO NOT allow effluent or runoff from mushroom houses containing this product to enter lakes, streams, ponds or other waters."

Under DIRECTIONS FOR USE **add**:

> "For all activities except handset irrigation (involving foliar contact), DO NOT enter or allow worker entry into treated areas during the restricted-entry interval (REI) of 12 hours. For handset irrigation (involving foliar contact) DO NOT enter or allow worker entry into treated areas during the restricted-entry interval (REI) of 18 days."

References

1. Information Considered in the Chemistry Assessment

PMRA Document Number	Reference
1905740	2010, Description of Production Process, DACO: 2.11.1,2.11.3 CBI
1905741	2010, Cyromazine - Starting Materials, DACO: 2.11.2 CBI
1905742	2010, Discussion of Formation of Impurities, DACO: 2.11.4 CBI
1905748	2009, Analysis of five representative production batches produced at [CBI Removed], DACO: 2.13.3 CBI
1905750	2010, Cyromazine Technical Insecticide Impurities of Toxicological Concern, DACO: 2.13.4 CBI
1963348	CYZ-SYZ-6 (WAS CYZ-CGCS-1) FROM LSS FILE - Product Identity Larvadex, Purity and by-products of technical active ingredient, Synthesis Procedure, Analytical Method, Leaflet on active ingredient characteristics for registration purpose only DACO: 2.13.1,2
792528	Anonymous, 1995, Cyromazine Technical Manufacturing Summary, DACO: 2.11.1 CBI
792530	Anonymous, 1995, Data Sheet - Cyromazine Manufacturing Process, DACO: 2.11.3 CBI
792529	[CBI Removed] 2003, Cyromazine Technical Description of Starting Materials – - Note to Reviewer, DACO: 2.11.2 CBI
792536	[CBI Removed] 2003, Chemical Composition of CGA72662 Tech. Analysis of 5 Representative Production Batches for Content of CGA72662 and Impurities, DACO: 2.13.3 CBI
1597050	Technical Chemistry file CYZ-SYZ-6. Appendices A to D, Overview of synthesis, Product specification, Identification number and Sample date, Formal report of Analysis for N-Nitroso Compounds, DACO: 2.99

2. Information Considered in the Toxicology Assessment

2A. List of Studies/Information Submitted by the Registrant

PMRA Document Number	Reference
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1206558	Staley, J. and Ballantyne, L. 1986. Distribution and Characterization of 14-C Cyromazine in Monkeys. Hazelton Report Number ABR-85100. Hazelton Laboratories America, Inc., Greensboro, NC. Dated January 3, 1986. Unpublished. DACO 4.5.9
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1165100	Strausser, F. 1986. Mammalian Spot Test in the Mouse. Ciba-Geigy Project Number 850616. Ciba-Geigy Ltd. Basle, Switzerland. Dated February 11, 1986. Unpublished. DACO 4.5.4

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2722218	US EPA. 1985. Review of Rabbit Teratology with Larvadex (Cyromazine). Toxicology Branch, Hazard Evaluation Division. Dated February 5, 1985. DACO 12.5.4
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2722215	US EPA. 2003. Revised Executive Summaries and DER's of Cyromazine. Health Evaluation Division, Office of Prevention, Pesticides and Toxic Substances. Dated June 30, 2003. DACO 12.5.4
2993955	US EPA. 2006. Triazine Cumulative Risk Assessment. Office of Pesticide Programs, Health Effects Division. Dated March 28, 2006. DACO 12.5.4
2722214	US EPA. 2007. Cyromazine Summary Document. Registration Review Initial Docket. Special Review and Reregistration Division, Office of Prevention, Pesticides and Toxic Substance. Dated March, 2007. DACO 12.5.4
2722212	US EPA. 2014. Cyromazine: Human Health Risk Assessment for Registration Review. Health Effects Division, Office of Chemical Safety and Pollution Prevention. Dated February 27, 2014. DACO 12.5.4
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2722223	EFSA. 2008. Scientific Report Number 168. Conclusion on Pesticide Peer-Review: Cyromazine. European Food Safety Authority. Dated September 17, 2008. DACO 12.5.4
2989793	EFSA. 2015. Reasoned opinion on the modification of the existing MRL's for cyromazine in various leaf vegetables and fresh herbs. EFSA Journal 13(1): 4004. European Food Safety Authority. DACO 12.5.4
2722224	FAO. 2010. FAO Specifications and Evaluations for Agricultural Pesticides. Cyromazine. Food and Agriculture Organization of the United Nations. DACO 12.5.4
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2722229	Brennecke, L.H. 1993b. Memorandum from L. Brennecke to Stephen Dapson (Toxicology Branch II, OPP, US EPA) regarding additional evaluation of rodent mammary tumor data in cyromazine rat and mouse studies. Pathology Associates, Inc. Frederick, MD. Dated February 22, 1993. DACO 4.8
2722230	Iyer, P., Gammon, D., Gee, J. and Pfeifer, K. 1999. Characterization of Maternal Influence on Teratogenicity: An assessment of Developmental Toxicity Studies for the Herbicide Cyanazine. Reg. Toxicol. Pharmacol. 29: 88-95. DACO 4.8
2722768	Geng, X. and Oliver, G. 2009. Pathogenesis of holoprosencephaly. J. Clin. Invest. 119: 1403-1413. DACO 4.8
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2722232	Tzimas, G., Burgin, H., Collins, M.D., Hummler, H. and Nau, H. 2011. The high sensitivity of the rabbit to the teratogenic effects of 14-cis-retinoic acid is a consequence of prolonged exposure of the embryo to 13-cis-retinoic acid and 13-cis-4-oxo-retinoic acid, and not of isomerization to all-trans-retinoic acid. Arch. Toxicol. 68:119-128. DACO 4.8
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2722771	Health Canada. 2015. Supporting Document for Screening Assessment of Certain Organic Flame Retardants Substance Grouping 1,3,5-Triazine-2,4,6-triamine (Melamine) CAS RN 108-78-1. Human Health Supplementary Data. Existing Substances Program, Health Canada. Dated June, 2015. DACO 4.8

