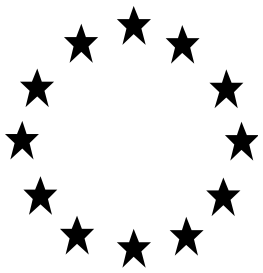
Regulation (EU) No 528/2012 concerning the making available on the market and use of biocidal products

Evaluation of active substances

Assessment Report



Cyromazine

Product-type 18
(Insecticides, acaricides and products to control other arthropods)

February 2016

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1. STATEMENT OF SUBJECT MATTER AND PURPOSE

1.1. Procedure followed

This assessment report has been established as a result of the evaluation of the active substance cyromazine as product-type 18 (Insecticdes, Acaricides and Products to Control other arthropods), carried out in the context of the work programme for the review of existing active substances provided for in Article 89 of Regulation (EU) No 528/2012, with a view to the possible approval of this substance.

Cyromazine (CAS no. 66215-27-8) was notified as an existing active substance, by two companies (Novartis animal health Inc and Hokochimie Sarl), hereafter referred to as the applicant(s), in product-type 18. With effect from 1/1/2015, the company Novartis animal health is fully owned by the company Elanco Europe Ltd, a division of El Lilly & Company, following a purchase.

Commission Regulation (EC) No 1451/2007 of 4 December 2007[1] lays down the detailed rules for the evaluation of dossiers and for the decision-making process.

In accordance with the provisions of Article 7(1) of that Regulation, Greece was designated as Rapporteur Member State to carry out the assessment on the basis of the dossier submitted by the applicant. The deadline for submission of a complete dossier for Cyromazine as an active substance in Product Type was 30/4/2006, in accordance with Annex V of Regulation (EC) No 1451/2007.

On 9/3/2006, the Greek competent authorities received a dossier from the applicant Novartis animal health Inc. On 28/4/2006, the Greek competent authorities received a dossier from the applicant Hokochimie Sarl. The Rapporteur Member State accepted the dossiers as complete for the purpose of the evaluation on 27/7/2006 and 2/11/2006 for Novartis animal health Inc and Hokochimie Sarl respectively.

On 04/09/2014, the Rapporteur Member State submitted to the Commission and the applicant a copy of the evaluation report, hereafter referred to as the competent authority report.

In order to review the competent authority report and the comments received on it, consultations of technical experts from all Member States (peer review) were organised by the Agency. Revisions agreed upon were presented at the Biocidal Products Committee and its Working Groups meetings and the competent authority report was amended accordingly.

1.2. Purpose of the assessment report

The aim of the assessment report is to support the opinion of the Biocidal Products Committee and a decision on the approval of Cyromazine for product-type 18 , and, should it be approved, to facilitate the authorisation of individual biocidal products. In the evaluation of applications for product-authorisation, the provisions of Regulation (EU) No 528/2012 shall be applied, in particular the provisions of Chapter IV, as well as the common principles laid down in Annex VI.

For the implementation of the common principles of Annex VI, the content and conclusions of this assessment report, which is available from the Agency web-site shall be taken into account.

However, where conclusions of this assessment report are based on data protected under the provisions of Regulation (EU) No 528/2012, such conclusions may not be used to the benefit of

[1] Commission Regulation (EC) No 1451/2007 of 4 December 2007 on the second phase of the 10-year work programme referred to in Article 16(2) of Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market. OJ L 325, 11.12.2007, p. 3

another applicant, unless access to these data for that purpose has been granted to that applicant.

2. OVERALL SUMMARY AND CONCLUSIONS

2.1. Presentation of the Active Substance

2.1.1. *Identity, Physico-Chemical Properties & Methods of Analysis*

2.1.1.1. Names/addresses of Applicant/manufacturer of the active substance

Novartis:

Applicant	Novartis Animal Health UK Ltd. Frimley Business Park, Frimley, Camberley, Surrey GU16 7SR, United Kingdom Point of contact is: Novartis Animal Health Inc. CH-4058 Basel, Switzerland Phone +41 61 6978333 Fax +41 61 696 1687 hiltrud.dornieden@novartis.com As of 1/1/2015 the company Novartis Animal Health UK Ltd is fully owned by Elanco Europe Ltd, a division of El Lilly & Company Elanco Europe Limited Lilly House, Priestley Road Basingstoke Hampshire RG24 9NL UK
Manufacturer of active substance (if different)	Shanghai Novartis Animal Health Co., Ltd. Wusi Farm, Fengxian County, Shanghai 201423, China Phone +86 21 5716 2070 Fax. +86 21 5716 2034

Hokochimie Sarl:

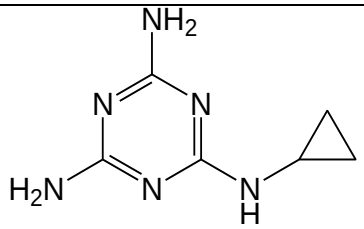
Applicant	Hokochimie Sarl 15, ave de Joinville FR-94130 Nogent-sur-Marne Phone +33 9 70 40 31 88 Fax +33-8- 26 33 57 31 E-mail info@hoko.fr Point of contact is:

	Hokochemie GmbH Pannerhofstrasse 7 6353 Weggis, Switzerland Phone: + 41 41 390 31 88 Fax : +41 41 390 31 89 munk@hoko.com
Manufacturer of active substance (if different)	Manufacturer for and on behalf of Hokochimie GmbH: Hokochimie GmbH c/o China National Chemical Construction Jiangsu Company Beijing Road (W) 17, 210024 Nanjing, China Phone +86-25-833 00 867 Fax +86-25-833 07 058 E-mail: info@hoko.com

2.1.1.2. Identity of the active substance

Cyromazine is an insecticide. Its identity is presented in the table below:

Table 1: Identity of the active substance cyromazine

Chemical name of Cyromazine	IUPAC nomenclature: N-cyclopropyl-1,3,5-triazine-2,4,6-triamine CAS-name: N-cyclopropyl-1,3,5-triazine-2,4,6-triamine
CAS registry number	66215-27-8
EEC number	266-257-8 (EINECS)
Minimum purity of the active substance as manufactured (g/kg of g/l)	950 g/kg
CIPAC number	420 (CIPAC)
Molecular formula	$C_6H_{10}N_6$
Structural formula:	
Molecular weight	166.19 g/mol

2.1.1.3. Physico-chemical properties

Cyromazine is a fine white powder (Novartis) - crystalline form (Hokochimie Sarl) at room temperature. Its melting point is 223.96°C and it decomposes at 300-400°C. The relative density of cyromazine technical is about 1.334 and its vapour pressure is 4.48×10^{-7} Pa at 25°C. It is not expected to have oxidising or explosive properties and shows no re-activity towards its container material.

Novartis:

Two representative formulations have been evaluated in support of Cyromazine by Novartis.

Neporex 2 SG is a water soluble granules containing 2% w/w Cyromazine. It is not expected to have oxidising or explosive properties. Storage stability studies show that it remains stable for 2 weeks at 54ºC and for 5 years at 25°C/60% and 5 years at 30°C/65%.

Neporex 50 SP is a water soluble powders containing 50% w/w Cyromazine. It is not expected to have oxidising or explosive properties. Storage stability studies show that it remains stable for 2 weeks at 54ºC, for 5 years at 25°C/60%, for 2 years at 40°C/75% and for 5 years at 30°C/65%.

Hokochimie Sarl:

One representative formulation has been evaluated in support of Cyromazine.

HOKOEX® is Water Soluble Granules (SG) containing 2% cyromazine. It is not expected to have oxidising or explosive properties. Storage stability studies show that it remains stable at 54±2°C for 14 days. A shelf life study is ongoing.

2.1.1.4. Methods of Analysis

Analysis of active substance as manufactured

Novartis:

A fully validated HPLC/UV (DAD) method has been submitted for the determination of the cyromazine in technical material which is acceptable. Finally, acceptable and sufficiently validated methods have been submitted for the determination of impurities and additives in the technical material.

Hokochimie Sarl:

The content of cyromazine is determined by HPLC/UV. Finally, acceptable and sufficiently validated methods have been submitted for the determination of impurities and additives in the technical material.

Residue analysis

An analytical method for residues of Cyromazine in body fluids and tissues is not required since Cyromazine is not considered toxic or highly toxic.

Since the dietary risk assessment was perfomed before agreed Guidance was available (see discussion Table point 11, 12, 13 and 17, Human Exposure) no analytical method is required at this point for food/feed of plant/animal origin. Pending on the dietary risk assessment, residue analytical methods for food/feed of plant, animal origin might be required at product authorization stage.

Novartis:

Fully validated analytical methods with acceptable data (The methods were considered acceptable in the EU Evaluation (EFSA Scientific Report (2008) 168, 1-94, Conclusion on the peer review of cyromazine) of Cyromazine as pesticide for Cyromazine and Melamine were

submitted for soil and water. A confirmatory method for drinking and surface water must be submitted.

Fully validated analytical method for the determination of Cyromazine in air has been submitted.

Hokochimie Sarl:

For residue analysis, fully validated analytical methods with acceptable data for Cyromazine and Melamine were submitted for soil.

Formulation analysis

Novartis:

The determination of the active ingredients Cyromazine in the formulations is performed HPLC/UV detection. The method is considered fully validated.

Hokochimie Sarl:

The determination of the active ingredients Cyromazine in the formulation is performed HPLC using a reversed phase (C18) column and UV detection (diode array detector, DAD) at 210 nm in isocratic mode. The method is considered fully validated.

2.1.2. Intended Uses and Efficacy

PT18, Insecticide (Insect Growth Regulator - IGR)

Cyromazine is an Insect Growth Regulator-IGR developed for the control of fly larvae in manure and other breeding sites in animal housing (e.g. cattle, swine, poultry facilities). The products of cyromazine are used by farmers, who are regarded as professional users.

According to the efficacy data submitted by two applicants (Hokochimie Sarl and Novartis) in the biocidal product dossiers, cyromazine after formulation into water soluble granule or water soluble powder biocidal products (SG or SP) is applied to manure or any decaying organic matter either by:

a) direct dispersal of the dry granules of granule formulations (in case of wet or liquid manure);

b) directional spraying after dissolution in water with any spray equipment - knapsack or automatic equipment - delivering the spray as a course low-pressure spray onto the fly breeding sites;

c) pouring by watering can after dissolution in water;

Hoko claims that the substance may be used as well outside of stables and animal housings on manure heaps, slurry reservoirs and waste dumps. This applicant claims also that the product may in the future be marketed formulated into a biocidal products for non-professional use on faeces and manure generated by small companion animals housed close to or in human living areas.

Since the dose rates and application methods are identical to the professional use in animal houses, the use on manure heaps, slurry reservoirs and waste dumps as well the general use

of biocidal products containing cyromazine are anticipated to provide effective control of fly larvae.

Effects:

Cyromazine is an Insect Growth Regulator (IGR) with larvicidal action against flies after ingestion leading to the reduction of the adult population below the nuisance level, for as long as organic matter containing the active ingredient remains accessible to the larvae.

It interferes with the moulting process of larvae and pupation, leading to deformed or/and dead larvae, pupae or adults.

No symptoms are observed prior to pupation or moulting into next larval instar, leading up to the death of the individual.

Pupae assume larviform shapes and adult eclosion is impaired by various degrees of malformations (Wilson 1997, Bel et al. 2000, *Hoko dossier*).

Cyromazine affects mainly the dipteran larval molt of the first larval stages (L1, L2) whereas the effect on elder larvae of the last larval stage (L3) that have stopped feeding, is limited. Early treatment of the breeding sites, before larval populations are well established, is therefore recommended (*5.3.1 of Doc-IIIA5, Novartis dossier*).

Cyromazine has larvicidal action onto housefly larvae after treatment of the larval medium inducing a range of delayed morphogenetic aberrations in treated 3^{rd} -instar larvae and subsequent developmental stages (pupae, adults). At the highest concentration (1.5 ppm), most of the morphogenetic aberrations are observed in the pupal stage, while at 0.5 ppm most of the morphogenetic aberrations occur in the adult stage. The aberrant puparia are rodlike, C-shaped, or elongate and generally twice as long as normal puparia. At a concentration of 0.5 ppm, failure of adults to emerge properly is the most prevalent effect while eclosion of adults is impaired by various malformations (B5.10/01 by Hoko).

Larvicidal effect of cyromazine has also been demonstrated on earlier stages of houseflies. After incorporation to larval medium cyromazine strongly affects the development of fly larvae from the earliest stages (1^{st}, 2^{nd}) inhibiting adult emergence. In a study of Kocisova *et al*. (2004) (*Hoko dossier*) after the treatment of larval medium at a rate of 0.5 gr cyromazine/m^2 the moulting process stopped, the larvae usually lost fluid, gradually blackened and finally died. The surviving larvae were abnormal, with decreased locomotion, atypical shapes and thickened central parts, various distortions, elongated puparia and larvae died or developed abnormal pupae.

Cyromazine is an IGR, which acts on fly larvae by ingestion and has no direct effect against adults, pupae and eggs although contamination of eggs may results subsequently in larval deaths [B5.10/01&10 by *Novartis,* Alam and Motoyama (2000) and Wilson (1997) by *Hoko*].

Organisms to be controlled and organisms to be protected:

Taking into account the efficacy studies submitted by both applicants (see section 2.3 of Doc II-A), target pest species of cyromazine include diptera larvae such as:

Nuisance flies:

Musca domestica (Muscidae) (Common Housefly)

Fannia canicularis (Muscidae) (Lesser house fly)

Muscina stabulans (Muscidae) (False stable fly)

Eristalinus taeniops (Syrphidae) (Band-eyed drone fly)

Drosophila repleta (Drosophilidae) (Common fruit fly)

Ophyra leucostoma (Muscidae) (Garbage fly)

Biting flies: *Stomoxys calcitrans* (Stable Fly)

Cyromazine is intended for the control of fly larvae in manure and other breeding sites, used by farmers in animal units, in order to protect the animals from adult fly populations. Nuisance and Biting Flies are vectors of disease and nuisance pests to animals in intensive animal housing. If left uncontrolled they can compromise animal health and can affect the quality and quantity of the output of the production facility – such as reduced milk production and reduced weight gain. The substance is also indented to reduce fly nuisance to humans working in intensive animal housing.

Although the active substance cyromazine has shown to be active against some dipteran larvae, further efficacy studies are required at product authorization in case of fly species specific claims.

Also, considering efficacy studies submitted by both applicants, the effect is significant to dipteran larvae and the development of other insects that may be found in fly breeding media is not expected to be significantly affected by cyromazine (see section 2.3 of Doc-IIA).

MODE OF ACTION INCLUDING TIME DELAY

Mode of action:

Cyromazine is an Insect Growth Regulator (IGR) with 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 cyromazine action remains unknown, though it has been shown not to inhibit the synthesis of chitin and cuticular proteins. The mode of action is different from the mode of action of both currently known adulticidal insecticides as well as urea insect growth regulators (e.g. diflubenzuron).

As the physiological effects of cyromazine are manifest in the cuticle, it has been hypothesized that cyromazine may target the cuticle [Van de Wouw *et al*. (2006) (*Hoko and Novartis dossier*)]. However, histological studies of the effects of cyromazine in treated larvae of houseflies demonstrated that there were no cuticular abnormalities and that there was no interference with normal cuticle deposition. Observations from these studies suggest that cyromazine affected puparium formation partially through its effect on the insect musculature [B5.10/01 (Awad et al. 1984), in *Hoko dossier*].

The morphogenetic and histopathologic effects, especially in the presence of teratogenic effects in treated fly larvae, suggest that cyromazine not only affects larval musculature but may also interferes with the hormonal balance controlling development (Van de Wouw *et al*. 2006).

Overall, despite numerous biochemical and some genetic studies, the precise mode of cyromazine action remains undetermined.

(In section 2.4 of Doc-IIA literature references about mode of action of cyromazine, submitted in both applicant dossiers, are overviewed).

Time delay:

Cyromazine accumulates in the larvae over time and there is a delay between cyromazine exposure and effect (Van de Wouw *et al*. 2006).

Due to the specific mode of action of cyromazine, effective larval control starts delayed and may take also some time before any effects are observed at an adult fly population level.

Time delay for effective control of adult fly population after treatments with the supportive products Neporex 2SG or 50SP (*Novartis dossier*) occurs gradually and depends on time of initial application. Generally, the effective management of adult fly population occurred in 1 or 2 weeks after the first application with the recommended doses.

Similarly, the results of the submitted efficacy field study B5.10/02 with the supportive product Hokoex in Hoko dossier showed that effective control of adult fly population with cyromazine recorded gradually and became visible 1 to 2 weeks after larvicidal treatment.

OCCURRENCE OF RESISTANCE

Cyromazine may be used repeatedly on the top layer of manure where the fly larvae are present. The aim is to control most of the fly larvae, however this may lead to a selection pressure and in due time resistance may develop. Hence, there is a risk of resistance development. Since this has happened in manure flies primarily via feed-through application technique it may occur when used according to the current label claim with direct application onto the manure.

It can be assumed that the use of cyromazine applied directly to fly-breeding sites may entail a risk of resistance development. Therefore the following general resistance management measures are proposed:

- 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.
- 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.

The detailed resistance management measures should be proposed at product authorisation stage, as relevant for the product.

The assessment of the biocidal activity of the active substance demonstrates that it has a sufficient level of efficacy against the target organism(s) and the evaluation of the summary data provided in support of the efficacy of the accompanying product, establishes that the product may be expected to be efficacious.

Cyromazine has been evaluated for its intended use as an insecticide (PT 18); In addition, in order to facilitate the work of Member States in granting or reviewing authorisations, the intended uses of the substance, as identified during the evaluation process, are listed in Appendix II.

