Biocidal Products Committee (BPC)

Opinion on the application for approval of the active substance:

Cyromazine

Product type: 18

ECHA/BPC/087/2015

Adopted

10 December 2015

Annankatu 18, P.O. Box 400, FI-00121 Helsinki, Finland | Tel. +358 9 686180 | Fax +358 9 68618210 | echa.europa.eu

Opinion of the Biocidal Products Committee

on the application for approval of the active substance cyromazine for product type 18

In accordance with Article 89(1) of Regulation (EU) No 528/2012 of the European Parliament and of the Council 22 May 2012 concerning the making available on the market and use of biocidal products (BPR), the Biocidal Products Committee (BPC) has adopted this opinion on the approval in product type 18 of the following active substance:

Common name:	**cyromazine**
Chemical name(s):	**N-cyclopropyl-1,3,5-triazine-2,4,6-triamine**
EC No.:	**266-257-8**
CAS No.:	**66215-27-8**

Existing active substance

This document presents the opinion adopted by the BPC, having regard to the conclusions of the evaluating Competent Authority. The assessment report, as a supporting document to the opinion, contains the detailed grounds for the opinion.

Process for the adoption of BPC opinions

Following the submission of an application by Hokochemie Sarl on 28 April 2006 and Novartis Animal Health UK Ltd on 09 March 2006, the evaluating Competent Authority Hellas (EL) submitted an assessment report for the application of Novartis Animal Health UK Ltd and the conclusions of its evaluation to the Commission on June 2011. A combined assessment report considering the data from the two applications was submitted to ECHA by Greece on 28 August 2014. In order to review the assessment report and the conclusions of the evaluating Competent Authority, the Agency organised consultations via the BPC and its Working Groups and the Commission via the Biocides Technical Meetings. Revisions agreed upon were presented and the assessment report and the conclusions were amended accordingly.

Adoption of the BPC opinion

Rapporteur: the BPC member from Greece

The BPC opinion on the approval of the active substance cyromazine in product type 18 was adopted on 10 December 2015.

The BPC opinion was adopted by simple majority of the members present having the right to vote. The minority position including its grounds is published on the ECHA webpage at: http://echa.europa.eu/regulations/biocidal-products-regulation/approval-of-active-substances/bpc-opinions-on-active-substance-approval.

Detailed BPC opinion and background

1. Overall conclusion

The overall conclusion of the BPC is that the cyromazine in product type 18 may be approved. The detailed grounds for the overall conclusion are described in the assessment report.

2. BPC Opinion

2.1. BPC Conclusions of the evaluation

a) Presentation of the active substance including the classification and labelling of the active substance

This evaluation covers the use of cyromazine in product type 18. Cyromazine belongs to the triazine group is an insect growth regulator with larvicidal action against flies. Specifications for the reference source are established.

The physico-chemical properties of the active substance and biocidal product have been evaluated and are deemed acceptable for the appropriate use, storage and transportation of the active substance and biocidal product.

Validated analytical methods are available for the active substance as manufactured and for the significant impurities. Validated analytical methods are available for soil, water and air. No analytical methods for food and feed of plant and animal origin are available.

A harmonised classification for cyromazine is not available. The CLH dossier is currently prepared and will be submitted to ECHA as soon as possible.

The eCA EL proposal for classification and labelling for cyromazine according to Regulation (EC) No 1272/2008 (CLP Regulation) is:

Classification according to the CLP Regulation	
Hazard Class and Category Codes	Long-term aquatic hazard Category 1 (Chronic 1)
Labelling	
Pictograms	GHS09
Signal Word	Warning
Hazard Statement Codes	H410
Specific Concentration limits, M-Factors	M = 1 (for chronic toxicity)
Justification for the proposal	
Cyromazine is classified as Chronic 1 based on its chronic toxicity to the aquatic insect *Chironomous riparius* (NOEC of 0.016 mg a.s./L) and the fact that it is not readily biodegradable.	

b) Intended use, target species and effectiveness

Cyromazine is an insect growth regulator for the control of fly larvae in manure and other breeding sites in animal housing. Biocidal products containing cyromazine can be used by professionals and non-professionals. Cyromazine exerts larvicidal effect against flies after ingestion. It interferes with the moulting process of larvae and pupation, leading to deformed or/and dead larvae, pupae or adults. The precise mode of action remains unknown, though it has been shown not to inhibit the synthesis of chitin and cuticular proteins. The representative products are water soluble granule or water soluble powder biocidal products applied to manure or any decaying organic matter either by: i) direct dispersal of the dry granules; ii) directional spraying after dissolution in water with any

spray equipment; or iii) pouring using watering can after dissolution in water. Water soluble granule and water soluble powder biocidal products of cyromazine are effective against flies with 1-5 and 3-5 applications, respectively, during the season of flies' activity (March/April to October/November) depending on the animal housing system. The efficacy data submitted on cyromazine and the representative biocidal products have demonstrated sufficient efficacy against the larvae of nuisance and biting flies.