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2722773	WHO. 2009. Toxicological and Health Aspects of Melamine and Cyanuric Acid. Report of a WHO Expert Meeting, in Collaboration with FAO and Supported by Health Canada. Dated December, 2008. World Health Organization. DACO 12.5.4
2722221	Cal EPA. 1993. Cyromazine Risk Characterization Document. California Environmental Protection Agency. Dated March 24, 1993. DACO 12.5.4
2722774	IARC. 1999. Volume 73: Some Chemicals that Cause Tumors of the Kidney or Urinary Bladder in Rodents and Some Other Substances: Melamine. Report of the IARC Working Group, Lyon, France, October, 1998. International Agency for Research on Cancer. DACO 12.5.4
2722227	JMPR. 1990. Cyromazine. Joint FAO/WHO Meeting on Pesticide Residues in Food and the Environment. International Program on Chemical Safety. DACO 12.5.4
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2722223	EFSA. 2008. Scientific Report Number 168. Conclusion on Pesticide Peer-Review: Cyromazine. European Food Safety Authority. Dated September 17, 2008. DACO 12.5.4
2991326	EFSA. 2010. Scientific opinion on melamine in food and feed. EFSA Journal 8(4):1573. European Food Safety Authority. DACO 12.5.4
2989793	EFSA. 2015. Reasoned opinion on the modification of the existing MRL's for cyromazine in various leaf vegetables and fresh herbs. EFSA Journal 13(1): 4004. European Food Safety Authority. DACO 12.5.4
2722775	NTP. 1983. Carcinogenesis Bioassay of Melamine in F344 Rats and B6C3F1 Mice (Feed Study). National Toxicology Program. U.S. Department of Health and Human Services. NTP Technical Report #245. NTP-81-86. Dated March, 1983. DACO 4.4.2, 4.4.3
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2722777	Melnick, R., Boorman, J.K., Haseman, R.J. and Huff, J. 1984. Urolithiasis and bladder carcinogenicity of melamine in rodents. Toxicol. Appl. Pharmacol. 72: 292-303. DACO 4.8
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2722780	Kim, S.H., Lee, I.C., Lim, J.H., Shin, I.S., Moon, C., Kim, S.H., Park, S.C., Kim, H.C. and Kim, J.C. 2011. Effects of melamine on pregnant dams and embryo-fetal development in rats. J. Appl. Toxicol. 31: 506-514. DACO 4.5.2
2722904	Stine, C.B., Reimschuessel, R., Keltner, Z., Nochetto, C.B., Black, T., Olejnik, N., Scott, M., Bandele, O., Nemser, S.M., Tkachenko, A., Evans, E.R., Crosby, T.C., Ceric, O., Ferguson, M., Yakes, B.T. and Sprando, R. 2014. Reproductive toxicity in rats with crystal nephropathy following high doses of oral melamine or cyanuric acid. Food Chem Toxicol. 68: 142-153. DACO 4.5.2
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2722906	Tu, H., Zhang, M., Zhou, C., Wang, Z., Huang, P. and Ou, H. 2015. Genotoxicity assessment of melamine in the in vivo Pig-a mutation assay and in a standard battery of assays. Mut. Res. 777: 62-67. DACO 4.5.8