2.1.3. *Classification and Labelling*

2.1.3.1 Classification and labelling of the active substance cyromazine

Classification of the active substance according to the Regulation (EC) 1272/2008

Classification	Aquatic Chronic Cat. 1 (M-factor for chronic toxicity: 1)
GHS Pictograms	
Signal Word	Warning
Hazard Statements	H410: Very toxic to aquatic life with long lasting effects
Precautionary Statements	P273: Avoid release to the environment P391: Collect spillage P501: Dispose of contents/container in accordance with local regulation

Justification for the classification assigned to the active substance (Regulation 1272/2008):

The active substance is classified as Chronic 1 based on its chronic toxicity to *Chironomous riparius* (e.g. NOEC of 0.016 mg a.s./L; Schmidt, 2004; III A7.4.3.5.1/02; Novartis) and the fact that it is not readily biodegradable. According to the ECHA Guidance Document on the Application of the CLP criteria (version 4.0, November 2013; chapter 4.1.3.2.3.1) valid data from short- and long-term tests on species other than the standard test species at the same trophic level shall be considered for classification purposes, provided they are equivalent in terms of species relevance, testing conditions and test endpoints. Taking into account the mode of action of cyromazine (insect growth regulator with larvicidal effect against flies after ingestion) and the greater sensitivity of aquatic insects compared to other aquatic organisms (e.g. fish, crustaceans, algae), the chronic toxicity data for *Chironomous riparius* should be used for the classification of long-term aquatic hazard. No classification is warranted with regard to physic/chemical and toxicological properties.

2.1.3.2 Classification and labelling of the biocidal products

Neporex 2 SG

Classification according to the Regulation (EC) 1272/2008

Classification	Aquatic Chronic Cat. 3
GHS Pictograms	No pictogram is required
Signal Word	No signal word is required
Hazard Statements	H412: Harmful to aquatic life with long lasting effects

Precautionary Statements	P280: Wear protective gloves and protective clothing P273: Avoid release to the environment P501: Dispose of contents/container in accordance with local regulation
Other phrases	Wear sturdy footwear/boots during the application or when entering the treated areas

Justification for the classification assigned to Neporex 2 SG according to the Regulation 1272/2008:

The recommendation to use protective equipment is based on the exposure assessment performed.

Neporex 2 SG is classified as Chronic 3 based on the sum of its classified ingredients (i.e. cyromazine).
No classification is warranted with regard to physic/chemical properties.

Neporex 50 SP

Classification according to the Regulation (EC) 1272/2008

Classification	Eye Irritation Cat. 2 Aquatic Chronic Cat.1
GHS Pictograms	
Signal Word	Warning
Hazard Statements	H319: Causes serious eye irritation H410: Very toxic to aquatic life with long lasting effects
Precautionary Statements	P264: Wash hands thoroughly after handling P280: Wear protective gloves, protective clothing and eye protection P273: Avoid release to the environment P391: Collect spillage P501: Dispose of contents/container in accordance with local regulation

Justification for the classification assigned to Neporex 50 SP according to the Regulation 1272/2008:

Neporex 50 SP is classified as Chronic 1 based on the sum of its components classified as Chronic 1. Due to the lack of testing toxicity data on the product as a whole, the classification was based on the summation of its classified ingredients and more specifically on the classification of the active substance cyromazine (50% w/w).

Based on the available eye irritation study Neporex 50 SP is classified as Eye irritant. The recommendation to use protective equipment is based on the exposure assessment performed.

No classification is warranted with regard to physic/chemical properties.

Hokoex

Classification according to the Regulation (EC) 1272/2008

Classification	Aquatic Chronic Cat.3
GHS Pictograms	No pictogram is required
Signal Word	No signal word is required
Hazard Statements	H412: Harmful to aquatic life with long lasting effects
Precautionary Statements	P280: Wear protective gloves and protective clothing P273: Avoid release to the environment P501: Dispose of contents/container in accordance with local regulation
Other phrases	Wear sturdy footwear/boots during the application or when entering the treated areas

Justification for the classification assigned to Hokoex according to the Regulation 1272/2008:

Hokoex is classified as Chronic 3 based on the sum of its classified ingredients (i.e. cyromazine).

The recommendation to use protective equipment is based on the exposure assessment performed.

No classification is warranted with regard to physic/chemical properties.Summary of the Risk Assessment.

2.2. Summary of the Risk Assessment

2.2.1. *Human Health Risk Assessment*

2.2.1.1 Hazard identification

Toxicokinetics

Following oral administration cyromazine was found to undergo rapid and almost complete absorption in the rat body (94-97 % of total urinary excreted radioactivity within 24 hours, greater than 97% of the applied dose within 72 hrs) (Novartis). Cyromazine is widely distributed with the highest residues of radioactivity detected in urinary bladder, kidney and liver. The excretion was found to be rapid primarily via urine (94-97 % of the dose) within 24 hours.

In rats, cyromazine was excreted in urine predominantly unchanged (greater than 80% of the radioactivity excreted). Metabolites methyl-cyromazine, hydroxy-cyromazine and melamine were also present, each representing less than 5% of the dose. It was found that the metabolic pattern was generally independent of sex, dose or pre-treatment, with only quantitative differences between the different groups tested. A similar metabolic profile was seen for faeces.

In monkeys, cyromazine accounted for more than 94% of urinary radioactivity with the

remainder characterized as melamine.

There is no potential for cyromazine accumulation in mammals.

An oral absorption value of 100% has been set for risk assessment purposes.

Dermal penetration

The dermal absorption value for cyromazine has been set at 26% for the dilution and 17% for a 2% undiluted product and 12% for a 50% undiluted product, based on *in vivo* rat data (Novartis).

Acute toxicity

Cyromazine is considered of low acute oral, dermal and inhalation toxicity (Novartis, Hokochimie Sarl). No classification is warranted according to Regulation (EC) 1272/2008.

Irritation and corrosivity

No ocular and only slight and rapidly reversible signs of dermal irritation were noted after application of cyromazine to the skin and eye of rabbits (Novartis, Hokochimie Sarl). The degree of irritation reactions was well below the respective thresholds for classification according to according to Regulation (EC) 1272/2008. Therefore, no classification for irritation is required for cyromazine.

Sensitisation

Two maximisation tests according to Magnusson and Kligman showed no evidence of skin sensitisation potential (sensitisation rate was 0%) (Novartis, Hokochimie Sarl). Therefore, no classification for skin sensitisation is required for cyromazine according to Regulation (EC) 1272/2008.

Repeated dose effects

Short-term oral toxicity of cyromazine was assessed in several studies in rats for 90-days (Novartis, Hokochimie Sarl) and in dogs for 90-days (Novartis, Hokochimie Sarl), 26-weeks (Novartis) and 1-year (Novartis). The critical effect identified was reduced body weight gain. Moreover, in dogs, haematological and clinical chemistry changes were observed and also the heart, kidneys and haematopoietic system were identified as target organs after 1-year oral exposure.

In the 90-day dog gavage study (Hokochimie Sarl) prostate atrophy was observed from the dose of 60 mg/kg b.w./day. This effect was reversed at 60 mg/kg b.w./day during the 4-week recovery period of the study and it was not reproduced in any of the feeding studies (90-day, 26-week, 1-year dog and 90-day rat). Prostate atrophy in dogs was therefore not attributed to cyromazine, but rather to the stress imposed to the animals by gavage administration for 90-days, as well as to the high bolus of the test substance introduced in the body by gavage swhich would result in high Cmax systemically available.

The highest relevant NOAEL for short-term oral toxicity in rats was set at 23 mg/kg b.w./day (Goldenthal, 1979) and in dogs was set at 5.74 mg/kg b.w./day from the 1-year dietary study (Altmann, 1997).

The short-term toxicity of cyromazine was also assessed by the dermal (Novartis) and inhalation (Novartis) routes.

In the dermal 21-day study in rabbits there was no evidence of target organ toxicity and the NOAEL was set at 2000 mg/kg b.w./day (Kuhn, 1992).

In the 28-day inhalation study in rats, treatment-related clinical signs including piloerection, dyspnea and hunched posture were observed in all animals tested from the lowest dose of 58 mg/m³ (Hartmann, 1988). The severity of these clinical signs increased with dose, from slight at the lowest dose to severe at 206 and 706 mg/m^3. These effects were considered as systemic and therefore a LOAEL was established at the lowest dose level instead of deriving a LOAEC/NOAEC. This point was agreed at the BPC WG-I-2015 virtual meeting (27 January 2015). Classification of cyromazine as 'possible risk of irreversible effects' is not warranted, as the effects observed at $\leq$ 250 mg/m^3 did not fulfil the criteria of severe damage including clear functional disturbances or toxicologically significant morphological changes.

It should be noted that the inhalation route of exposure by cyromazine is not of practical relevance, since cyromazine is neither a gas, nor volatile, nor is it used as a fumigant or aerosol and has a low vapour pressure (4.48 x 10-7 Pa at 25° C). Therefore, despite the toxicity observed in the 28-day inhalation study in rats, testing by inhalation over 90-days was not considered necessary.

Chronic toxicity and carcinogenicity of cyromazine was assessed in mice and rats (Novartis). The critical effect identified in both species after 2-year oral exposure was decreased body weight gain. The NOAEL for chronic oral toxicity in rats was set at 14.7 mg/kg b.w./day and in mice was set at 6.5 mg/kg b.w./day. (Details on the carcinogenic potential of cyromazine is presented in section 3.7 of this document.)

Genotoxicity

As far as the genotoxicity data package by Novartis is concerned, it is noted that the majority of the studies are quite old with major deviations from the current guidelines. The submitted *in vitro* chromosomal aberration assay and both gene mutation assays are of limited validity. A valid *in vivo* micronucleus assay obtained negative results.

As far as the genotoxicity data package by Hokochimie Sarl is concerned, three *in vitro* genotoxicity studies were submitted. All of them were well-conducted and valid. No genotoxic potential was detected in the bacterial reverse mutation test and in the chromosomal aberration assay. In the mouse lymphoma gene mutation test, in the absence of metabolic activation and in the long treatment time, statistically significant increases in mutant frequency were observed. In the absence of any valid gene mutation assay in the Novartis genotoxicity data package, no read across was possible. The eCA originally proposed the conduction of a new mouse lymphoma gene mutation assay which would include reporting of the incidence of small and large colonies.

In the BPC WG-I-2015 virtual meeting (27 January 2015), a point in the discussion table was left open for the WG to consider the necessity of conducting a new *in vitro* gene mutation study with cyromazine.

In response to this question the applicant (Hokochemie) provided a statistical analysis on the mutation frequency of large and small colonies in the mouse lymphoma gene mutation assay after 24-hour treatment with the test item in the absence of S9 metabolic activation (Cinelli, 2006c; see CAR Doc IIIA6.6.3). This analysis revealed that the large colony mutant frequency was significantly increased at 625 µg/mL (P<5%) and 1250 µg/mL (P<1%). This was in line with the results of the mutation frequency (small and large colonies in total) originally presented in the study.

A consensus was reached by the WG members that a new *in vitro* gene mutation study with cyromazine would not add substantially to the already available information and should not be conducted. However, the justification behind this conclusion was not agreed. According to the majority opinion the study result should be regarded as equivocal for the following reasons:

- the statistically significant increase in the mutant frequency of large colonies (indicating possible point mutations) at the two highest concentrations was observed in the absence of S9 only after 24 hr of treatment at concentrations which are cytotoxic to the cells;

- the response was not concentration-dependent;
- there was no positive response at the 3 hr treatment in the absence or presence of S9.

Repetition of the study however is not justified since:

1. Mammalian cell gene mutation (MCGM) assays have been recently recognised as highly variable and uninterpretable, producing a high number of false positives. State-of-the-art mutagenicity testing strategies, e.g. that produced by the UK Committee on Mutagenicity (https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/315793/testing_chemicals_for_genotixicity.pdf) or by EFSA (http://www.efsa.europa.eu/en/efsajournal/doc/2379.pdf) propose that two in vitro tests (Ames and micronucleus test) are sufficient to investigate the in vitro genotoxic potential of a substance;
2. There are other two MCGM assays already available on cyromazine - although these have some limitations, they are both negative;
3. There are three negative good-quality Ames tests and a negative mutation assay in *S.cerevisiae* D7.
4. There are two *in vitro* UDS assays in rat hepatocytes - although these have some limitations, they are both negative.

Consequently, cyromazine is not considered to be genotoxic, and there is no need to conduct another gene mutation assay *in vitro* or *in vivo*.

Carcinogenicity

Carcinogenicity of cyromazine was assessed in 2-year oral exposure studies in rats and mice (Novartis). No relevant increases in tumour incidence were observed in either species.

Cyromazine was considered to be non-carcinogenic and no classification for this parameter is warranted. Other toxic effects as well as NOAEL/ LOAEL values of the studies were discussed in section 3.5 of this document.

Toxicity to reproduction and development

The teratogenic potential of cyromazine was investigated in totally seven studies after oral application of the test substance. One study was carried out in rats (Novartis) and six in rabbits (Novartis & Hokochimie Sarl). The rabbit was considered to be more sensitive than the rat. Increased incidence in the number of early and late resorptions (rabbit), delayed ossification (rats), skeletal malformations and variations (rabbits) and decreased foetal body weight (rats and rabbits) were noted in the presence of substantial maternal toxicity (body weight loss). The overall NOAEL for both developmental and maternal effects was set at 15 mg/kg b.w./day based on data from rabbit teratology studies.

In the BPC WG-I-2015 virtual meeting (27 January 2015) members recognised that the critical developmental effects in rabbits were seen above the maximum tolerated dose (MTD). However, **the effects should be highlighted in the CLH report to be submitted.** The eCA considered that no classification regarding developmental toxicity is warranted.

Effects on reproduction (fertility) were investigated in a 2-generation feeding study (Novartis) and a 2-generation gavage study in rats (Hokochimie Sarl). Reproductive toxicity (increased post-implantation losses and dystocia in females and reduced fecundity index in males) and offspring effects (decreased live birth index) were observed in the gavage study from the dose of 80 mg/kg b.w./day, in the presence of substantial maternal toxicity evidenced as decreased bodyweight. The overall NOAEL for reproductive, parental and offspring effects was set at 20 mg/kg b.w./day (Ganiger, 2008).

In the BPC WG-I-2015 virtual meeting (27 January 2015), several members expressed their concern on reproductive toxicity (fertility) of cyromazine. The basis of the concerns raised were the effects observed in the 2-generation study in rats by Ganiger (2008), i.e. reduced

fecundity index in males and increased post-implantation losses and dystocia in females at 80 mg/kg b.w/day and in the 90-day dog study (Venugopala Rao, 2007), i.e. prostate atrophy at 60 and 120 mg/kg b.w./day in males. **It was noted by ECHA that a final conclusion on reproductive toxicity should be made by RAC in the context of C&L.** The eCA opinion is that cyromazine is not a reproductive toxicant.

Neurotoxicity

Cyromazine is not an organophosphorous or related pesticide and is not expected to induce delayed neurotoxicity. Therefore, it is considered that specific studies on delayed neurotoxicity are not relevant to this molecule. In addition, no neurotoxic effects were observed in the acute, sub-chronic, chronic, reproduction and teratogenicity studies. Therefore, no specific testing for the investigation of neurotoxic effects is required.

Human data

No adverse health effects have been reported in connection with the handling of cyromazine in the synthesis or formulation. Based on animal testing, poisoning symptoms may constitute body weight loss. There is no specific antidote for cyromazine. First aid measures for cases of poisoning with cyromazine should comprise standard decontamination measures and symptomatic treatment.

2.2.1.2 Effects assessment

Cyromazine did not show a relevant genotoxic, 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.

A comparison of the 90-day studies in rats and the 90-day and 1-year studies in dogs indicated that the dog is more sensitive than the rat to repeated cyromazine administration. On that background, the NOAEL of 5.74 mg/kg b.w./day from the 1-year dog study is the most relevant end-point for the setting of medium and long term reference values, i.e. $AEL_{medium\text{-}term}$, $AEL_{long\text{-}term}$ and ADI.

Moreover, cyromazine is of low acute dermal (LD_{50} > 2000 mg/kg b.w.) and inhalation (LC_{50} > 5.27 mg/L air) toxicity and no local effects were noted in repeated exposure oral studies. Thus, there is no toxicological alert to trigger the derivation of dermal and inhalative route-specific reference values.

The critical acute effect is body weight loss of pregnant female rabbits at 25 mg/kg b.w./day. This proposal is justified since the onset of the effect was early after exposure (decreased in body weight on days 6-12 in the rabbit teratology study) and considering that body weight decrease is the critical effect for cyromazine. Maternal mortality was also evident at the same dose but only after gestation day 10, and it was therefore not considered to be an acute effect.

In the BPC WG-I-2015 virtual meeting (27 January 2015), it was remarked that according to the ECHA guidance on risk assessment (Section 2.3), at least a 2-fold difference should be set between the NOAEL and the LOAEL. Thus, although the highest relevant NOAEL is 15 mg/kg b.w./day from the developmental toxicity studies in rabbits, this value was not considered appropriate for the setting of acute reference values. Most of the WG members supported the use of the NOAEL of 10 mg/kg bw/day from Nemec (1986) and Blair (1981) studies for the setting of AEL_{acute} and ARfD.

According to the guidance document for the setting and application of AOELs[2], no correction factor for systemic availability is required in the calculation of the AEL values, since the oral absorption of cyromazine within 72 hours is greater than 97% of the dose.

The default assessment factor of 100 [10 (interspecies variation) x 10 (intraspecies variation)] is considered appropriate for the calculation of reference values.