According to the submitted efficacy studies with the representative products, cyromazine was assessed and proved efficacious against fly larvae in closed (indoors) and open (outdoors) animal houses by dry scattering, spraying or pouring.

The substance may also be intended to be used by professionals outside of stables and animal housings on manure heaps, slurry reservoirs and waste dumps; and by non-professionals on faeces and manure generated by small companion animals housed close to or in human living areas. These uses were not assessed, except for the use on manure heaps for human health.

In terms of efficacy, eCA considers that the professional use on manure heaps, slurry reservoirs and waste dumps and the general use of biocidal products containing cyromazine onto manure produced by small companion animals are anticipated to provide effective control of fly larvae, provided that the dose rates and application methods are identical to the professional use assessed in animal houses.

The use of cyromazine applied directly to fly-breeding sites may entail a risk of resistance development.

c) Overall conclusion of the evaluation including need for risk management measures

Human health

Following oral administration cyromazine is rapidly and almost completely absorbed, it is widely distributed with the highest residues detected in urinary bladder, kidney and liver, and it is excreted unchanged primarily *via* urine. Metabolites methyl-cyromazine, hydroxy-cyromazine and melamine are identified, each representing less than 5% of the dose. There is no potential for cyromazine accumulation in mammals. Cyromazine is considered of low acute oral, dermal and inhalation toxicity. No ocular and only slight and rapidly reversible signs of dermal irritation are noted. No evidence of skin sensitisation potential is identified. Cyromazine did not show a relevant genotoxic, neurotoxic, teratogenic and/or carcinogenic potential or reproductive toxicity. The critical effect identified in rats, mice and dogs after repeated and/or prolonged oral exposure to cyromazine was decreased body weight and body weight gain.

The table below summarises the exposure scenarios assessed.

Summary table: human health scenarios			
Scenario	**Primary or secondary exposure and description of scenario**	**Exposed group**	**Conclusion**
Dry scattering	Primary exposure during indoor/outdoor manual scattering	Professionals	Acceptable with long trousers, short-sleeved shirt and gloves
Spraying	Primary exposure during indoor/outdoor spraying using portable spray equipment	Professionals	Acceptable with gloves
Watering	Primary exposure during indoor/outdoor pouring using a watering can	Professionals	Acceptable with gloves and coverall
Spraying	Primary exposure during spraying using hand-held pumped sprayer	Non-professionals	Acceptable
Dry scattering	Secondary exposure during indoor/outdoor manual scattering	Bystanders (adults)	Acceptable
Spraying	Secondary exposure during indoor/outdoor spraying using portable spray equipment	Bystanders (adults)	Acceptable
Watering	Secondary exposure during indoor/outdoor pouring using a watering can	Bystanders (adults)	Acceptable

Professional use of cyromazine products *via* dry scattering is considered to be safe when PPE (gloves and long trousers, short-sleeved shirt) is used. Application by spraying is safe when gloves are used, while application by watering is considered to be safe when gloves and coated coverall are used.
Non-professional application of cyromazine products by spraying using hand-held pumped sprayer is considerd to be safe.
Bystanders (adults) are considered to be safe in all cases. Children are not expected to be present during the application of cyromazine products by professional users in animal-production or dairy facilities. Therefore, a bystander (child) exposure assessment has not been performed.
Exposure of persons re-entering/working in animal housing after application is considered negligible.

Environment

The table below summarises the exposure scenarios assessed.