3. Information Considered in the Occupational/Residential Assessment

3A. List of Studies/Information Submitted by the Registrant

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2337329	2013, Use Description/Scenario - Mushroom Production, DACO: 5.2
1571553	2007, Determination of Operator Exposure to Imidacloprid During Loading/Sowing of Gaucho Treated Maize Seeds Under Realistic Field Conditions in Germany and Italy, DACO: 5.4

3B. List of Studies/Information Provided by Task Forces (ARTF, AHETF, ORETF)

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PMRA Document Number	Reference
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2572743	AHETF, 2014. Agricultural Handler Exposure Scenario Monograph: Open Cab Airblast Application of Liquid Sprays. Report Number AHE1006. October 20, 2014.
2572746	AHETF, 2015a. Agricultural Handler Exposure Scenario Monograph: Closed Cab Airblast Application of Liquid Sprays
1563628 1563634	Johnson, D.; Thompson, R.; Butterfield, B. 1999. Outdoor Residential Pesticide Use and Usage Survey and National Gardening Association Survey. Unpublished study prepared by Doane Marketing Research, Inc. EPA MRID 46883825 (also EPA MRID 44972202). ORETF
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1563670 1563673 1563654 1563664 1563636 1563641	Klonne, D. 1999. Integrated Report on Evaluation of Potential Exposure to Homeowners and Professional Lawn Care Operators Mixing, Loading, and Applying Granular and Liquid Pesticides to Residential Lawns. Sponsor/Submitter: Outdoor Residential Exposure Task Force. OMA003 & OMA004. EPA MRID # 44972201. ORETF Volumes 1-6
1560575	Merricks, D.L. 1997. Carbaryl Mixer/Loader/Applicator Exposure Study during Application of RP-2 Liquid (21%), Sevin Ready to Use Insect Spray or Sevin 10 Dust to Home Garden Vegetables. ORETF OMA006. EPA MRID # 44459801
1945969	Merricks, D.L. 1998. Carbaryl Mixer/Loader/Applicator Exposure Study during Application of RP-2 Liquid (21%) to Fruit Trees and Ornamental Plants: Lab Project Number: 1518. Unpublished study prepared by Agrisearch Inc., Rhone-Poulenc Ag Co., and Morse Laboratories, Inc. 320 p. OMA005. EPA MRID # 44518501. ORETF

4. Information Considered in the Dietary Assessment

4A. List of Studies/Information Submitted by the Registrant

PMRA Document Number	Reference
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PMRA Document Number	Reference
782352	1995. CGA 72662: Cyromazine - Magnitude of the Residues in or on Potatoes, Including Processed Fractions, Following Post Foliar Applications of Trigard.
1035069	2002. Magnitude of Residue and Residue Decline of Cyromazine and its Metabolite, Melamine, in Mushroom Following the Treatment with Citation 75WP to the Casing Layer.
1060182	1999. CGA-245704 and Cyromazine - Magnitude of the Residues in or on Crop Group 5: Brassica (Cole) Leafy Vegetables.
1092810	2002. Analytical Report for URMULE 2000 1482. Cyromazine: Magnitude of the Residue on Celery
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1149022	1991. Determination of Residues of Parent Compound and Metabolite Melamine in Cucumbers (Fruits)-Greenhouse Trials.
1149023	1987. Cyromazine Cucumber Residue Data (05-IR-001-86).
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1149026	1989. Cyromazine and Melamine in Melons Treated with Trigard 75WP.
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1149028	1983. Cyromazine and Melamine in Chili Peppers Treated with Trigard 75WP.
1149030	1987. Determination of Cyromazine Beside Melamine in Tomatoes After Application of Trigard 15WP.

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1149031	1989. Determination of Residues in Tomatoes After Application of Trigard 75WP.
1149032	1984-1987. Determination of Cyromazine Besides Melamine in Tomatoes After Application of Trigard (Various Trials).
1149033	1986-1988. Determination of CGA 72662 in Tomatoes (France Trials).
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1149035	1992. Determination of Residues of Parent Compound + Metabolite Melamine in Tomatoes-Field Trial (Under Plastic).
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1149037	1991. Determination of Residues of Cyromazine as 1-Methyl-Cyromazine in Tomatoes After Treatment with Trigard (0W-1R-201-90).
1149038	1991. Determination of Residues Cyromazine as Cyromazine and Melamine in Tomatoes & Tomato Processed Fractions After Treatment with Trigard.
1149039	1992. Magnitude of Residues of Cyromazine and Melamine in Tomatoes and Tomato Processed Fractions Resulting from Foliar Applications Of Trigard.
1149041	1986. Determination of Cyromazine Besides Melamine in Lettuce After Application of Trigard 75WP.
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1149051	1983-1988. Determination of Cyromazine Besides Melamine in Mushrooms After Application of Trigard (Various Trials).
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5. Information Considered in the Environmental Assessment