Based on the above, the following reference values are estimated:

Table 2.2.1.2: Reference values

Parameter	Reference value (mg/kg b.w./day)	Study	NOAEL (mg/kg b.w./day)	Safety factor
AEL_{acute}*	0.1	Rabbit developmental studies	10	100
$AEL_{medium-term}$*	0.06	1-year dog study supported by 2-year mouse study	5.74	100
$AEL_{long-term}$*	0.06	1-year dog study supported by 2-year mouse study	5.74	100
ARfD	0.1	Rabbit developmental studies	10	100
ADI	0.06	1-year dog study supported by 2-year mouse study	5.74	100

* no correction for oral absorption is required

It is noted that taking into account the intended uses of all cyromazine products (Neporex 2 SG, Neporex 50 SP, HOKOEX), indirect exposure to cyromazine as a result of residues in food or feed is concluded to be negligible considering the consumption of edible parts of plants but this is not the case for exposure through consumption of animal products for which an exposure assessment has been performed. Therefore, the establishment of ADI and ARfD values has been required for cyromazine as a biocide.

2.2.1.3 Exposure assessment

Neporex 2 SG & Neporex 50 SP, Novartis

Manual scattering of Neporex 2 SG

A human exposure study for Neporex 2 SG and manual scattering is available. Inhalation (sampling at the breathing space) and dermal exposure had been measured in 13 applicators, applying Neporex 2 SG in swine stables (treated area at least 200 m^2). The risk assessment was based on the exposure rates for inhalation and dermal exposure determined in this study.

For the normal use, 500 m^2 was chosen as area to be treated (by one person on one day), applicator body weight was 60 kg, and gloves were considered as personal protective equipment beside a long-sleeved shirt, long trousers and sturdy footwear. The median and the 75th percentiles of the use rate, dermal and inhalation exposure rates were used.

[2] EC (2006) Guidance for the setting and application of acceptable operator exposure level (AOEL). Draft rev. 10, & July 2006

For the reasonable worst case, 750 m^2 was chosen as area to be treated (by one person on one day), applicator body weight was 60 kg, and gloves were considered beside a short-sleeved shirt, long trousers and sturdy footwear. The 95th percentiles of the use rate, dermal and inhalation exposure rates were used.

Application by spraying

As for the manual scattering, users are considered to be professionals (i.e. farmers or farm workers).

Portable spray equipment is required (e.g. knapsack sprayers) for low pressure spraying.

Neporex 2 SG and Neporex 50 SP have to be diluted with water before spraying. An amount of 500 g Neporex 2 SG or 20 g Neporex 50 SP is to be diluted in 5 L water, each resulting in a spray concentration of 2 g cyromazine/L. The application rate is then 250 mL/m^2 corresponding to 0.5 g cyromazine/m^2.

No exposure study is available for this application type with the two cyromazine products.

Following the comments received on the 1st Draft CAR and the discussion held in the Technical Meeting II 2012 the exposure assessment in case of spraying has been updated and new calculations have been performed considering the TNsG document recommendations, i.e. Spraying Model 1 (PT18).

It is noted that Spraying Model 1is proposed as a Tier I approach for exposure assessment in case of spraying (low pressure) downwards in the Draft recommendation of the Ad hoc Working Group on Human Exposure (July 2014).

Application by watering

No human exposure study is available where Neporex 2 SG or 50 SP is applied with a watering can.

Following the discussions held during the WG meeting (January 2015), the Mixing and Loading model 5 was agreed to be the most relevant model for the mixing and loading phase (TNsG 2002) and the TNsG 2007 model for watering cans, as Tier 1, for the application phase.

For the mixing/loading phase the treated area was assumed to be 400 m2 which is in line with the ESD Insecticides tables 5.2 and 5.3 about floor and slatted areas in stables (400 m2 is the slatted area in stable for fattering pigs).

The actual dermal exposure has been calculated considering that protection by gloves is 90%. A body weight of 60 kg was used for the operator/applicator while dermal penetration was considered to be 17 & 12% in case of Neporex 2 SG and Neporex 50 SP, respectively.

Fort he application (watering) phase a task duration of 120 min has been assumed to be the most relevant value. The actual dermal body exposure has been calculated considering that protection by coated coverall is 90%. A body weight of 60 kg was used for the operator/applicator while dermal penetration was considered to be 26% in case of both formulation (Neporex 2 SG & Neporex 50 SP).

Taking into account the intended uses the appropriate reference value for the human exposure assessment is the $AEL_{medium\text{-}term}$.

HOKOEX (Cyromazine 2 SG), HOKOCHIMIE Sarl

Manual scattering (direct dispersal)

In case of manual scattering and following the discussions held during the WG-I Meeting

(January 2015), the model for pellet rodenticide from User Guidance, (2002) has been considered as the most relevant to be used in exposure assessment. Total inhalation and dermal exposure has been estimated to be 0.0434 mg/kg b.w./day, corresponding to 72% of the $AEL_{medium-term}$, provided that gloves are used.

Application by spraying

As for the manual scattering, users are considered to be professionals (i.e. farmers or farm workers).

Portable spray equipment is required (e.g. knapsack sprayers) for low pressure spraying.

HOKOEX formulation has to be diluted with water before spraying. An amount of 500 g of the formulation is to be diluted in 5 L water resulting in a spray concentration of 2 g cyromazine/L. The application rate is then 250 mL/m^2 corresponding to 0.5 g cyromazine/m^2.

No exposure study is available for this application type with HOKOEX formulation.

Following the comments received on the 1st Draft CAR for Cyromazine (Novartis) and the discussion held in the Technical Meeting II 2012 the exposure assessment in case of spraying has been updated and new calculations have been performed considering the TNsG document recommendations, i.e. Spraying Model 1 (PT18).

It is noted that Spraying Model 1 is proposed as a Tier I approach for exposure assessment in case of spraying (low pressure) downwards in the Draft recommendation of the *Ad hoc* Working Group on Human Exposure (July 2014).

Application by watering (pouring)

In case of application by watering and following the discussions held during the WG-I Meeting (January 2015), the Mixing and Loading model 5 was agreed to be the most relevant model for the mixing and loading phase (TNsG 2002) and the TNsG 2007 model for watering cans, as Tier 1, for the application phase.

Mixing & Loading conditions (assumptions)
The treated area was assumed to be 400 m^2 which is in line with the ESD Insecticides tables 5.2 and 5.3 about floor and slatted areas in stables (400 m^2 is the slatted area in stable for fattering pigs).
The actual dermal exposure has been calculated considering that protection by gloves is 90%. A body weight of 60 kg was used for the operator/applicator while dermal penetration was considered to be 17 % for the undiluted product. The $AEL_{medium-term}$ was 0.06 mg/kg b.w./day.

Application conditions (assumptions)
A task duration of 120 min has been assumed to be the most relevant value. The actual dermal body exposure has been calculated considering that protection by coated coverall is 90%. A body weight of 60 kg was used for the operator/applicator while dermal penetration was considered to be 26% for the spray dilution. The $AEL_{medium-term}$ was 0.06 mg/kg b.w./day.

Taking into account the intended uses the appropriate reference value for the human exposure assessment is the $AEL_{medium-term}$.

2.2.1.4 Risk characterisation

Primary exposure – Professional exposure (*application*)

Neporex 2 SG & Neporex 50 SP - NOVARTIS

Concerning the intended applications of Neporex 2SG and Neporex 50 SP the estimated operator/applicator exposure varied depending on the model and use conditions applied (Table 2.2.1.4-1).

Application of Neporex 2 SG by scattering is considered to be safe for both normal and worst case application scenarios when appropriate PPE is used.

Application of Neporex 2 SG and Neporex 50 SP by spraying is safe when gloves are used according to the calculations performed using the Spraying Model 1 (TNsG part 2, p143) concerning "Hand-held low pressure (1-3 bar) spraying".

Application of Neporex 2 SG and Neporex 50 SP by watering is safe when gloves and coated coverall are used.

Table 2.2.1.4-1: Operator/applicator exposure levels to cyromazine during the intended application of Neporex 2 SG and Neporex 50 SP

Intended use ***Application technique***	**Product**	**Model used**	**PPE**	**Estimated Exposure** % $AEL_{medium-term}$		**Appendix / Table no.**
				normal use	rwc	
Dry scattering *Manual*	Neporex 2 SG	Operator exposure study	PPE*	**≤27** (75^{th} percentiles)	**≤81** (95^{th} percentiles)	Appendix 1 / Table A3
Spray application	Neporex 2 SG & Neporex 50 SP	TNsG Model 1[a]	Gloves	**25**	**75**	Appendix 2 / Table A4
Watering application	Neporex 2 SG	TNsG Model 5 (ML) & TNsG 2007 for watering cans (A)[b]	Gloves & Coated Coverall	**49**	**-**	Appendix 3 / Table A4
	Neporex 50 SP	TNsG Model 5 (ML) & TNsG 2007 for watering cans (A)[b]	Gloves & Coated Coverall	**52**	**-**	

[a] Spraying Model 1 TNsG part 2, p143; Hand-held low pressure (1-3 bar) spraying
[b] Mixing/loading Model 5 TNsG (2002) & TNsG (2007) for watering cans
* Coveralls and gloves are considered for the normal use situation; long trousers, short-sleeved shirt and gloves are considered for the reasonable worst case.

HOKOEX (Cyromazine 2 SG) - HOKOCHIMIE SARL

Concerning the intended applications of HOKOEX (Cyromazine 2% SG) the estimated operator/applicator exposure varied depending on the model and use conditions applied (Table 2.2.1.4-2).

Application of HOKOEX by scattering is considered to be safe when appropriate PPE is used.

Application of HOKOEX by spraying is safe when gloves are used according to the calculations performed using the Spraying Model 1 (TNsG part 2, p143) concerning "Hand-held low

pressure (1-3 bar) spraying".

Application of HOKOEX by watering is safe when gloves and coated coverall are used.

Table 2.2.1.4-2: Operator/applicator exposure levels to cyromazine during the intended application of HOKOEX (Cyromazine 2% SG)

Intended use ***Application technique***	**Model used**	**PPE**	**Estimated Exposure** % $AEL_{medium-term}$		**Appendix / Table no.**
			normal use	rwc	
Dry scattering *Manual*	User Guidance, (2002) Model for pellet rodenticide	Gloves	72	-	-
Spray application	TNsG Model 1[a]	Gloves	25	75	Appendix 2 / Table A1
Watering application	TNsG Model 5 (ML) & TNsG 2007 for watering cans (A)[b]	Gloves & Coated Coverall	49	-	Appendix 3 / Tables A2

[a] Spraying Model 1 TNsG part 2, p143; Hand-held low pressure (1-3 bar) spraying (see Appendix 2)
[b] Mixing/loading Model 5 TNsG (2002) & TNsG (2007) for watering cans

Primary exposure – Non-professional exposure (*application*)

Neporex 2 SG & Neporex 50 SP (Novartis)

The use of biocidal products containing cyromazine by non-professional users is not foreseen. Therefore, non-professionals are not exposed and no risk assessment has to be performed for this group.

HOKOEX (Cyromazine 2 SG) - HOKOCHIMIE SARL

The use 0f HOKOEX by non-professional users is supported. In the efficacy section the applicant has stated that the product may in the future be marketed as biocidal products for use on faeces and manure generated by small companion animals housed close to or in human living areas. However, no supportive data have been submitted for human exposure assessment. Therefore, only the case of use in stables has been considered in the exposure assessment.

Following the discussions held during the WG-I Meeting (January 2015), the Consumer spraying and dusting model 1 TNsG part 2, p 194; 2, Hand-held pumped spray has been considered as the most relevant for the non-professional exposure assessment.

The exposure has been estimated to be 0.02025 mg/kg b.w. corresponding to 34% of the AELmedium-term.

For non-professional users, it is concluded that there is a safe use even without PPE when considering the Consumer spraying and dusting model 1 TNsG part 2, p 194; 2, Hand-held pumped spray.

Worker exposure

Exposure of persons entering/working in animal housing after application might not be completely excluded. However, actual inhalation exposure is considered negligible due to the low vapour pressure of cyromazine. Dermal exposure would be limited to direct contact with the treated surfaces, i.e. manure. The first is considered to be negligible as shoes (boots) are expected to be worn into animal housing. For the latter at least a small amount of exposure of (mostly) hands might not be excluded while cleaning animal housing. However, due to dilution of the product within the manure and potential degradation of cyromazine, this exposure is considered negligible as well.

No difference is considered between the potential exposure routes of adults and children old enough to work in stables.

Bystander exposure

Bystander exposure (other workers present in animal housing during application) is considered to be negligible. Due to the low vapour pressure of cyromazine, there will be no relevant inhalation exposure (compare also low inhalation exposure of applicators). Scattering of granules to the floor or watering is regarded not to cause any relevant exposure for bystanders (no relevant amount of dust). Also for the spray application no relevant bystander exposure is considered, as the direction of the application by hand-held sprayers (low pressure) is downward (floor). Moreover, in animal housing no relevant spray drift is expected, which is also due to the comparatively large droplet size following this mode of application. In addition, the access of the general public to stables is considered to be limited.

Bystander exposure during the treatment of dung heaps and lagoons might not be excluded, as this takes place outdoors. For the manual scattering application, no relevant bystander exposure is expected due to the low vapour pressure of cyromazine and as no relevant amounts of inhalable particles are generated.

The potential routes of exposure for bystanders for the spray application are via dermal and inhalation exposure. Given the low vapour pressure of cyromazine exposure to vapour is likely to be negligible and bystander exposure will result primarily from drift. Such exposure is likely to be short-term and unlikely to occur repeatedly to the same individual. Estimation of the bystander exposure results in 0.08549 mg/kg b.w. corresponding to 86% of the AEL_{acute}.

Secondary exposure – Dietary exposure

Crops are not directly treated with biocidal products containing cyromazine as active substance nor are residues expected to occur in the edible part of the crops that are treated with manure containing cyromazine after application of the products in animal housing according to the recommendations proposed in the label. However, exposure though animal feed cultivated in soil treated with manure cannot be excluded. Following the discussions held during the WG-I Meeting (January 2015), the scenarion has not been considered in the draft guidance and it is not required in any guidance. Thus the assessment presented is indicative. An updated assessment might be required, at authorization level with the actual information on the product. The calculations provided by the applicants is sufficient to estimate livestock exposure to cyromazine from dermal and inhalation exposure. As agreed in the BPC 6 and in TOX WG-III-2014, dietary risk assessment should be performed at product authorisation stage, with the actual information on the product. Guidance document on dietary risk assessment should not be used before it is finalised. As to exclude any other routes of exposure the following restrictions are proposed:

"Avoid any direct contact with animals".

"Do not apply to feeding or drinking equipment or to any equipment and storage spaces in direct contact with feeding stuff."

"Do not use in the presence of animals."

Taking into consideration the above, these restrictions are also indicative since they concern the dietary risk assessment for which there is no agreed guidance.
As to estimate the magnitude of residues in product of animal origin the applicant relied on published data summarized in DOCIIIA. The *EFSA Scientific Report (2008) 168, 1-94* was also taken into consideration and a residue definition of cyromazine (for monitoring) and *cyromazine + 1-methyl cyromazine + melamine, expressed as cyromazine* (for risk assessment). However, taken into consideration the routes of exposure, a residue definition of *cyromazine only* is proposed. This residue definition might need to be modified based on the dietary risk assessment performed at product authorization level. Thus, MS during product authorization should pay particular attention to the following:

1. setting or amending of existing MRLs, if required.

2. At product authorisation level a dietary risk assessment needs to be performed taking into account potential exposure of livestock animals following application of the biocidal product in the animal house and transfer of residues via feed into livestock animals[3].

Combined exposure

Considering the exposure assessment performed for professional exposure, bystanders and indirect – dietary exposure it can be concluded that there is no human risk considering combined exposure for the operators applying cyromazine products by either dry scattering or spraying when the label instructions/PPE recommendations are followed.

2.2.2. *Environmental Risk Assessment*

2.2.2.1 Fate and distribution in the environment

Hydrolysis: Cyromazine was shown to be hydrolytically stable at pH 5, 7 and 9 even at elevated temperatures (30^0C, 50^0C, 70^0C).

Photolysis: The originally submitted studies by both of the Applicants (Novartis and Hokochimie Sarl) have been considered as non acceptable. A new study (Reischmann, F.J., 2000) is now submitted by Novartis. According to this study cyromazine is stable to photolysis.

Phototransformation in air:

The chemical lifetime of Cyromazine in the troposphere was calculated using the computer program Atmospheric Oxidation program V 1. 92. Based on the molecular structure of cyromazine, a half-life of 305 hrs (12.7 days) has been assumed considering a 24 hr-day (based on an overall OH rate constant of 1.262 x 10^{-12} cm^3/molecule sec and 0.5x10^6 OH radicals/cm^3).

Ready biodegradability: Cyromazine was investigated for its ready biodegradability in a CO_2 evolution test based on EU Commission Directive 92/69 EEC, C.4-C.

Under the test conditions Cyromazine was found to be not biodegradable within 29 days.

[3] With the condition that the relevant guidance is finalised and provided well in advance of the date of Cyromazine approval.

Accordingly, cyromazine is classified as not readily biodegradable.

Furthermore, a second study based on EU Comission Directive 92/69 EEC, C.4-C (modified Sturm test) which is in compliance with OECD Guideline 301 B, has been submitted. At the end of the test (28 days) 6% of the tets substance had degraded resulting that Cyromazine is classified as not readily biodegraable.

Inherent Biodegradability

Three studies from open literature have been submitted by Hokochemie in order to test the inherent biodegradability of Cyromazine and Melamine. However, these studies are considered as non-acceptable due to the significant deviations from the respective guidelines (for more details please refer to the corresponding Sections in Doc IIIA).