Summary table: environment scenarios		
Scenario	**Description of scenario including environmental compartments**	**Conclusion**
Spraying 5 applications/year, considering an application rate of 0.5 g Cyromazine/m^2 (Professional use, indoor applications)	Dairy cows, beef cattle, veal calves, sows, fattening pigs. Emissions from spray application to the manure/slurry: the manure/slurry will be spread on grassland or arable land and lead to exposure of soil, groundwater, surface water and sediment.	Unacceptable risks for soil for veal calves and sows in individual pens. Acceptable risks for soil for the other animal categories. Acceptable risks for groundwater, surface wate and sediment for all animal categories.
	Laying hens, broilers, turkeys, ducks and geese in free range with litter floor, parent broilers and laying hens in rearing with grating floor. Emissions from spray application to the manure/slurry and waste water. The manure/slurry will be spread on grassland or arable land and lead to exposure of soil and groundwater. Emissions to surface water, soil and groundwater via a sewage treatment plant (STP).	Unacceptable risks for surface and sediment water for laying hens for emission via STP. Acceptable risks for surface water for the other animal categories. Unacceptable risks were identified for soil for laying hens for emission via spreading of manure/slurry on grassland or arable land and via STP. Acceptable risks for soil for the other animal categories. Acceptable risks for groundwater for all animal categories.

No unacceptable risk to the aquatic compartment (including surface water and sediment) from the parent compound cyromazine is expected following treated manure application to land (grassland and arable land) according to the proposed use pattern. Regarding indirect exposure to cyromazine via STP, an unacceptable risk has been identified for surface water and sediment-dwelling organisms for laying hens (in battery cages with aeration (belt drying) and in free range with litter floor (partly litter floor, partly slatted)). In respect to the groundwater, the PECgw calculated for cyromazine were above the trigger value of 0.1 µg/L for all animal housing categories with exception of the following categories: broilers (in free range with litter floor), turkeys (in free range with litter floor), ducks (in free range with litter floor) and geese (in free range with litter floor) (<0.1 µg/L). PECgw for cyromazine were also calculated using FOCUS PEARL 4.4.4 (including the worst case scenario, i.e. cat. 3 veal calves). The results were well below the trigger value of 0.1 µg/L for all examined scenarios.

No aquatic risk (including surface water and sediment) via spreading of manure/slurry on grassland or arable land and via STP exposure was identified for cyromazine's metabolite melamine. Regarding grounwater, PECgw results were above the trigger value of 0.1 µg/L for all animal categories with exception of broilers (in free range with litter floor), turkeys (in free range with litter floor), ducks (in free range with litter floor) and geese (in free range with litter floor) (<0.1 µg/L). Further PEC_{gw} calculations for melamine were performed using FOCUS PEARL. The respective results exceed the threshold value of 0.1 µg/L (max. 2.41 µg/L). However, melamine is considered as non-relevant metabolite. Nevertheless, a refined risk assessment of indirect exposure via consumption of contaminated drinking water was conducted indicating that the presence of melamine in groundwater at the maximum level of 2.41µg/L poses no risk to the consumer.

For soil compartment, a risk was identified following application of treated manure or slurry on grassland or arable land in 8 out of 18 animal housing categories. More specifically, for veal calves, sows and laying hens, $PEC_{soil}/PNEC_{soil}$ ratios were above the trigger of 1. No

unacceptable risk has been identified to soil-dwelling organisms from melamine following the intended use pattern.

In conclusion, taking into consideration the risk assessment performed for all relevant environmental compartments including indirect exposure via STP for poultry housing, safe uses were demonstrated for the following animal housing categories: dairy cows; beef cattle; sows in groups; fattening pigs; broilers in free range with litter floor; parent broilers in rearing with grating floor; parent broilers in rearing with grating floor; turkeys in free range with litter floor; ducks in free range with litter floor; geese in free range with litter floor. The spraying scenario used is considered to be a worst-case in compariso to the other application methods (dry scattering of granules and application via watering can) as it covers a larger treatment area.

It should be also noted that no unacceptable effects to bees and non-target arthropods as well as to top predators (birds and mammals; via both primary and secondary poisoning) were identified following the intended use pattern of cyromazine.

Overall conclusion

In human health risk assessment all relevant scenarios i.e. spraying, dry scattering and watering have been assessed separately and have been considered acceptable for professional users with the use of the appropriate personal protective equipment. For non-professional users the risk is acceptable without the use of personal protective equipment.

In case of environment only the spraying scenario has been assessed which however, is considered as a worst-case and therefore, covers the dry scattering and watering scenarios. Safe uses have been identified for the following animal categories: dairy cows, beaf cattle, sows in groups, pigs, broilers, turkeys, ducks and geese.