5A. List of Studies/Information Submitted by the Registrant

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1158191	1995, Soil dissipation study at four trial sites with CGA 72662.Final Report (CER 03310/93) (TRIGARD 75WP)., DACO: 8.3.2.3
1159661	1984,"Cyromazine –soil dissipation studies" California, Nebraska and Florida (7205, 7594, 7568, 7279; EIR-87003)., DACO: 8.3.2.3

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1198612	1980, Photolysis of CGA-72662 on soil surfaces under artificial sunlight conditions., DACO: 8.2.1
1198613	1979, Photolysis of CGA-72662 in aqueous solution under artificial sunlight conditions., DACO: 8.2.1
1198614	1981, Adsorption & Desorption of CGA-72662 (Vetrazin) in various soil types., DACO: 8.2.4.1
1198616	1980, Leaching Model Study w/Insecticide/Larvicide CGA-72662 in four different soils., DACO: 8.2.4.1
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2767391	1986, Degradation of CGA 72 662 In Aquatic Systems, DACO: 8.2.3.4.2
2767393	2000, Rate of Degradation of ^{14}C-Labelled CGA 72662 in one Soil under Laboratory Conditions at 20 degrees C and 10 degrees C, DACO: 8.2.3.4.2
2767394	1995, Aerobic Soil Metabolism of ^{14}C-Cyromazine, DACO: 8.2.3.4.2
2767395	2003, Rate of Transformation of Cyromazine and Melamine in Three Soils Under Aerobic Laboratory Conditions at 20 degrees C, DACO: 8.2.3.4.2
2767397	1994, Anaerobic Soil Metabolism of ^{14}C-Cyromazine Data Requirement, DACO: 8.2.3.4.4
2767398	2003, Degradation and Metabolism of ^{14}C-labelled Cyromazine in two Aerobic Aquatic Systems under Laboratory Conditions, DACO: 8.2.3.5.4
2767399	2001, Adsorption/Desorption Test Substance [14C]-CGA 235129, DACO: 8.2.4.2
2767400	2003, ^{14}C-Labelled Melamine (CGA 235129): Time Dependent Sorption in one soil, DACO: 8.2.4.2
2767401	2011, Cyromazine - Rate of Degradation of Metabolite NOA435343 under Aerobic Laboratory Conditions, in Three Soils, at 20 degrees C, DACO: 8.2.4.2
2767402	2011, Cyromazine - Adsorption/Desorption Properties of NOA435343 in Three Soils, DACO: 8.2.4.2
2767403	1992, Small-Scale Prospective Ground Water Monitoring Study for Cyromazine (Trigard 75WP), DACO: 8.6
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1148709	1989, The acute toxicity of melamine to the Earthworm (CBG464/8991) (Larvadex)., DACO: 9.2.3.1
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1198625	1978, Acute Oral LD 50 in the Adult Japanese Quail of Technical CGA-72662 (Project No.:SISS6446)., DACO: 9.6.2.1
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1198703	1978, Acute Toxicity to Rainbow Trout & Carp of Technical (72662). Project No.: SISS 6446, DACO: 9.5.2.1
1198715	1980, Accumulation & Elimination of ^{14}C – Residues by Bluegill Sunfish exposed to ^{14}C (CGA-72662)., DACO: 9.5.2.1
1198727	1979, Laboratory test on bee toxicity. Study finalized: August 30, 1979., DACO: 9.2.4.1

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2337334	2009, Cyromazine- Life-Cycle Toxicity Test with Saltwater Mysid, *Americanysis bahia*, Conducted under Flow-Through Conditions, DACO: 9.4.5
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2767409	2002, CGA72662: A rate response extended laboratory test to evaluate the effects of a 75 WP formulation (A6808A) on egg hatch and pre-imaginal development of the seven-spotted ladybird *Coccinella septempunctata* (Coleoptera: Coccinellidae), DACO: 9.2.5
2767410	1997, Acute Toxicity of CGA 72662 WP 75 (A-6808 A) to the ground dwelling predator Poecilus cupreus L., DACO: 9.2.5
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