Aerobic soil degradation in soil

Based on a GLP study, conducted according to SETAC publications (1995), Cyromazine's DT50 has been calculated to be 2.9 days at 20^0C (5.5 days at 12^0C) and 5.6 days at 10^0C (10 days at 12^0C) in one soil. Melamine was identified as a major metabolite reaching a peak level of 73.1% on day 28 and considering a DT_{50}value of 125 days at 20^0C (237 days at 12^0C).
According to a second study Melamine was identified as the major metabolite as well, reaching its maximum level of 60% on day 121. The DT_{50} value for the degradation of Cyromazine was calculated according to "Generic guidance for Estimating Persistence and Degradation Kinetics from Environmental Fate Studies on Pesticides in EU Registration, (December, 2014)" to be 31.33 days (90.1 days at 12^0C). However, the duration of the study exceeds the 120 days proposal in the corresponding OECD Test no 307.
Furthermore, two additional studies have been submitted after the ENV-WG Meeting I 2015. The two studies have been performed according to OECD Guideline 307.

In the first study (Deerner, 2003) Cyromazine's DT_{50} values have been calculated to be 46 days (Horst soil), 15 days (Westmaas soil) and 56 days (Naaldwijk soil) at 20^0C. Melamine identified as the sole degradation product with DT_{50} values of 135, 194 and 217 days. In addition to that, Melamine has been used as test substance in order to investigate it's, degradation rates, resulting three DT_{50} values (88, 211, 120 days) at 20^0C.

In the second additional study (Adams, 2003), Cyromazine's DT_{50} values calculated to be 38.2 and 49.6 days at 20^0C. Melamine was identified as the major metabolite, reaching a maximum formation factor of 74.5%.

In conclusion for Cyromazine and its metabolite Melamine a geometric mean of 37.89 days (n=8) and 307.6 days (n=8) have been calculated respectively, out of all available data set submitted by both Applicants.

Anaerobic soil degradation in soil:

The degradation of Cyromazine has been envestigated under anaerobic conditions and a DT_{50} of 97.6 days has been calculated. Melamine was identified as the major metabolite reaching a maximum concentration of about 36% on day 90.

Aerobic aquatic degradation

Cyromazine's degradation investigated in two water/sediment systems. Cyromazine was dissipated slowly from the whole system and the DT_{50} values have been calculated to be 401 and 464 days in river and pond respectively.
Melamine was detected to be the main metabolite, however never exceeded 3.5% of applied radioactivity in both compartments.

Adsorption desorption Study:

The Koc values in four soils varied between 79 and 1784. Based on the mean value of 768 (n=4) for adsorption on soil, Cyromazine can be classified as a low mobility molecule.

Bioaccumulation:

Although cyromazine has a log K_{OW} less than 3 (i.e. -0.36 at pH 5.4 and 25° C; -0.069 at pH 7.0 and 25° C; -0.039 at pH 9.0 and 25° C; -0.0644 at pH 8.0 and 22° C – Chapter 1, List of endpoints, Document I), the potential for aquatic and terrestrial bioaccumulation has been investigated via testing and open literature data, respectively. In addition, the aquatic and terrestrial bioconcentration factors have been estimated theoretically by applying the relationships developed by Veith et al. (1979) and Jager (1998), respectively. Both the experimentally determined and theoretically estimated fish BCF, as well as the calculated earthworm BCF are lower than the trigger value of 100 (e.g. < 1; sections Doc IIA 4.1.3-1 and 4.1.3-2) indicating that cyromazine has a negligible potential of bioaccumulation via the aquatic and terrestrial food chain.

2.2.2.2 Effects assessment

Effects on aquatic organisms (including sediment organisms and STP microorganisms)

The toxicity of cyromazine to aquatic organisms was investigated through a number of acute and chronic toxicity tests with fish and aquatic invertebrates as well as toxicity tests on inhibitory effects on algae growth and aquatic microbial activity.

The available aquatic toxicity data have demonstrated that aquatic invertebrates are the most sensitive of the aquatic organisms tested. In fact, aquatic crustaceans, represented by the freshwater flea *Daphnia magna*, were found to be the most sensitive aquatic organisms against cyromazine under acute exposure conditions. Under long-term exposure conditions, the toxicity of cyromazine was found to increase from algae to aquatic insects (algae < fish < aquatic crustaceans < aquatic insects). Acute and chronic toxicity data on aquatic insects (e.g. *Chironomous riparius*) have been considered appropriate for use in the aquatic risk assessment since the estimated toxicity to this group of aquatic organisms was related to their waterborne exposure to the active substance cyromazine.

Based on the available acute toxicity data, cyromazine is characterized as toxic to crustaceans (e.g. *Daphnia magna*), while as nontoxic to fish, algae and aquatic insects (e.g. *Chironomous riparius*). Based on the available chronic toxicity data, the sediment-dwelling insect *Chironomous riparius* is the most sensitive aquatic organism to cyromazine under long-term exposure conditions. In fact, the NOEC calculated for *Chironomous riparius* (0.016 mg a.s./L; Schmidt, 2004; Novartis) is by approximately one order of magnitude lower than the respective endpoint for *Daphnia magna* (0.31 mg a.s./L; Iley, 1984b; Novartis) and two orders of magnitude lower than the NOEC values for fish (14 mg a.s./L; Iley, 1984a; Novartis) and algae (31.3 mg a.s./L; Scheerbaum, 2006; Hokochimie Sarl). Regarding aquatic microbial activity, cyromazine has no growth inhibitory effects on STP aerobic microorganisms up to and including the concentration of 100 mg a.s./L (Spare, 1979; Novartis) and it is not considered acutely toxic to the ciliated protozoa *Colpoda aspera* (calculated EC_{50}: 342 mg a.s./L; Norihide et al., 1996; Hokochimie Sarl).

The $PNEC_{aquatic}$ for cyromazine, e.g. 0.0016 mg a.s./L, has been derived by applying an assessment factor of 10 to the lowest available NOEC of 0.016 mg a.s./L for *Chironomous riparius*. The $PNEC_{sediment}$, e.g. 0.0280 mg/kg wwt, has been derived by applying the equilibrium partitioning method as no testing toxicity data from whole-sediment tests with benthic organisms using spiked sediment were available for cyromazine. The $PNEC_{STP}$, e.g. 10 mg a.s./L, has been derived by applying an assessment factor of 10 to the NOEC of 100 mg

a.s./L related to growth inhibition effects on aerobic microorganisms.

Basic laboratory tests on aquatic organisms have also been conducted with cyromazine's metabolite melamine comprising acute toxicity endpoints for representative species of the three basic trophic levels, e.g. algae, aquatic invertebrates and fish. With regard to the available toxicity values (LC/EC_{50}), aquatic invertebrates represented by the freshwater flea *Daphnia magna* are the most sensitive aquatic organisms tested to melamine. In consequence, the $PNEC_{aquatic}$ for melamine, e.g. 0.060 mg/L, has derived by applying an assessment factor of 1000 to the lowest available short-term endpoint of 60 mg/L for *Daphnia magna*. The $PNEC_{sediment}$, e.g. 0.116 mg/kg wwt, has been derived by applying the equilibrium partitioning method as no testing toxicity data from whole-sediment tests with benthic organisms using spiked sediment were available for melamine.

Melamine is characterized as harmful to aquatic invertebrates (calculated EC_{50} for *Daphnia magna*: 60 mg/L; Knauer, 2002a; Novartis), while as nontoxic to algae (calculated E_bC_{50} for *Selenastrum capricornutum*: > 100 mg/L; Knauer, 2002b; Novartis) and fish (calculated LC_{50} for *Oncorhynchus mykiss* > 128 mg/L; Palmer et al., 2001; Novartis).

Effects on terrestrial organisms

The potential effects of cyromazine on terrestrial organisms were investigated in laboratory toxicity tests conducted with the three basic trophic levels of the soil environment, e.g. primary producers (terrestrial plants), soil invertebrates (earthworms and soil-dwelling non-target arthropods) and soil microorganisms. Considering the (geometric mean) DT_{50} of cyromazine in soil (i.e. 37.9 days at 12^0C and 19.4 days at 20^0C) and due to the lack of cyromazine concentration measurements during the available soil toxicity tests, the soil effect endpoints for cyromazine were re-calculated based on the TWA (Time Weighted Average) approach.

Based on the available soil microbial toxicity data, cyromazine has no adverse effects on carbon mineralization up to and including the concentration of 131 mg a.s./kg standard soil dw (nominal) equivalent to 56.6 mg/kg standard soil dw (twa) and no adverse effects on nitrogen transformation up to and including the concentration of 13.1 mg a.s./kg standard soil dw (nominal) equivalent to 5.66 mg/kg standard soil dw (twa). In addition, based on the 14-day LC_{50} > 340 mg a.s./kg standard soil dw equivalent to >268 mg/kg standard soil dw (twa) for *Eisenia foetida* (Rufli, 1986; Novartis) cyromazine is not considered to be acutely toxic to earthworms. The acute toxicity (LR_{50}) of cyromazine to the soil-dwelling arthropods *Aleochara bilineata* (Taruza, 2001; Novartis) was calculated to be greater than 12.9 mg a.s./kg standard soil dw (nominal) equivalent to 8.15 mg/kg standard soil dw (twa). Testing toxicity data (e.g. visual observations) on non-target terrestrial plants demostrated that no adverse phytotoxic effects (greater than 50% compared to the control) are expected following application of cyromazine up to 300 g a.s./ha (Wälder, 2000; Novartis).

The potential effects of cyromazine on terrestrial invertebrate fauna were also investigated in a field trial (Hughes and Murphy, 2003; Novartis) conducted under worst-case exposure conditions compared to the intended use pattern of the active substance. Based on the lack of any adverse effects at population level and the recovery of transiently affected invertebrate populations, an overall NOEAEC (No Observed Ecologically Adverse Effect Concentration) of 284 g a.s./ha, equivalent to the nominal concentration of 0.189 mg a.s./kg soil dw and the TWA mean concentration of 0.0804 mg a.s./kg soil dw, has derived from the study. Taking into account the quality and limitations of the field study, it was decided (WGI-2015) that an assessment factor of 5 should be applied to the NOEAEC of 0.0804 mg a.s./kg soil dw (equivalent to 0.0711 mg a.s./kg soil wwt) resulting to a $PNEC_{soil}$ of 0.0142 mg a.s./kg soil wwt. This effect concentration is considered sufficiently protective of the soil environment.

Taking into account that no long-term laboratory toxicity data on non-target soil-dwelling arthropods (e.g. *Folsomia candida* or *Aleochara bilineata*) were available and in order to address any concerns related to the specific toxicity of cyromazine to non-target insects, the $PNEC_{soil}$ for cyromazine was additionally calculated based on the equilibrium partitioning

method. The estimated $PNEC_{soil}$, e.g. 0.0219 mg a.s./kg soil wwt, was greater than the $PNEC_{soil}$ based on the field study, e.g. 0.0142 mg a.s./kg soil wwt, and thus the latter endpoint was employed in the soil risk assessment. It should be noted that the use of the Equilibrium Partitioning Method as an approach for the $PNEC_{soil}$ calculation is subject to data submission at product authorization level (e.g. submission of data appropriate to address cyromazine's toxicity to non-target soil-dwelling arthropods).

Regarding cyromazine's metabolite melamine, laboratory tests on soil organisms are available comprising acute and long-term toxicity endpoints for two basic trophic levels of the soil environment, e.g. soil microorganisms and earthworms. The lowest NOEC value for melamine (0.425 mg/kg standard soil dw) was calculated in the study of Meinerling (1998; A7.5.2.1/02; Novartis) which investigated the sublethal effects of the metabolite on the earthworm *Eisenia fetida*. However, the effect concentration estimated from the similar study of Ganßmann and Münz (2014; A7.5.2.1/03; Novartis), although higher, was considered more appropriate to form the basis for the $PNEC_{soil}$ derivation. In hence, the $PNEC_{soil}$ for melamine, e.g. 0.241 mg a.s./kg soil wwt, has been derived by applying an assessment factor of 50 to the NOEC of 13.6 mg/kg standard soil dw estimated for both soil microorganisms (Van der Kolk, 2002; A7.5.1.1/03; Novartis) and earthworms (Ganßmann and Münz, 2014; A7.5.2.1/03; Novartis).

In addition to soil organisms, testing toxicity data are available for other groups of terrestrial organisms, e.g. honeybees and other non-target arthropods. The calculated acute oral and contact LD_{50}s of cyromazine to the honeybee *Apis mellifera* are 186 µg a.s./bee and >200 µg a.s./bee, respectively. Regarding non-target foliar arthropods, exposure to cyromazine is unlikely and therefore a respective effects assessment is considered unnecessary. However, open literature data on cyromazine's toxicity to foliar arthropods are available and are presented in Document IIA. In contrast to foliar, exposure of soil-dwelling arthropods is likely following spreading of treated manure or slurry on agricultural grass or arable land. The potential effects of cyromazine on soil-dwelling arthropods were investigated in a laboratory toxicity test using the rove beetle *Aleochara bilineata* (Taruza, 2001; Novartis). In addition, open literature data presented in Doc IIA (Sections 2.3 and 4.2.3.4.2) show that cyromazine will not pose any adverse effects or exhibit any biological activity on manure-breeding or manure-inhabiting beneficial arthropods and parasitoids.

2.2.2.3 PBT and POP assessment

Persistence criteria (P)

Cyromazine was found to be not biodegradable under the test conditions within 28 days. Eight DT_{50} values for aerobic soil degradation of cyromazine have been calculated (longest DT_{50} value 106.20 days, at 12^0C), with a geometric mean value of 37.9 days (n=8).

The degradation of Cyromazine was investigated in two water/sediment systems. The DT_{50} values in water, sediment and whole system have been normalised to 12^oC and presented in the following table.

Half-lives of cyromazine in the water and sediment systems "River" and "Pond" at 12^0C

	DT_{50} (days) River	**DT_{50} (days) Pond**	**DT_{50} (days) mean**
Water phase	30.4	27.6	29
Sediment phase	272	270	271
Whole system	401	464	432

Moreover, cyromazine was shown to be hydrolytically stable at pH 5, 7 and 9 even at elevated temperatures. Furthermore, cyromazine seems to be stable to photolysis.

Taking into account the submitted data on biodegradation (ready biodegradability test), degradation on aerobic soil (geometric mean of 37.9 days, at 12^0C), in aquatic systems (longest sytem DT50 of 464 days at 12^0C), and its behavior with regards to hydrolysis and photolysis, cyromazine should be considered as vP compound, based on the DT_{50} values regarding the degradation of Cyromazine in the tested water/sediment systems.

Conclusion on persistence (P) criterion:

Cyromazine fulfils the vP criterion.

Bioaccumulation criteria (B)

The decision whether or not a substance fulfils the B criterion should in principle be based on measured data concerning the bioaccumulation potential of the substance in aquatic species. These data may have derived from laboratory bioconcentration studies in marine or freshwater organisms (e.g. fish BCF values) and/or field studies on biomagnification or bioaccumulation (fish BMF values).

According to EU TGD on environmental risk assessment (TGD, Part II, 2003; chapter 3, section 4.4.4.2), a substance is considered to fulfil the B criterion when the estimated bioconcentration factor (BCF) in aquatic species (e.g. fish) exceeds the trigger value of 2000 L/kg. In case the estimated BCF exceeds the trigger value of 5000 L/kg, the substance is considered to be very bioaccumulative (vB). The bioconcentration factor (BCF) for cyromazine in fish (*Lepomis macrochirus*) was experimentally determined to be < 1 L/kg (Barrows and Mastone, 1980; III A7.4.3.3.1; Novartis), e.g. lower than both trigger values of 2000 and 5000 L/kg.

Conclusion on bioaccumulation (B) criterion:

Considering the measured fish BCF value of < 1 L/kg, cyromazine is considered neither a bioaccumulative (B) nor a very bioaccumulative substance (vB).

Toxicity criteria (T)

No classification of concern, e.g. carcinogenic (cat. 1A or 1B), germ cell mutagenic (cat. 1 or 1B), toxic to reproduction (cat. 1A, 1B or 2), STOT RE 1 or STOT RE 2, has been assigned to cyromazine based on the available mammalian toxicity data. Regarding aquatic toxicity, the lowest chronic toxicity endpoint (NOEC) determined, e.g. 0.016 mg a.s./L for *Chironomous riparius* (Schmidt, 2004; III A7.4.3.5.1/02; Novartis), is above the trigger value of 0.01 mg/L (TGD, Part II, 2000; chapter 3, section 4.4.5.2), while the lowest acute toxicity endpoint (EC_{50}) determined, e.g. 5.00 mg a.s./L for *Daphnia magna* (Noack, 2006; III A7.4.1.2/01; Hokochimie Sarl), is above the trigger value of 0.1 mg/L (ECHA Guidance on information requirements and chemical safety assessment - Part C: PBT assessment; version 1.1; December, 2011). In hence, T criterion is considered not to be fulfilled or potentially fulfilled based on the available mammalian and aquatic toxicity data.

Conclusion on toxicity (T) criterion:

Considering the available toxicological and ecotoxicological data, cyromazine is considered not to fulfil the T criterion.

Overall conclusion on the PBT assessment for cyromazine

The testing strategy presented above shows that B and T criteria are not fulfilled, while vP criterion is potentially fulfilled. Therefore, cyromazine does not meet the requirements for being classified as a PBT substance. However, it is noted that the current PBT assessmen may be amended as a result of the RAC opinion release and thus the availability of a definite conclusion on the T criterion.

PBT assessment for melamine

Persistence criteria (P)

Based on the geometric mean (n=8) aerobic soil degradation DT50 of 307.58 days (corrected at 12^0C, with a longest value of 573.5 days), melamine should be characterised as vP substance.