2.2. Exclusion, substitution and POP criteria

2.2.1. Exclusion and substitution criteria

The table below summarises the relevant information with respect to the assessment of exclusion and substitution criteria:

<table>
<tr><th colspan="2">Property</th><th colspan="2">Conclusions</th></tr>
<tr><td rowspan="3">CMR properties</td><td>Carcinogenicity (C)</td><td>No classification required</td><td rowspan="3">Cyromazine does not fulfil criterion (a), (b) and (c) of Article 5(1)</td></tr>
<tr><td>Mutagenicity (M)</td><td>No classification required</td></tr>
<tr><td>Toxic for reproduction (R)</td><td>No classification required</td></tr>
<tr><td rowspan="3">PBT and vPvB properties</td><td>Persistent (P) or very Persistent (vP)</td><td>vP</td><td rowspan="3">Cyromazine does not fulfil criterion (e) of Article 5(1) and does not fulfil criterion (d) of Article 10(1)</td></tr>
<tr><td>Bioaccumulative (B) or very Bioaccumulative (vB)</td><td>Not B and vB</td></tr>
<tr><td>Toxic (T)</td><td>Not T</td></tr>
<tr><td>Endocrine disrupting properties</td><td colspan="3">Nnot considered to have endocrine disrupting properties. Cyromazine does not fulfil criterion (d) of Article 5(1).</td></tr>
</table>

Respiratory sensitisation properties	No classification required. Cyromazine does not fulfil criterion (b) of Article 10(1).
Concerns linked to critical effects	Cyromazine does not fulfill criterion (e) of Article 10(1).
Proportion of non-active isomers or impurities	With regard to the proportion of non-active isomers or impurities, Cyromazine is put on the market with 95% w/w minimum purity. Given this, Cyromazine does not fulfil criterion (f) of Article 10.

Consequently, the following is concluded:

Cyromazine does not meet the exclusion criteria laid down in Article 5 of Regulation (EU) No 528/2012.

Cyromazine does not meet the conditions laid down in Article 10 of Regulation (EU) No 528/2012, and is therefore not considered as a candidate for substitution. The exclusion and substitution criteria were assessed in line with the "Note on the principles for taking decisions on the approval of active substances under the BPR"[1] and in line with "Further guidance on the application of the substitution criteria set out under article 10(1) of the BPR"[2] agreed at the 54th and 58th meeting respectively, of the representatives of Member States Competent Authorities for the implementation of Regulation 528/2012 concerning the making available on the market and use of biocidal products. This implies that the assessment of the exclusion criteria is based on Article 5(1) and the assessment of substitution criteria is based on Article 10(1)(a, b, d, e and f).

2.2.2. POP criteria

Cyromazine is considered persistent and demonstrates the potential of long-range transport. However, the available (eco)toxicological data do not indicate a concern to human health, animals and the environment. Therefore, cyromazine does not meet the POP criteria.

2.3. BPC opinion on the application for approval of the active substance cyromazine in product type 18

In view of the conclusions of the evaluation, it is proposed that cyromazine shall be approved and be included in the Union list of approved active substances, subject to the following specific conditions:

1. Specification: minimum purity of the active substance evaluated: 950 g/kg.

2. The authorisations of biocidal products are subject to the following condition(s):

    a. The product assessment shall pay particular attention to the exposures, the risks and the efficacy linked to any uses covered by an application for authorisation, but not addressed in the Union level risk assessment of the active substance.

    b. In view of the risks identified for the uses assessed, the product assessment

[1] See document: Note on the principles for taking decisions on the approval of active substances under the BPR (available from https://circabc.europa.eu/d/a/workspace/SpacesStore/c41b4ad4-356c-4852-9512-62e72cc919df/CA-March14-Doc.4.1%20-%20Final%20-%20Principles%20for%20substance%20approval.doc)
2 See document: Further guidance on the application of the substitution criteria set out under article 10(1) of the BPR (available from https://circabc.europa.eu/d/a/workspace/SpacesStore/dbac71e3-cd70-4ed7-bd40-fc1cb92cfe1c/CA-Nov14-Doc.4.4%20-%20Final%20-%20Further%20guidance%20on%20Art10(1).doc)

shall pay particular attention to:

i. professional users;

ii. the surface water, sediment and soil compartment for products used in animal housing.

c. For products that may lead to residues in food or feed, the need to set new or to amend existing maximum residue levels (MRLs) in accordance with Regulation (EC) No 470/2009[3] or Regulation (EC) No 396/2005[4] shall be verified, and any appropriate risk mitigation measures shall be taken to ensure that the applicable MRLs are not exceeded.