Conclusion on persistence (P) criterion:

Considering the available data (e.g. DT_{50} in soil), melamine fulfils the vP criterion.

Bioaccumulation criteria (B)

According to the EU TGD on environmental risk assessment, when no experimentally derived BCF values are available, the potential for bioaccumulation should be determined on the basis of the surrogate measure of the octanol:water partition coefficient. However, no measured data on either fish BCF or log K_{OW} values are available for melamine. Nevertheless, the log K_{OW} has been estimated by the applicant (Novartis) by using the EPI Suite QSAR program. . The estimated log K_{OW} value of -1.37 is lower than the trigger of 4.5 (TGD, Part II, 2000), indicating that melamine does not fulfill the B criterion.

Conclusion on bioaccumulation (B) criterion

Based on the calculated log K_{OW} of -1.37, melamine is considered not to fulfil the B criterion. However, further information, e.g. a detailed and comprehensive report on the QSAR approach followed by the applicant (Novartis) is required.

Toxicity criteria (T)

Since no classification of concern has been assigned to melamine based on the available mammalian toxicity data, e.g. carcinogenic (cat. 1A or 1B), germ cell mutagenic (cat. 1 or 1B), toxic to reproduction (cat. 1A, 1B or 2), STOT RE 1 or STOT RE 2 and no long-term aquatic toxicity data have been generated on melamine, the toxicity property should be assessed on the basis of the available acute aquatic toxicity data. Taking into account that the lowest acute toxicity endpoint for aquatic organisms, e.g. 60 mg/L for *Daphnia magna* (Knauer, 2002a; III A7.4.1.2/02; Novartis) is significantly greater than the trigger value of 0.1 mg/L (ECHA Guidance on information requirements and chemical safety assessment - Part C: PBT assessment; version 1.1; December, 2011), T criterion is considered not to be fulfilled for melamine.

Conclusion on toxicity (T) criterion:

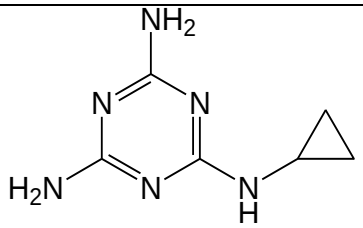
Considering the available toxicological and ecotoxicological data, melamine is considered not to fulfil the T criterion.

Overall conclusion on the PBT assessment for melamine

The testing strategy presented above shows that B and T criteria are not fulfilled, while vP criterion is fulfilled. Therefore, melamine does not meet the requirements for being classified as a PBT substance.

POP assessment

Chemical Identity

Name	Cyromazine
CAS No	66215-27-8
Chemical name (IUPAC)	N-cyclopropyl-1,3,5-triazine-2,4,6-triamine
Structural formula	
Chemical class	Triazine

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 Art 10.

Persistency

Cyromazine was concluded to be persistent and **fulfils persistency** criteria for POP assessment. More specific, the longest DT50 value in sediment was found to be 272 days (corrected at 12^0C) and the longest DT50 value for whole system was found to be 464 days (corrected at 12^0C). Furthermore in soil Cyromazine is degraded with a geometric mean DT_{50} value of 37.9 days at 12^0C. Based on the above mentioned DT50 values, there is evidence that Cyromazine is persistent in sediment since its half-life is greater than 6 months.

Bio-accumulation

Cyromazine was concluded to be non-bioaccumulative in aquatic species. The bioconcentration factor (BCF) for cyromazine in fish (*Lepomis macrochirus*) was experimentally determined to be <1 L/kg, e.g. lower than the trigger value of 5000 L/kg.

Potential for long-range environmental transport

Long-range environmental transport is expected. Based on overall OH rate constant of 0.5E6 OH radicals/cm^3 a half-life of 305 hrs (12.7 days) using a 24-hour days. Based on the estimated half-life in air there is a potential for long range transport.

Adverse effects

No classification of concern has been assigned to cyromazine based on the available mammalian toxicity data, i.e. carcinogen, germ cell mutagen, reproductive toxicant and/or STOT RE. Therefore, the interim criteria for the determination of endocrine-disrupting properties are not fulfilled. However, these conclusions may be revised pending on the outcome of the RAC on the potential classification of cyromazine as toxic for reproduction category 2 and/or the availability of specific criteria for the determination of endocrine-disrupting properties.

Although cyromazine has been classified as *Very toxic to aquatic life with long-lasting effects* (H410), the lowest chronic NOEC for aquatic organisms was determined to be 0.016 mg a.s./L (*Chironomous riparius*), e.g. greater than the trigger value of 0.01 mg/L (T criterion).

Conclusion: Cyromazine is considered persistent and demonstrates the potential of long-range transport. However, the available (eco)toxicological data do not indicate any concern to human health, animals and the environment. Hence, cyromazine does not have the POPs-like characteristics (outlined in Annex D 'Information Requirements & Screening Requirements' of the Convention Stockholm Convention on Persistent Organic Pollutants 2001) and global control is not warranted.

2.2.2.4 Exposure assessment

The environmental exposure assessment has been performed in accordance with the emission scenario document for Insecticides for Stables and Manure Storage Systems (OECD, 2006) and was based on information relating to the use patterns of the products from both Applicants.

For a detailed presentation of the results and the used scenarios please refer to the corresponding IIB documents.

2.2.2.5 Risk characterisation

Using the ecotoxicity endpoints (PNEC values) identified in Document IIA (Section 4.3) and the predicted environmental exposure concentrations estimated in Document IIB (Section 3.3 for both applicants).Only spraying sceanrio (as worst case) has been considered for PEC calculations. Moreover, 5 applications per year with an application rate of 0.5 g of cyromazine/m^2 for indoor uses only by professionals. PEC/PNEC ratios are calculated in order to assess the environmental risk associated with the use of cyromazine containing products (e.g. Neporex 2 SG (Novartis), Neporex 50 SP (Novartis) and Hokoex (Hokochimie Sarl)). A PEC/PNEC ratio less than 1 indicates no unacceptable risk, while a PEC/PNEC ratio greater than 1 indicates an unacceptable risk to the environmental compartment under consideration. The PEC/PNEC risk characterization ratios for the active substance cyromazine and its metabolite melamine calculated for each environmental compartment of concern are presented in the following tables.

Aquatic compartment (including surface water, sediment, STP)

Risk assessment for STP

Compartment	$PEC_{STP(microorganisms)}$ (mg a.s./L)	$PNEC_{STP(microorganisms)}$ (mg a.s./L)	PEC/PNEC	acceptable risk
STP microorganisms	3.75×10^{-2}	10	3.75×10^{-3}	yes

Risk assessment for surface water

A. Surface water PEC/PNEC for cyromazine

Table 1: Aquatic compartment PEC/PNEC ratios for cyromazine following manure application to land for all animal categories

Cat.	Type of housing	PEC/PNEC				Acceptable risk (yes/no)
		N		P		
		Arable	Grassland	Arable	Grassland	
1	Dairy cows	1.55E-02	1.96E-02	2.51E-02	2.60E-02	yes
2	Beef cattle	1.42E-02	1.79E-02	2.88E-02	2.98E-02	yes

3	Veal calves	1.13E-01	1.43E-01	9.50E-02	9.81E-02	yes
4	Sows, in individual pens	6.63E-02	8.31E-02	4.22E-02	4.37E-02	yes
5	Sows in groups	4.74E-02	5.99E-02	3.03E-02	3.13E-02	yes
6	Fattening pigs	4.98E-02	6.31E-02	3.73E-02	3.86E-02	yes
7	Laying hens in battery cages without treatment	8.13E-02	1.03E-01	6.75E-02	7.00E-02	yes
8	Laying hens in battery cages with aeration (belt drying)	9.06E-02	1.14E-01	7.38E-02	7.69E-02	yes
9	Laying hens in battery cages with forced drying (deep pit, high rise)	1.11E-01	1.41E-01	9.06E-02	9.38E-02	yes
10	Laying hens in compact battery cages	5.89E-02	7.44E-02	4.80E-02	4.97E-02	yes
11	Laying hens in free range with litter floor (partly litter floor, partly slatted)	5.44E-02	6.88E-02	4.19E-02	4.34E-02	yes
12	Broilers in free range with litter floor	5.18E-04	6.56E-04	6.13E-04	6.31E-04	yes
13	Laying hens in free range with grating floor (aviary system)	7.50E-02	9.44E-02	5.77E-02	5.97E-02	yes
14	Parent broilers in free range with grating floor	1.94E-02	2.44E-02	1.54E-02	1.59E-02	yes
15	Parent broilers in rearing with grating floor	4.26E-02	5.38E-02	3.79E-02	3.93E-02	yes
16	Turkeys in free range with litter floor	1.01E-03	1.27E-03	1.06E-03	1.09E-03	yes
17	Ducks in free range with litter floor	1.77E-03	2.24E-03	1.48E-03	1.53E-03	yes
18	Geese in free range with litter floor	1.01E-03	1.27E-03	1.06E-03	1.09E-03	yes

Table 2: Aquatic compartment PEC/PNEC ratios for cyromazine following STP effluent discharge (relevant for poultry housings: Categories 8, 11, 12, 16, 17 and 18)

Cat.	Type of housing	PEC/PNEC	Acceptable risk (yes/no)
8	Laying hens in battery cages with aeration (belt drying)	7.31E+00	no
11	Laying hens in free range with litter floor (partly litter floor, partly slatted)	3.28E+00	no
12	Broilers in free range with litter floor	**5.70E-02**	yes
16	Turkeys in free range with litter floor	**1.71E-01**	yes
17	Ducks in free range with litter floor	**1.71E-01**	yes
18	Geese in free range with litter floor	**1.71E-01**	yes

PEC/PNEC values below the trigger of 1 are highlighted in bold

B. Surface water PEC/PNEC for melamine

Table 3: Aquatic compartment PEC/PNEC ratios for melamine following manure application to land for all animal categories

Cat.	Type of housing	PEC/PNEC		Acceptable risk (yes/no)
		N	P	

		Arable	Grassland	Arable	Grassland	
1	Dairy cows	3.13E-04	8.47E-04	5.08E-04	6.93E-04	yes
2	Beef cattle	2.88E-04	7.77E-04	5.82E-04	7.93E-04	yes
3	Veal calves	2.28E-03	6.18E-03	1.92E-03	2.62E-03	yes
4	Sows, in individual pens	1.34E-03	3.62E-03	8.53E-04	1.17E-03	yes
5	Sows in groups	9.60E-04	2.58E-03	6.13E-04	8.35E-04	yes
6	Fattening pigs	1.01E-03	2.72E-03	7.55E-04	1.03E-03	yes
7	Laying hens in battery cages without treatment	1.65E-03	4.45E-03	1.36E-03	1.87E-03	yes
8	Laying hens in battery cages with aeration (belt drying)	1.83E-03	4.97E-03	1.50E-03	2.05E-03	yes
9	Laying hens in battery cages with forced drying (deep pit, high rise)	2.25E-03	5.77E-03	1.83E-03	2.50E-03	yes
10	Laying hens in compact battery cages	1.19E-03	3.22E-03	9.72E-04	1.33E-03	yes
11	Laying hens in free range with litter floor (partly litter floor, partly slatted)	1.10E-03	2.97E-03	8.48E-04	1.16E-03	yes
12	Broilers in free range with litter floor	1.05E-05	2.83E-05	1.24E-05	1.68E-05	yes
13	Laying hens in free range with grating floor (aviary system)	1.52E-03	4.08E-03	1.17E-03	1.59E-03	yes
14	Parent broilers in free range with grating floor	3.92E-04	1.06E-03	3.12E-04	4.23E-04	yes
15	Parent broilers in rearing with grating floor	8.63E-04	2.33E-03	7.68E-04	1.05E-03	yes
16	Turkeys in free range with litter floor	2.03E-04	5.50E-04	2.13E-04	2.92E-04	yes
17	Ducks in free range with litter floor	3.58E-05	9.67E-05	3.00E-05	4.08E-05	yes
18	Geese in free range with litter floor	2.03E-05	5.50E-05	2.13E-05	2.92E-05	yes

Table 4: Aquatic compartment PEC/PNEC ratios for melamine following STP effluent discharge (relevant for poultry housings: Categories 8, 11, 12, 16, 17 and 18) [1]

Cat.	Type of housing	PEC/PNEC	Acceptable risk (yes/no)
8	Laying hens in battery cages with aeration (belt drying)	2.12E-01	yes
11	Laying hens in free range with litter floor (partly litter floor, partly slatted)	9.52E-02	yes

[1] the exposure and risk assessment for melamine via STP has been performed only for Cat. 8 and 11 which are considered to represent worst-case scenarios

The calculated $PEC_{surface\ water}/PNEC_{aquatic}$ ratios are below the trigger value of 1 indicating no unacceptable risk to aquatic organisms from cyromazine following treated manure application to land (grassland or arable land). In addition, no unacceptable risk to the aquatic compartment is expected following exposure to cyromazine's metabolite melamine. However,

the calculated PEC/PNEC ratios for cyromazine following STP effluent discharge into the aquatic environment are above the trigger value of 1 for the animal housing **categories 8 (Laying hens in battery cages with aeration (belt drying)) and 11 (Laying hens in free range with litter floor (partly litter floor, partly slatted))**. In order to prevent any unacceptable effects to the aquatic environment, the following label restriction should be established: "Biocidal products containing the active substance cyromazine should not be applied in animal housing categories 8 and 11 where releases to sewage treatment plants or direct emissions to surface water cannot be prevented".

Risk assessment for sediment

A. Sediment PEC/PNEC ratios for cyromazine

Table 5: Sediment PEC/PNEC ratios for cyromazine following manure application to land for all animal categories

Cat.	Type of housing	PEC/PNEC				Acceptable risk (yes/no)
		N		P		
		Arable	Grassland	Arable	Grassland	
1	Dairy cows	1.77E-02	1.95E-02	2.51E-02	2.60E-02	yes
2	Beef cattle	1.42E-02	1.79E-02	2.87E-02	2.97E-02	yes
3	Veal calves	1.13E-01	1.43E-01	9.50E-02	9.79E-02	yes
4	Sows, in individual pens	6.61E-02	8.29E-02	4.21E-02	4.36E-02	yes
5	Sows in groups	4.75E-02	5.96E-02	3.02E-02	3.13E-02	yes
6	Fattening pigs	4.96E-02	6.32E-02	3.71E-02	3.86E-02	yes
7	Laying hens in battery cages without treatment	8.11E-02	1.03E-01	6.75E-02	7.00E-02	yes
8	Laying hens in battery cages with aeration (belt drying)	9.04E-02	1.14E-01	7.36E-02	7.68E-02	yes
9	Laying hens in battery cages with forced drying (deep pit, high rise)	1.11E-01	1.40E-01	9.04E-02	9.36E-02	yes
10	Laying hens in compact battery cages	5.89E-02	7.43E-02	4.79E-02	4.96E-02	yes
11	Laying hens in free range with litter floor (partly litter floor, partly slatted)	5.43E-02	6.86E-02	4.18E-02	4.32E-02	yes
12	Broilers in free range with litter floor	5.18E-04	6.57E-04	6.11E-04	6.32E-04	yes
13	Laying hens in free range with grating floor (aviary system)	7.50E-02	9.43E-02	5.75E-02	5.96E-02	yes
14	Parent broilers in free range with grating floor	1.94E-02	2.44E-02	1.54E-02	1.59E-02	yes
15	Parent broilers in rearing with grating floor	4.25E-02	5.36E-02	3.79E-02	3.93E-02	yes
16	Turkeys in free range with litter floor	1.00E-03	1.27E-03	1.05E-03	1.09E-03	yes
17	Ducks in free range with litter floor	1.77E-03	2.24E-03	1.48E-03	1.53E-03	yes

18	Geese in free range with litter floor	1.00E-03	1.27E-03	1.05E-03	1.09E-03	yes

Table 6: Sediment PEC/PNEC ratios for cyromazine following STP effluent discharge (relevant for poultry housings: Categories 8, 11, 12, 16, 17 and 18)

Cat.	Type of housing	PEC/PNEC	Acceptable risk (yes/no)
8	Laying hens in battery cages with aeration (belt drying)	7.29E+00	no
11	Laying hens in free range with litter floor (partly litter floor, partly slatted)	3.27E+00	no
12	Broilers in free range with litter floor	**5.68E-02**	yes
16	Turkeys in free range with litter floor	**1.71E-01**	yes
17	Ducks in free range with litter floor	**1.71E-01**	yes
18	Geese in free range with litter floor	**1.71E-01**	yes

PEC/PNEC values below the trigger of 1 are highlighted in bold

B. Sediment PEC/PNEC ratios for melamine

Table 7: Sediment PEC/PNEC ratios for melamine following manure application to land for all animal categories

Cat.	Type of housing	PEC/PNEC				Acceptable risk (yes/no)
		N		P		
		Arable	Grassland	Arable	Grassland	
1	Dairy cows	3.14E-04	8.47E-04	5.09E-04	6.94E-04	yes
2	Beef cattle	2.89E-04	7.78E-04	5.82E-04	7.94E-04	yes
3	Veal calves	2.28E-03	6.19E-03	1.92E-03	2.62E-03	yes
4	Sows, in individual pens	1.34E-03	3.62E-03	8.54E-04	1.16E-03	yes
5	Sows in groups	9.57E-04	2.59E-03	6.14E-04	8.35E-04	yes
6	Fattening pigs	1.01E-03	2.72E-03	7.55E-04	1.03E-03	yes
7	Laying hens in battery cages without treatment	1.65E-03	4.46E-03	1.36E-03	1.87E-03	yes
8	Laying hens in battery cages with aeration (belt drying)	1.84E-03	4.97E-03	1.50E-03	2.05E-03	yes
9	Laying hens in battery cages with forced drying (deep pit, high rise)	2.25E-03	5.77E-03	1.84E-03	2.50E-03	yes
10	Laying hens in compact battery cages	1.19E-03	3.22E-03	9.74E-04	1.33E-03	yes
11	Laying hens in free range with litter floor (partly litter floor, partly slatted)	1.10E-03	2.97E-03	8.49E-04	1.16E-03	yes
12	Broilers in free range with litter floor	1.05E-05	2.84E-05	1.24E-05	1.68E-05	yes
13	Laying hens in free range with grating floor (aviary system)	1.52E-03	4.09E-03	1.16E-03	1.59E-03	yes

14	Parent broilers in free range with grating floor	3.92E-04	1.06E-03	3.12E-04	4.23E-04	yes
15	Parent broilers in rearing with grating floor	8.62E-04	2.34E-03	7.69E-04	1.05E-03	yes
16	Turkeys in free range with litter floor	2.03E-04	5.50E-04	2.14E-04	2.92E-04	yes
17	Ducks in free range with litter floor	3.59E-05	9.66E-05	3.00E-05	4.09E-05	yes
18	Geese in free range with litter floor	2.03E-05	5.50E-05	2.14E-05	2.92E-05	yes

Table 8: Sediment PEC/PNEC ratios for melamine following STP effluent discharge (relevant for poultry housings: Categories 8, 11, 12, 16, 17 and 18) [1]

Cat.	Type of housing	PEC/PNEC	Acceptable risk (yes/no)
8	Laying hens in battery cages with aeration (belt drying)	2.15E-01	yes
11	Laying hens in free range with litter floor (partly litter floor, partly slatted)	9.66E-02	yes

[1] the exposure and risk assessment for melamine via STP has been performed only for Cat. 8 and 11 which are considered to represent worst-case scenarios

The calculated $PEC_{sed}/PNEC_{sed}$ ratios are below the trigger value of 1 indicating no unacceptable risk to sediment dwelling organisms from cyromazine following treated manure application to land (grassland or arable land). In addition, no unacceptable effects to sediment dwellers are expected following exposure to cyromazine's metabolite melamine. However, the calculated PEC/PNEC ratios for cyromazine following STP effluent discharge into the aquatic environment are above the trigger value of 1 for the animal housing **categories 8 (Laying hens in battery cages with aeration (belt drying)) and 11 (Laying hens in free range with litter floor (partly litter floor, partly slatted))**. In order to prevent any unacceptable effects to sediment-dwelling organisms, the following risk label restriction should be established: "Biocidal products containing the active substance cyromazine should not be applied in animal housing categories 8 and 11 where releases to sewage treatment plants or direct emissions to surface water cannot be prevented".

Terrestrial compartment

Risk assessment for soil

A. Soil PEC/PNEC ratios for cyromazine

Table 9: Soil compartment PEC/PNEC ratios for cyromazine following manure application to land for all animal categories

Cat.	Type of housing	PEC/PNEC				Acceptable risk (yes/no)
		N		P		
		Arable	Grassland	Arable	Grassland	
1	Dairy cows	**2.39E-01**	**3.03E-01**	**3.87E-01**	**6.34E-01**	yes
2	Beef cattle	**2.18E-01**	**2.75E-01**	**4.44E-01**	**7.25E-01**	yes
3	**Veal calves**	1.74E+00	2.20E+00	1.46E+00	2.39E+00	no

4	Sows, in individual pens	1.01E+00	1.28E+00	**6.48E-01**	1.06E+00	no
5	Sows in groups	**7.32E-01**	**9.23E-01**	**4.65E-01**	**7.61E-01**	yes
6	Fattening pigs	**7.75E-01**	**9.72E-01**	**5.77E-01**	**9.37E-01**	yes
7	Laying hens in battery cages without treatment	1.25E+00	1.58E+00	1.06E+00	1.70E+00	no
8	Laying hens in battery cages with aeration (belt drying)	1.39E+00	1.77E+00	1.14E+00	1.86E+00	no
9	Laying hens in battery cages with forced drying (deep pit, high rise)	1.71E+00	2.16E+00	1.39E+00	2.28E+00	no
10	Laying hens in compact battery cages	**9.15E-01**	1.15E+00	**7.39E-01**	1.20E+00	no
11	Laying hens in free range with litter floor (partly litter floor, partly slatted)	**8.45E-01**	1.06E+00	**6.48E-01**	1.06E+00	no
12	Broilers in free range with litter floor	**7.96E-03**	**7.04E-03**	**9.44E-03**	**1.41E-02**	yes
13	Laying hens in free range with grating floor (aviary system)	1.15E+00	1.46E+00	**8.87E-01**	1.45E+00	no
14	Parent broilers in free range with grating floor	**2.99E-01**	**3.80E-01**	**2.37E-01**	**3.87E-01**	yes
15	Parent broilers in rearing with grating floor	**6.57E-01**	**8.31E-01**	**5.85E-01**	**9.58E-01**	yes
16	Turkeys in free range with litter floor	**1.55E-02**	**2.11E-02**	**1.63E-02**	**2.82E-02**	yes
17	Ducks in free range with litter floor	**2.73E-02**	**3.52E-02**	**2.28E-02**	**3.52E-02**	yes
18	Geese in free range with litter floor	**1.55E-02**	**2.11E-02**	**1.63E-02**	**2.82E-02**	yes

PEC/PNEC values below the trigger of 1 are highlighted in bold

Table 10: Soil compartment PEC/PNEC ratios for cyromazine following STP sludge deposition (relevant for poultry housings: Categories 8, 11, 12, 16, 17 and 18)

Cat.	**Type of housing**	**PEC/PNEC**		**Acceptable risk (yes/no)**
		Grassland	**Agricultural**	
8	Laying hens in battery cages with aeration (belt drying)	**3.39E-01**	2.25E+00	no
11	Laying hens in free range with litter floor (partly litter floor, partly slatted)	**1.53E-01**	1.01E+00	no
12	Broilers in free range with litter floor	**2.65E-03**	**1.76E-02**	yes
16	Turkeys in free range with litter floor	**7.96E-03**	**5.59E-02**	yes
17	Ducks in free range with litter floor	**7.96E-03**	**5.59E-02**	yes
18	Geese in free range with litter floor	**7.96E-03**	**5.59E-02**	yes

B. Soil PEC/PNEC ratios for melamine

Table 11: Soil compartment PEC/PNEC ratios for melamine following manure application to land for all animal categories

Cat.	Type of housing	PEC/PNEC				Acceptable risk (yes/no)
		N		P		
		Arable	Grassland	Arable	Grassland	
1	Dairy cows	1.07E-02	2.90E-02	1.74E-02	6.06E-02	yes
2	Beef cattle	9.79E-03	2.66E-02	1.98E-02	6.93E-02	yes
3	Veal calves	7.80E-02	2.10E-01	6.53E-02	2.28E-01	yes
4	Sows, in individual pens	4.55E-02	1.23E-01	2.90E-02	1.02E-01	yes
5	Sows in groups	3.27E-02	8.80E-02	2.08E-02	7.30E-02	yes
6	Fattening pigs	3.43E-02	9.25E-02	2.57E-02	8.96E-02	yes
7	Laying hens in battery cages without treatment	5.60E-02	1.51E-01	4.65E-02	1.62E-01	yes
8	Laying hens in battery cages with aeration (belt drying)	6.25E-02	1.69E-01	5.06E-02	1.78E-01	yes
9	Laying hens in battery cages with forced drying (deep pit, high rise)	7.66E-02	2.07E-01	6.24E-02	2.18E-01	yes
10	Laying hens in compact battery cages	4.05E-02	1.10E-01	3.31E-02	1.15E-01	yes
11	Laying hens in free range with litter floor (partly litter floor, partly slatted)	3.75E-02	1.01E-01	2.88E-02	1.01E-01	yes
12	Broilers in free range with litter floor	3.57E-04	8.30E-04	4.23E-04	1.66E-03	yes
13	Laying hens in free range with grating floor (aviary system)	5.15E-02	1.39E-01	3.97E-02	1.39E-01	yes
14	Parent broilers in free range with grating floor	1.34E-02	3.61E-02	1.06E-02	3.69E-02	yes
15	Parent broilers in rearing with grating floor	2.95E-02	7.93E-02	2.61E-02	9.13E-02	yes
16	Turkeys in free range with litter floor	6.93E-04	2.07E-03	7.26E-04	2.49E-03	yes
17	Ducks in free range with litter floor	1.22E-03	3.32E-03	1.02E-03	3.73E-03	yes
18	Geese in free range with litter floor	6.93E-04	2.07E-03	7.26E-04	2.49E-03	yes

Table 12: Soil compartment PEC/PNEC ratios for melamine following STP sludge deposition (relevant for poultry housings: Categories 8, 11, 12, 16, 17 and 18)

Cat.	Type of housing	PEC/PNEC		Acceptable risk (yes/no)
		Grassland	Agricultural	
8	Laying hens in battery cages with aeration (belt drying)	4.23E-04	1.34E-02	yes
11	Laying hens in free range with litter floor (partly litter floor, partly slatted)	1.90E-03	6.02E-03	yes

[1] the exposure and risk assessment for melamine via STP has been performed only for Cat. 8 and 11 which are considered to represent worst-case scenarios

For the parent compound cyromazine, ten safe uses have been identified regarding the soil compartment. The calculated $PEC_{soil}/PNEC_{soil}$ ratios are below the trigger of 1 for the following animal housing categories:

- Dairy cows (**Cat. 1**)
- Beef cattle (**Cat. 2**)
- Sows in groups (**Cat. 5**)
- Fattening pigs (**Cat. 6**)
- Broilers in free range with litter floor (**Cat. 12**)
- Parent broilers in rearing with grating floor (**Cat. 14**)
- Parent broilers in rearing with grating floor (**Cat. 15**)
- Turkeys in free range with litter floor (**Catg. 16**)
- Ducks in free range with litter floor (**Cat. 17**)
- Geese in free range with litter floor (**Cat.18**)

Regarding the risk assessment performed for the poultry scenarios through STP, no unacceptable effects to soil organisms are expected except for cyromazine applications to animal housing categories 8 and 11.

Concerning cyromazine's metabolite melamine, all of the calculated $PEC_{soil}/PNEC_{soil}$ ratios are below the trigger of 1 indicating no unacceptable risk to the soil compartment.

Risk assessment for groundwater

PECgw for Cyromazine have been calculated according to ESD for PT 18 (2006) were above the trigger value of 0.1 µg/L in 14 types of animal housing types, except animal housing categories 12, 16, 17 and 18 (<0.1 µg/L), reaching a maximum of 2.29 µg/L for **Cat. 3** (veal calves) considering application on grassland (N imission). For this reason, PECgw have been recalculated using FOCUS PEARL 4.4.4 model, considering an application rate of Cyromazine which is calculated from the respective PECsoil (arable and grassland) for the worst case "veal calves" scenario. PECgw values were well below the trigger value (<0.0001 µg/L) in all the tested scenarios both for application on grassland (alfalfa) and arable land (winter cereals). Based on the results the application of the Cyromazine on arable and grassland does not pose any potential risk for groundwater.

For Melamine, PECgw exceeded 0.1 µg/L in 14 types of animal housing types, except animal housing categories 12, 16, 17 and 18 (<0.1 µg/L). Additional calculations have been performed using FOCUS PEARL, for Melamine, Cyromazine's major metabolite, using the same application pattern as for the parent compound. In addition to that, two separate runs for alkaline and acidic soils, have been performed for arable and grassland due to Melamine's adsorption pH dependency. For the worst case "veal calves" scenario, PECgw results exceeded the trigger value of 0.1 µg/L in 17 out of 18 the tested scenarios with a global max of 2.41 µg/L. Therefore, PECgw have been calculated considering a lower application rate, derived from PECsoil values for **Cat. 6** which consists a safe use regarding the soil risk assessment. PECgw results for Melamine were above 0.1 µg/L in 16 out of 18 groundwater scenarios, with a global max of 0.82 µg/L.

Toxicological relevance of Melamine

No toxicological data have been submitted by the applicant for melamine. However, in the frame of cyromazine evaluation under Dir. 91/414/EEC, EL being the Rapporteur Member State (RMS) had conducted an open literature search and had prepared a review on the toxicological profile of melamine in order to address the relevance of melamine as a metabolite in ground water (see attachment: Annex I). This document was included in the Draft Assessment Report for cyromazine and subjected to peer review (PRAPeR meeting) according to EFSA procedures.

The RMS proposal for non-relevance of melamine was adopted by PRAPeR experts and EFSA and was included in the EFSA conclusion on the peer review of cyromazine (EFSA Scientific Report (2008) 168, 1-94, see attachment: Annex II). In the EFSA conclusion it was indicated that:

- Melamine has the same toxicological profile as the parent (Page 2 of EFSA conclusion).
- Melamine was found mainly in urine at levels up to 10.7 % of the administered dose (Page 10 of EFSA conclusion).
- Melamine appears as a rat and plant metabolite, and it is found in groundwater at levels exceeding the threshold value of 0.1 µg/L. No study has been submitted by the applicant. The Rapporteur Member State conducted an open literature search and downloaded the more recently released evaluations of melamine toxicity to prepare a review on the toxicological profile of melamine. According to this review, melamine was found to have no toxicological relevance for groundwater according to the guidance document on groundwater metabolites. The rapporteur Member State proposed to set an ADI of 0.063 mg/kg bw/day for melamine based on the review, however the meeting considered that the ADI of the parent (cyromazine) should be considered relevant for melamine risk assessment (Page 13 of EFSA conclusion).

Moreover, the EFSA Panels on Contaminants in the Food Chain (CONTAM) and on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) have more recently published a scientific opinion on melamine in food and feed (EFSA Journal 2010; 8(4):1573). In this opinion a detailed review of the toxicological properties of melamine are presented (see attachment: Annex III).


'Εγγραφο του Microsoft Word 97 - 2


Adobe Acrobat Document


Adobe Acrobat Document

The aforementioned conclusions and related documents have been considered by the BPC WG-I-2015 (e-consultation) and the conclusions have been uploaded on CIRCABC:

Path: /CircaBC/echa/Biocides TM/Library/ca-reports/ca-reports_programme/a-d/cyromazine_el/product_type_18/e-consultation TOX relevance of impurity Feb 2015

Browse url: https://circabc.europa.eu/w/browse/0cdd06ce-7e20-4298-ae85-aa6e268b488c

According to the Guidance Document on the Assessment of the Relevance of Metabolites in Groundwater of Substances regulated under Council Directive 91/414/EEC (Sanco/221/2000 – rev.10- final, 25 February 2003), non-relevant metabolites 'for which levels of estimated concentrations of metabolites in groundwater lie between 0.75 µg/L and 10 µg/L will require a refined assessment of their potential toxicological significance for consumers.'

Provided that melamine is a major metabolite in ground water (5.77 µg/L) and its non-relevance has been agreed, the toxicological significance for consumers should be further addressed.

The applicant has presented the following justification:

'… the limit of 10 µg/L applies which is still significantly lower than the TDI for melamine as calculated in the WHO report: 0.175 mg/kg bodyweight per day.'

The eCA has performed a refined risk assessment for melamine, taking into account a maximum level of 2.41 µg/L. The results are indicated in the following Table.

Refined risk assessment for consumers.

Consumer group	Water consumption (L/day)	Body weight (Kg)	Estimated exposure * (mg/kg b.w./day)	% ADI*
adults	2	60	0.000080	0.13
toddlers	1	10	0.000241	0.4
infants	0.75	5	0.0003615	0.6

* Estimated exposure = Maximum level in ground water x Water consumption / body weight

** ADI = 0.06 mg/kg b.w./day (same as for cyromazine, see above justification)

The ADI is not exceeded and thus the presence of melamine in ground water at a level of 2.41µg/L is of low toxicological significance for consumers.

Taking into account all the data presented above, Melamine is considered to be non relevant metabolite and the application of Cyromazine on arable land and grassland, in the tested application rates, does not pose any unacceptable risk regrading groundwater.

Risk assessment for bees and other non-target arthropods

The risk to bees was addressed by following both a quantitative and a semi-quantitative risk assessment approach. The semi-quantitative risk assessment was based on the assumption that the effective annual emission rate to land could be indicative of the exposure via systemic uptake by plants and subsequent consumption of pollen, nectar or guttation water by bees. Based on the available field toxicity data on bees and the respective risk assessment conducted for cyromazine considering its use as a plant protection product (*EFSA Scientific Report (2008) 168, 1-94*) and taking into account that the estimated annual application rate from use as PT18 is lower than the maximum field application rate as PPP, it was concluded that the risk to bees from cyromazine's use as PT18 is acceptable.

The quantitative bee risk assessment was based on the assumption that the expected residue levels in pollen/nectar, i.e. $PEC_{nectar/pollen}$, is equivalent to the expected concentration in soil, i.e. 100% uptake of cyromazine from soil by plants and 100% transfer to nectar and pollen. The $PNEC_{bee}$ was derived by applying an assessment factor of 10 to the 48-hour oral LD_{50} of 186 µg a.s./bee (A.7.5.4.1/01; Kleiner, 1994; Novartis), after the latter was converted into concentration of the active substance in pollen/nectar. The calculated PEC/PNEC ratios were well below the trigger value of 1, indicating no unacceptable risk to bees from systemic intoxication through feeding on nectar or pollen following the intended uses of cyromazine in PT18 applications.