The placing on the market of treated articles is subject to the following condition(s):

1. The person responsible for placing on the market of a treated article treated with or incorporating the active substance cyromazine shall ensure that the label of that treated article provides the information listed in the second subparagraph of Article 58(3) of the Regulation (EU) 528/2012.

The active substance is very persistent (vP) and therefore gives rise to concern according to Article 28(2) being of an equivalent level of concern and can therefore not be included in Annex I of Regulation (EU) 528/2012.

2.4. Elements to be taken into account when authorising products

1. The following recommendations and risk mitigation measures have been identified for the uses assessed. Authorities should consider these risk mitigation measures when authorising products, together with possible other risk mitigation measures, and decide whether these measures are applicable for the concerned product:

a. If an unacceptable risk for industrial and professional users is identified for the product, safe operational procedures and appropriate organisational measures shall be established. Where exposure cannot be reduced to an acceptable level by other means, products should be used with appropriate personal protective equipment.

b. An unacceptable risk for surface water and sediment is identified for products used in animal housings where direct release via waste water to STP and/or surface water occurs. If the risk cannot be reduced to an acceptable level by appropriate risk mitigation measures or by other means, these uses should not be authorised.

c. An unacceptable risk for soil is identified for the concerned product for uses in animal housings other than dairy cows, beef cattle, fattening pigs. , If the risk cannot be reduced to an acceptable level by appropriate risk mitigation measures or by other means, these uses should not be authorised.

d. The potential resistance of fly larvae to cyromazine could be of concern and, as such, resistance management measures should be included in the authorisation of products. These could include (but should not be restricted to the following factors:

- The use of this product should be alternated with use of products based on other active substances with different mode of action to avoid development of resistance.

[3] Regulation (EC) No 470/2009 of the European Parliament and of the Council (OJ L 152, 16.6.2009, p. 11
[4] Regulation (EC) No 396/2005 of the European Parliament and of the Council (OJ L 70, 16.3.2005, p. 1

- Use of sufficiently high doses (0.5 g/m^2) to get good control (90% or more) is recommended.
- Systematic (covering entire populations), uninterrupted and excessive (inappropriately high concentrations) selection pressure on fly populations should be avoided.
- Fly infestation in the animal house can be estimated by monitoring methods (e.g. monitoring of (re)-appearance of larvae in the manure or adult fly population with glue strips) prior to chemical treatment.
- The use of biocidal products can be combined with other sanitation measures (e.g. frequent removal of dung) or non-chemical means of control (for example biological including the use of parasitoids, where this is commercially viable) within an integrated fly control program.
- The control of housefly populations resistant to cyromazine is possible through an integrated management scheme that includes cultural and biological strategies plus chemicals (larvicides and adulticides) in a rational manner.

e. An assessment of the risk in food and feed areas may be required at product authorisation where use of the product may lead to contamination of food and feeding stuffs.

f. An assessment of secondary exposure of children may be required at product authorisation. If an unacceptable risk is identified, the following safety phrase should be included: "children should not have access to the application area during and directly after application".

2.5. Requirement for further information

Sufficient data have been provided to verify the conclusions on the active substance, permitting the proposal for the approval of Cyromazine. However the following further data must be submitted to the evaluating Competent Authority (Greece) as soon as possible but no later than 6 months before the date of approval of the active substance:

1. The applicant Hokochemie should provide the following data: a study for the dissociation constant; for the solubility in organic solvents, including the effect of temperature on solubility; a flammability study; a validated analytical method for the determination of cyromazine and melamine residues in water; a validated analytical method the determination of cyromazine residues in air, a phototransformation in water including identity of the products of transformation, a water/sediment degradation study; an aerobic soil degradation study; a study regarding the rate and route of degradation including identification of the processes involved and identification of any metabolites and degradation products in at least three soil types under appropriate conditions; an adsorption and desorption study; and a mobility in at least three soil types and, where relevant, mobility of metabolites and degradation products.

2. The applicant Novartis should provide a confirmatory method for drinking and surface water.

3. For both applicants, pending on the dietary risk assessment, residue analytical methods for food/feed of plant, animal origin might be required at product authorization stage.