Regarding non-target foliar arthropods, both direct and indirect exposure to cyromazine residues is considered to be unlikely. In contrast, exposure of soil-dwelling arthropods is likely following spreading of treated manure or slurry on agricultural grass or arable land. The effects on soil-dwelling arthropods and associated risk are covered by the terrestrial risk assessment (Document IIA, Section 4.3.4; Document IIC, Section 2.3.1).

Summary of environmental risk characterization

Cyromazine

Cat.	Type of housing	Acceptable risk (Y/N)		
		Surface water	Sediment	Soil
1	**Dairy cows**	Y	Y	Y
2	**Beef cattle**	Y	Y	Y
3	Veal calves	Y	Y	N
4	Sows, in individual pens	Y	Y	N
5	**Sows in groups**	Y	Y	Y
6	**Fattening pigs**	Y	Y	Y
7	Laying hens in battery cages without treatment	Y	Y	N
8	Laying hens in battery cages with aeration (belt drying)	N*	N*	N
9	Laying hens in battery cages with forced drying (deep pit, high rise)	Y	Y	N
10	Laying hens in compact battery cages	Y	Y	N
11	Laying hens in free range with litter floor (partly litter floor, partly slatted)	N*	N*	N
12	**Broilers in free range with litter floor**	Y	Y	Y
13	Laying hens in free range with grating floor (aviary system)	Y	Y	N
14	**Parent broilers in free range with grating floor**	Y	Y	Y
15	**Parent broilers in rearing with grating floor**	Y	Y	Y
16	**Turkeys in free range with litter floor**	Y	Y	Y
17	**Ducks in free range with litter floor**	Y	Y	Y
18	**Geese in free range with litter floor**	Y	Y	Y

* non acceptable risk for the aquatic compartment and sediment was identified considering exposure via STP

Animal Housing categories that show acceptable risk following the use of the representative products are highlighted with bold.

Melamine

Cat.	**Type of housing**	**Acceptable risk (Y/N)**		
		Surface water	**Sediment**	**Soil**
1	Dairy cows	Y	Y	Y
2	Beef cattle	Y	Y	Y
3	Veal calves	Y	Y	Y
4	Sows, in individual pens	Y	Y	Y
5	Sows in groups	Y	Y	Y

6	Fattening pigs	Y	Y	Y
7	Laying hens in battery cages without treatment	Y	Y	Y
8	Laying hens in battery cages with aeration (belt drying)	Y	Y	Y
9	Laying hens in battery cages with forced drying (deep pit, high rise)	Y	Y	Y
10	Laying hens in compact battery cages	Y	Y	Y
11	Laying hens in free range with litter floor (partly litter floor, partly slatted)	Y	Y	Y
12	Broilers in free range with litter floor	Y	Y	Y
13	Laying hens in free range with grating floor (aviary system)	Y	Y	Y
14	Parent broilers in free range with grating floor	Y	Y	Y
15	Parent broilers in rearing with grating floor	Y	Y	Y
16	Turkeys in free range with litter floor	Y	Y	Y
17	Ducks in free range with litter floor	Y	Y	Y
18	Geese in free range with litter floor	Y	Y	Y

2.2.2.6 Assessment of endocrine disruptor properties

No endocrine specific studies, e.g. in vitro or in vivo screening assays or in vivo confirmatory tests, have been submitted to investigate the potential endocrine mode of action of the active substance. Therefore, the assessment of the potential endocrine disrupting activity of cyromazine is based on the available mammalian toxicity data.

No criteria are currently specified for the determination of endocrine-disrupting properties.

According to interim criteria as described in Article 5(3) to the Biocidal Product Regulation, substances shall be considered as having endocrine-disrupting properties in case:

- they are classified in accordance with Regulation (EC) No 1272/2008 as, or meet the criteria to be classified as, carcinogen category 2 and toxic for reproduction category 2,

or

- they are classified in accordance with Regulation (EC) No 1272/2008 as, or that meet the criteria to be classified as, toxic for reproduction category 2 and that have toxic effects on the endocrine organs.

Cyromazine is not classified as carcinogen category 2 or toxic for reproduction category 2 based on the available toxicological data. However, toxic effects on endocrine organs have been identified: prostate atrophy at 60 and 120 mg/kg b.w./day in male dogs (90-day oral toxicity study in the dog; Venugopala Rao, 2007).

In the BPC WG-I-2015 virtual meeting (27 January 2015), several members expressed their concern on reproductive toxicity (fertility) of cyromazine. The basis of the concerns raised were the effects observed in the 2-generation study in rats by Ganiger (2008), i.e. reduced fecundity index in males and increased post-implantation losses and dystocia in females at 80

mg/kg b.w/day and in the 90-day dog study (Venugopala Rao, 2007), i.e. prostate atrophy at 60 and 120 mg/kg b.w./day in males. **It was noted by ECHA that a final conclusion on reproductive toxicity should be made by RAC in the context of C&L.**

The eCA opinion is that cyromazine is not a reproductive toxicant and therefore the interim criteria for the determination of endocrine-disrupting properties are not fulfilled.

However, this conclusion may be revised pending on the outcome of the RAC on the potential classification of cyromazine as toxic for reproduction category 2 and/or the availability of specific criteria for the determination of endocrine-disrupting properties.

2.3. Overall conclusions

The outcome of the assessment for Cyromazine in product-type 18 is specified in the BPC opinion following discussions at the [**BPC-13-2015**] meeting of the Biocidal Products Committee (BPC). The BPC opinion is available from the ECHA website.

2.4. List of endpoints

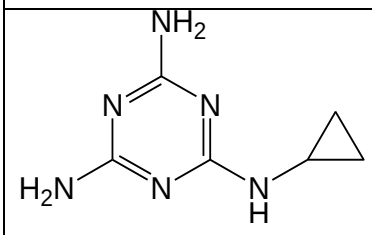
The most important endpoints, as identified during the evaluation process, are listed in Appendix I.

Appendix I: List of endpoints

Chapter 1:Identity, Physical and Chemical Properties, Classification and Labelling

Active substance (ISO Name)	Cyromazine
Product-type	PT 18 (insecticides, acaricides and products to control other arthropods)

Identity

Chemical name (IUPAC)	N-cyclopropyl-1,3,5-triazine-2,4,6-triamine
Chemical name (CA)	N-cyclopropyl-1,3,5-triazine-2,4,6-triamine
CAS No	66215-27-8
EC No	266-257-8 (EINECS)
Other substance No.	420 (CIPAC)
Minimum purity of the active substance as manufactured (g/kg or g/l)	950 g/kg
Identity of relevant impurities and additives (substances of concern) in the active substance as manufactured (g/kg)	None.
Molecular formula	C6H10N6
Molecular mass	166.19 g/mol
Structural formula	

Physical and chemical properties

Melting point (state purity)	223.2 °C (99.2%) (Novartis) 223.96 °C (99.61%) (Hokochimie Sarl)
Boiling point (state purity)	No boling point could be determined due to decomposition.
Thermal stability / Temperature of decomposition	No thermal effect was observed between room temperature and 150°C with or without air (technical material) (Novartis) 300-400 °C (99.61%) (Hokochimie Sarl)
Appearance (state purity)	Novartis: fine, white odourless powder (99.2%) fine, off-white odourless powder (97.5%) Hokochemie Sarl: White crystalline form odourless (99.6%)
Relative density (state purity)	1.334 (99.61%) at 20±1^{0}C

Surface tension (state temperature and concentration of the test solution)	59.0 mN/m (97.4%) (Novartis) 63.3±0.44 mN/m (99.6%) (Hokochimie Sarl)
Vapour pressure (in Pa, state temperature)	4.48 10^{-7} Pa (99.3%) at 25°C
Henry's law constant (Pa m^3 mol^{-1})	5.8x10^{-9} Pa m^3/mol
Solubility in water (g/l or mg/l, state temperature)	13 g/L at pH 7.1 and pH 9 (25°C) 8.0 g/L (as phosphate salt) at pH 5.3 (25°C) (Novartis) pH 5: 14.5 g/L(20°C) pH 7:10.7 g/L (20°C) pH 9:11.2 g/L (20°C) (Hokochemie Sarl) At purity: 99.6%
Solubility in organic solvents (in g/l or mg/l, state temperature)	solubility at 25°C in g/L: acetone: 1.4 dichloromethane: 0.210 ethyl acetate: 0.660 hexane: < 1x10^{-3} methanol: 17 octanol: 1.5 toluene: 0.011 At purity: 97.5%
Stability in organic solvents used in biocidal products including relevant breakdown products	Not required, since the TGAI does not contain residues of organic solvents.
Partition coefficient (log P_{OW}) (state temperature)	log Pow = -0.36 at pH 5.4 and 25°C log Pow = -0.069 at pH 7.0 and 25°C log Pow = -0.039 at pH 9.0 and 25°C At purity: 99.6%(Novartis) log Pow = -0.0644 at pH 8.0 and 22 °C At purity: 99.61% (Hokochemie Sarl)
Dissociation constant	pKa = 5.22 at 20°C At purity: 99.6%

UV/VIS absorption (max.) (if absorption > 290 nm state ε at wavelength)	UV/vis –spectrum UV Absorption Characteristics: Absorption maxima: 208 nm in neutral solution 215 and 241 nm in acidic solution 230 nm in basic solution
Flammability or flash point	Not highly flammable.
Explosive properties	Not oxidising.
Oxidising properties	Not explosive.
Auto-ignition or relative self ignition temperature	Not auto-flammable.

Classification and proposed labelling

with regard to physical hazards	None.
with regard to human health hazards	None
with regard to environmental hazards	Classification: Long-term aquatic hazard Category 1 (M-factor for chronic toxicity: 1) GHS pictogram:  Signal word: Warning Hazard statement: H410: Very toxic to aquatic life with long lasting effects Precautionary statements: P273: Avoid release to the environment P391: Collect spillage P501: Dispose of contents/container in accordance with local regulation

Chapter 2:Methods of Analysis

Analytical methods for the active substance

Technical active substance (principle of method)	HPLC/UV (230 nm) (DAD) (Novartis) HPLC/UV (214 nm) (Hokochimie Sarl)
Impurities in technical active substance (principle of method)	HPLC/UV (230 nm) (Novartis) HPLC/UV (214 nm) (DAD) (Hokochimie Sarl)

Analytical methods for residues

Soil (principle of method and LOQ)	HPLC-MS/MS: LOQ (Cyromazine): 0.0025 mg/kg LOQ (Melamine): 0.005 mg/kg The HPLC/UV method can be considered as confirmatory. (Novartis) HPLC/UV (214nm), GC/MS: LOQ (Cyromazine) HPLC/UV: 10 µg/kg LOQ (Melamine) HPLC/UV: 10 µg/kg LOQ (Cyromazine) GC/MS: 10 µg/kg LOQ (Melamine) GC/MS: 10 µg/kg (Hokochemie Sarl)
Air (principle of method and LOQ)	LC-MS/MS LOQ: Cyromazine: 1 µg/m^3 (Novartis)
Water (principle of method and LOQ)	HPLC-MS/MS River Water, Ground Water, Drinking Water LOQ (Cyromazine): 0.1 µg/L LOQ (Melamine): 9.0 µg/L (Novartis) A confirmatory method for drinking and surface water must be submitted.
Body fluids and tissues (principle of method and LOQ)	Not required.
Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes)	No fully validated method has been submitted. It should be noted that since the dietary risk assessment was perfomed before agreed Guidance was available (see Discussion Table point 11, 12, 13 and 17, Human Exposure) therefore no analytical method is required at this point for food/feed of animal origin.

Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)	HPLC/UV (215nm): Substrate: Muscle, Kidney, Liver and Fat LOQ (Cyromazine): 0.02mg/kg (muscle, kidney) and 0.04mg/kg (liver and fat) Additional Data required. (Novartis) HPLC-MS/MS: Substrate: Muscle, Kidney, Liver and Fat LOQ (Cyromazine): 0.1 mg/kg Additional Data required. (Hokochemie Sarl) It should be noted that since the dietary risk assessment was perfomed before agreed Guidance was available (see Discussion Table point 11, 12, 13 and 17, Human Exposure) therefore no analytical method is required at this point for food/feed of animal origin.

Chapter 3:Impact on Human Health

Absorption, distribution, metabolism and excretion in mammals

Rate and extent of oral absorption:	Rapidly (94-97 % of total urinary excreted radioactivity within 24 hours) and almost completely absorbed (greater than 97% of the applied dose within 72 hrs).
Rate and extent of dermal absorption*:	26% for the dilution and 17% for a 2% undiluted product & 12% for a 50% undiluted product based on *in vivo* rat data
Distribution:	Widely distributed. Highest residues of radioactivity in urinary bladder, kidney and liver.
Potential for accumulation:	No potential.
Rate and extent of excretion:	The excretion was rapid primarily via urine (94-97 % of the dose) within 24 hours.
Toxicologically significant metabolite(s)	Parent compound.

* the dermal absorption value is applicable for the active substance and might not be usable in product authorization

Acute toxicity

Rat LD_{50} oral	> 2500 mg/kg b.w.
Rat LD_{50} dermal	> 2000 mg/kg b.w.
Rat LC_{50} inhalation	> 5.27 mg/L air

Skin corrosion/irritation	Slight skin irritant
Eye irritation	Not eye irritant
Respiratory tract irritation	No data available on respiratory tract irritation. No data required.
Skin sensitisation (test method used and result)	Non skin sensitizer (Magnusson-Kligman Maximization Method)
Respiratory sensitisation (test method used and result)	Not available. Not required.

Repeated dose toxicity

Short term

Species / target / critical effect	Oral: Decreased body weight gain and liver weight changes (rat, dog), haematological and clinical chemistry changes (dog) Inhalation: Decreased body weight, liver and pituitary weight changes, clinical signs, haematological changes (rat)
Relevant oral NOAEL / LOAEL	5.74 mg/kg bw/day, 1-year, dog 23 mg/kg bw/day, 90-day rat
Relevant dermal NOAEL / LOAEL	2000 mg/kg bw/day, 21-day, rabbit
Relevant inhalation NOAEL / LOAEL	NOAEC = 58 mg/m3, 28-day, rat

Long term

Species/ target / critical effect	Decreased body weight gain (rat, mouse)
Relevant oral NOAEL / LOAEL	6.5 mg/kg bw/day, 2-year mouse (gavage) 14.7 mg/kg bw/day, 2-year rat (oral)
Relevant dermal NOAEL / LOAEL	Not available. Not required.
Relevant inhalation NOAEL / LOAEL	Not available. Not required.

Genotoxicity	Equivocal result in gene mutation assay *in vitro*. No potential for induction of chromosomal aberrations *in vivo*. No further testing required.

Carcinogenicity

Species/type of tumour	No carcinogenic potential.
Relevant NOAEL/LOAEL	Rat: 156 mg/kg b.w./day Mouse: 384 mg/kg b.w./day

Reproductive toxicity

Developmental toxicity

Species/ Developmental target / critical effect	Delayed ossification (rats), skeletal malformations and variations (rabbits) and decreased foetal body weight (rats and rabbits) were noted in the presence of substantial maternal toxicity (body weight loss)
Relevant maternal NOAEL	15 mg/kg b.w./day (rabbit teratology)
Relevant developmental NOAEL	45 mg/kg b.w./day (rabbit teratology)

Fertility

Species/critical effect	Increased post-implantation losses and dystocia in females, reduced fecundity index in males and decreased live birth index in the presence of substantial maternal toxicity (decreased bodyweight)

Relevant parental NOAEL	20 mg/kg b.w./day (2-generation, rat)
Relevant offspring NOAEL	20 mg/kg b.w./day (2-generation, rat)
Relevant fertility NOAEL	20 mg/kg b.w./day (2-generation, rat)

Neurotoxicity

Species/ target/critical effect	Not available. Not required.

Developmental Neurotoxicity

Species/ target/critical effect	Not available. Not required.

Immunotoxicity

Species/ target/critical effect	Not available. Not required.

Developmental Immunotoxicity

Species/ target/critical effect	Not available. Not required.

Other toxicological studies

By-product CGA 72095 tech.:
No mutagenic potential (Ames test), acute oral LD_{50} >2000 mg/kg bw
Metabolite 1-methylcyromazine:
No structural alerts others than those of the parent compound (Derek analysis)

Metabolite melamine (toxicity evaluation based on public literature studies):
Acute oral toxicity (rats): LD_{50} = 3100 mg/kg bw
Acute dermal toxicity (rats): LD_{50} = 1000 mg/kg bw
Not an eye irritant or a skin sensitizer.
Short term toxicity: *13-week feeding, rat*: NOAEL = 63 mg/kg bw/day
Target organ: urinary bladder
Effects: calculi formation
Genotoxicity: not genotoxic
Chronic toxicity: 102-week feeding, rat: NOAEL = 126 mg/kg bw/day
Target organ: urinary bladder
Effects: carcinomas in urinary bladder (induction of carcinomas by irritation of the bladder epithelium in the presence of calculi – not relevant to the risk assessment for humans)

Medical data

No adverse health effects reported from production of active substance or formulations; no known clinical cases and poisoning incidents; Based on animal testing poisoning symptoms may constitute body weight loss. There is no specific antidote for cyromazine. First aid measures for cases of poisoning with cyromazine should comprise standard decontamination measures and symptomatic treatment.

Summary

Value	Study	Safety

			factor
$AEL_{long-term}$	0.06	1-year dog study supported by 2-year mouse study	100
$AEL_{medium-term}$	0.06	1-year dog study supported by 2-year mouse study	100
AEL_{acute}	0.1	Rabbit developmental studies	100
ADI[4]	0.06	1-year dog study supported by 2-year mouse study	100
ARfD	0.1	Rabbit developmental studies	100

MRLs

Relevant commodities	0.3 mg/kg Ovine muscle, fat, liver, kidney (Regulation 37/2010). 0.3 mg/kg in sheep meat and offals (Regulation 61/2014). 0.01 mg/kg in animal products (except sheep) and milk (Regulation 61/2014). The values represent the current EUMRLs.

Reference value for groundwater

According to BPR Annex VI, point 68	-

Dermal absorption

Study (*in vitro/vivo*), species tested	*in vivo*, rat
Formulation (formulation type and including concentration(s) tested, vehicle)	Cyromazine 75 WP
Dermal absorption values used in risk assessment	26% for the dilution and 17% for a 2% undiluted product & 12% for a 50% undiluted product

Acceptable exposure scenarios (including method of calculation)

Formulation of biocidal product	**Neporex 2 SG**
Intended uses	Insect Growth Regulator (IGR). Larvicide used in animal housing.
Industrial users	Not applicable

[4] If residues in food or feed.

Professional users	***Primary exposure, % AELmedium-term (normal use):*** Dry scattering (manual) < 37% (PPE - Operator exposure study) Spray application 25% (PPE - TNsG Model 1) Watering application 49% (PPE - Mixing/loading Model 5 TNsG (2002) & TNsG (2007) for watering cans) ***Primary exposure, % AELmedium-term (worst-case use):*** Dry scattering (manual) < 81% (PPE - Operator exposure study) Spray application 75% (PPE - TNsG Model 1) Watering application - ***Secondary exposure: workers*** Secondary exposure of stable workers after the application is considered to be negligible as the product is present on the floor in the manure (protection by working shoes/boots).
Non professional users	Not intended
General public	***Bystander exposure*** Spray application: 86% of the AEL_{acute} Negligible for dry scattering and watering
Exposure via residue in food	**Secondary exposure** The assessment conducted is indicative since no guidance document is available. The scenario has not been considered in the draft guidance and it is not covered in any guidance. At product authorisation level a dietary risk assessment needs to be performed taking into account potential exposure of livestock animals following application of the biocidal product in the animal house and transfer of residues via feed into livestock animals.

Formulation of biocidal product	**Neprorex 50 SP**
Intended uses	Insect Growth Regulator (IGR). Larvicide used in animal housing.
Industrial users	Not applicable

Professional users	***Primary exposure, % $AEL_{medium-term}$ (normal use):*** Spray application 25% (PPE - TNsG Model 1) Watering application 52% (PPE - Mixing/loading Model 5 TNsG (2002) & TNsG (2007) for watering cans)***Primary exposure, % $AEL_{medium-term}$ (worst-case use):*** Spray application 75% (PPE - TNsG Model 1) Watering application -
	Secondary exposure: workers Secondary exposure of stable workers after the application is considered to be negligible as the product is present on the floor in the manure (protection by working shoes/boots).
Non professional users	Not intended
General public	***Bystander exposure*** Spray application: 86% of the AEL_{acute} Negligible for watering application
Exposure via residue in food	***Secondary exposure*** The assessment conducted is indicative since no guidance document is available. The scenario has not been considered in the draft guidance and it is not covered in any guidance. At product authorisation level a dietary risk assessment needs to be performed taking into account potential exposure of livestock animals following application of the biocidal product in the animal house and transfer of residues via feed into livestock animals.

Formulation of biocidal product	**HOKOEX (Cyromazine 2SG)**
Intended uses	Insect Growth Regulator (IGR). Larvicide used in animal housing.
Industrial users	Not applicable

Professional users	***Primary exposure, % $AEL_{medium-term}$ (normal use):*** Dry scattering (manual) 72% (PPE- User Guidance, (2002) Model for pellet rodenticide) Spray application 25% (PPE - TNsG Model 1) Watering application 49% (PPE - Mixing/loading Model 5 TNsG (2002) & TNsG (2007) for watering cans) ***Primary exposure, % $AEL_{medium-term}$ (worst-case use):*** Dry scattering (manual) - Spray application 75% (PPE - TNsG Model 1) Watering application -
	Secondary exposure: workers Secondary exposure of stable workers after the application is considered to be negligible as the product is present on the floor in the manure (protection by working shoes/boots).
Non professional users	***Primary exposure, % $AEL_{medium-term}$*** 34% (Consumer spraying and dusting model 1 TNsG part 2, p 194; 2, Hand-held pumped spray)
General public	***Bystander exposure*** Spray application: 86% of the AEL_{acute} Negligible for dry scattering and watering
Exposure via residue in food	***Secondary exposure*** The assessment conducted is indicative since no guidance document is available. The scenario has not been considered in the draft guidance and it is not covered in any guidance. At product authorisation level a dietary risk assessment needs to be performed taking into account potential exposure of livestock animals following application of the biocidal product in the animal house and transfer of residues via feed into livestock animals.

Chapter 4: Fate and Behaviour in the Environment

Route and rate of degradation in water

Hydrolysis of active substance and relevant metabolites (DT_{50}) (state pH and temperature)	Hydrolytically stable in pH 4,7 and 9 at 50 ^{0}C.
pH 5	Stable at pH 4

pH 9	Stable
Other pH: *[indicate the value]*	Stable at pH 7
Photolytic / photo-oxidative degradation of active substance and resulting relevant metabolites	Photolytically stable.
Readily biodegradable (yes/no)	No
Inherent biodegradable (yes/no)	Not allocated
Biodegradation in freshwater	Not allocated
Biodegradation in seawater	Not allocated
Non-extractable residues	-
Distribution in water / sediment systems (active substance)	Not allocated
Degradation in water/sediment	
DT50 water	14.5 to 16 days (20^0C) 27.6 to 30.4 days (12^0C)
DT50 sediment	142 to 143 days (20^0C) 270 to 272 days (12^0C)
DT50 whole system	211 to 244 days (20^0C) 401 to 464 days (12^0C)
Distribution in water / sediment systems (metabolites)	Max in water 96% at 0 d. Max. in sediment 54.2% after 56 d.
Distribution in water / sediment systems (metabolites)	Melamine never exceeded 3.5% AR.

Route and rate of degradation in soil

Mineralization (aerobic)	-
Laboratory studies (range or median, with number of measurements, with regression coefficient)	DT_{50} 4.77-106.2 days (n=8) at 12^0C. Geometric mean of 37.89 days (n=8) used for PEC calculations.
DT_{50lab} (20°C, aerobic):	2.9, 31.3 (at 25^0C), 46, 15, 56, 38.2, 49.6 days.
DT_{90lab} (20°C, aerobic):	-
DT_{50lab} (10°C, aerobic):	5.6 days
DT_{50lab} (20°C, anaerobic):	97.6 d (at 25^0C)
degradation in the saturated zone:	-
Field studies (state location, range or median with number of measurements)	-
DT_{50f}:	-
DT_{90f}:	-
Anaerobic degradation	DT_{50} 276.1 days at 12^0C

Soil photolysis	-
Non-extractable residues	-
Relevant metabolites - name and/or code, % of applied a.i. (range and maximum)	Melamine: 73.1 % AR after 28 days DT_{50} = 237 days at 12^0C
Soil accumulation and plateau concentration	-

Adsorption/desorption

Ka , Kd Ka_{oc} , Kd_{oc} pH dependence (yes / no) (if yes type of dependence)	Ka= 0.607-50.4 mL/kg (n=4) Kd= 17.0-54.6 mL/kg (n=4) Kaoc= 80.5-1810 mL/kg (n=4) Kdoc=2255-10460 mL/kg (n=4) No pH dependence

Fate and behaviour in air

Direct photolysis in air	DT_{50}= 12.7 days (24 h-day)
Quantum yield of direct photolysis	-
Photo-oxidative degradation in air	-
Volatilization	

Reference value for groundwater

According to BPR Annex VI, point 68	-

Monitoring data, if available

Soil (indicate location and type of study)	Small-scale groundwater monitoring study, Florida USA. Cyromazine: <10.0-47.2 µg a.s./kg (0-15 cm) <10.0 µg a.s./kg (> 15 cm) Melamine: <10.0-76.1 µg /kg (0-15 cm) <10.0-27.8 µg /kg (15-30 cm) <10 µg /kg (30-45cm)
Surface water (indicate location and type of study)	-
Ground water (indicate location and type of study)	Small-scale groundwater monitoring study, Florida USA. Cyromazine: <0.1 µg/L Melamine: 0.10-0.21 µg/L
Air (indicate location and type of study)	-

Chapter 5: Effects on Non-target Species

Toxicity data for aquatic species (most sensitive species of each group)

Species	Time-scale	Endpoint	Toxicity (mg/L)[1]
Cyromazine			
Fish			
Cyprinus carpio	96-hour – Static	LC_{50}	> 100 (nom.) (Novartis)
Oncorhynchus mykiss	96-hour – Static	LC_{50}	1888 (nom.) (Hokochimie Sarl)
Pimephales promelas	32-day – Flow-through	NOEC	14 (m.m.) (Novartis)
Invertebrates			
Daphnia magna	48-hour – Static	EC_{50}	5.00 (nom.) (Hokochimie Sarl)
Daphnia magna	21-day – Flow-through	NOEC	0.31 (m.m.) (Novartis)
Algae			
Scenedesmus subspicatus	120-hour – Static	E_rC_{50}	124 (nom.) (Novartis)
		NOEC	< 100 (nom.) [2] (Novartis)
Pseudokirchneriella subcapitata	96-hour – Static	E_rC_{50}	129 (nom.) (Hokochimie Sarl)
		E_bC_{50}	52.4 (nom.) (Hokochimie Sarl)
		NOEC	31.3 (nom.) [3] (Hokochimie Sarl)
Sediment-dwelling organisms			
Chironomous riparius	48-hour – Semi-static	LC_{50}	> 120 (nom.) (Novartis)
Chironomous riparius	26-day - Static	NOEC	0.016 (m.m.) (Novartis)
Microorganisms			
Aerobic microorganisms (growth inhibition)	5 subsequent test cycles each at 23 hours - Static	NOEC	> 100 (nom.) (Novartis)
Anaerobic microorganisms (evolution of biogas)	62-hour - Static	EC_{50}	> 9.5 (Novartis)
		NOEC	9.5 (Novartis)
Colpoda aspera	36-hour - Static	EC_{50}	342 (Hokochimie Sarl)
Melamine			
Fish			
Oncorhynchus mykiss	96-hour – Static	LC_{50}	> 128 (m.m.) (Novartis)

Invertebrates			
Daphnia magna	48-hour – Static	EC_{50}	60 (nom.) (Novartis)
Algae			
Selenastrum capricornutum	72-hour – Static	E_rC_{50}	> 100 (nom.) (Novartis)
		E_bC_{50}	> 100 (nom.) (Novartis)
		NOEC	100 (nom.) [4] (Novartis)

[1] nom.: Results are based on nominal concentrations, m.m: Results are based on mean measured concentrations
[2] based on growth rate
[3] based on growth rate
[4] based on both growth rate and biomass production

Effects on earthworms or other soil non-target organisms

Cyromazine

Acute toxicity to earthworms (*Eisenia fetida*)	14-day LC_{50} > 340 mg/kg standard soil dw (nominal) equivalent to > 268 mg/kg standard soil dw (TWA; based on the DT_{50} of 19.4 days (20ºC) and a test duration of 14 days) (Novartis)
Acute toxicity to *Aleochara bilineata*	28-day LR_{50} > 12.9 mg/kg standard soil dw (nominal) equivalent to > 8.15 mg/kg standard soil dw (TWA; based on the DT_{50} of 19.4 days (20ºC) and a test duration of 28 days) (Novartis)
Reproductive toxicity to earthworms (*Eisenia fetida*)	56-day NOEC = 113 mg/kg standard soil dw (nominal) equivalent to 48.8 mg/kg standard soil dw (TWA; based on the DT_{50} of 19.4 days (20^0C) and the test duration of 56 days) (Novartis)

Melamine

Acute toxicity to earthworms (*Eisenia fetida*)	14-day LC_{50} > 340 mg/kg standard soil dw (Novartis)
Reproductive toxicity to earthworms (*Eisenia fetida*)	56-day NOEC = 0.425 mg/kg standard soil dw (Novartis)
	56-day NOEC = 13.6 mg/kg standard soil dw (Novartis)

Effects on soil micro-organisms

Cyromazine

Nitrogen mineralization	56-day EC_{50} > 131 mg/kg standard soil dw (nominal) equivalent to > 56.6 mg/kg standard soil dw (TWA; based on the DT_{50} of 19.4 days (20^0C) and the test duration of 56

	days) (Novartis) 56-day NOEC = 13.1 mg/kg standard soil dw (nominal) equivalent to 5.66 mg/kg standard soil dw (TWA; based on the DT_{50} of 19.4 days (20^0C) and the test duration of 56 days) (Novartis)
Carbon mineralization	28-day EC_{50} > 131 mg/kg standard soil dw (nominal) equivalent to > 82.2 mg/kg standard soil dw (TWA; based on the DT_{50} of 19.4 days (20^0C) and the test duration of 28 days) (Novartis) 28-day NOEC = 131 mg/kg standard soil dw (nominal) equivalent to 82.2 mg/kg standard soil dw (TWA; based on the DT_{50} of 19.4 days (20^0C) and the test duration of 28 days) (Novartis)

Melamine

Nitrogen mineralization	28-day EC_{50} > 13.6 mg/kg standard soil dw (Novartis) 28-day NOEC = 13.6 mg/kg standard soil dw (Novartis)
Carbon mineralization	28-day EC_{50} > 13.6 mg/kg standard soil dw (Novartis) 28-day NOEC = 13.6 mg/kg standard soil dw (Novartis)

Effects on terrestrial vertebrates

Acute toxicity to mammals	Refer to Chapter 3
Acute toxicity to birds	Data not required
Dietary toxicity to birds	Data not required
Reproductive toxicity to birds	Data not required

Effects on honeybees

Acute oral toxicity	48-hour LD_{50}: 186 µg a.s./bee (Novartis)
Acute contact toxicity	48-hour LD_{50}: > 200 µg a.s./bee (Novartis)

Effects on other beneficial arthropods

Acute oral toxicity to the Black Soldier fly (incorporation into larval diet)	LC_{50} > 0.15 mg a.s./L (public domain)
Acute contact toxicity to *Orius laevigatus*	LC_{50} > 638 mg a.s./L (public domain)
Chronic contact toxicity to *Ceratitis capitata* and *Orius concolor*	NOEC = 10000 mg a.s./L (public domain)
Chronic contact toxicity to *Hemiptarsenus varicornis* and *Diglyphus isaea*	NOEC = 225 mg a.s./L (public domain)

Bioconcentration

Bioconcentration factor (BCF): earthworm	0.85 L/kg (theoretically estimated value by using the QSAR equation of Jager (1998))
Bioconcentration factor (BCF): fish	< 1 L/kg (experimentally derived value) 0.17 L/kg (theoretically estimated value by using the QSAR equation of Veith et al. (1979))
Depration time (DT_{50})	< 14 days [1]
Depration time (DT_{90})	< 14 days [1]
Level of metabolites (%) in organisms accounting for > 10 % of residues	Not applicable

[1] ^{14}C-residue concentrations in non-edible tissues decreased steadily and were below the limit of detection by day 10 of the depuration phase. For the edible tissue and also for whole fish, ^{14}C-residue concentrations were below the limit of detection during the entire depuration phase

Chapter 6: Other End Points

Effects on higher terrestrial plants

Seedling emergence	ER_{50} > 300 g a.s./ha (equivalent to 0.2 mg/kg artificial soil dw) [1] NOER = 18.75 g a.s./ha (equivalent to 0.0125 mg/kg artificial soil dw) [1]
Vegetative vigour	ER_{50} > 300 g a.s./ha [1] NOER = 75 g a.s./ha [1]

[1] results are based on visual phytotoxicity rating; relevant for use in a screening-level (not quantitative) risk assessment

Soil field study:

The potential effects of cyromazine on terrestrial invertebrate fauna and slurry degradation were investigated under natural conditions in a GLP field trial (III A7.5.6; Novartis) conducted using the formulated product Neporex 2 SG. Based on the lack of any adverse effects at population level and the recovery of transiently affected invertebrate populations, the overall NOEAEC (No Observed Ecologically Adverse Effect Concentration) determined was 284 g a.s./ha, equivalent to the nominal concentration of 0.189 mg a.s./kg soil dw and to the TWA mean concentration of 0.0804 mg a.s./kg soil dw (based on the DT_{50} of 37.9 at 12ºC and the test duration of 16 weeks). Taking into account the quality and limitations of the field study, an assessment factor of 5 should be applied to the NOEAEC of 0.0804 mg a.s./kg soil dw (equivalent to 0.0711 mg a.s./kg soil wwt). This AF was agreed in the WGI-2015 and provides an overall protection of the soil environment.

Appendix II: List of Intended Uses

Cyromazine has been evaluated for its intended uses as an insecticide (PT 18); Data on efficacy of Cyromazine were provided by two applicants (*HokoChemie Sarl* and *Novartis*) and accepted in support of the intended uses as follows:

(*Hokochemie Sarl* dossier)

Object and/or situation	Product name	Organisms controlled	Formulation		Application			Applied amount per treatment			Remarks:
			Type (d-f)	Conc. of a.s. (i)	method kind (f-h)	number min max	interval between applications (min)	g a.s./L min max	water L/m^2 min max	g a.s./m^2 min max	
Insect Growth Regulator (IGR). Larvicide used in animal housing. Applied to manure and other breeding sites for the control of fly larvae in animal housing (e.g. cattle,	HOKOEX	Fly larvae	SG (Soluble Granules)	20 g/ Kg (2 % w/w)	Direct dispersal (dry scattering by hand) Pouring (watering by can) Spraying (hand pressurized or power-operated sprayer - knapsack	1 – 5 per year from March/April to October/November	The product should be applied after removal of manure at intervals exceeding two weeks, while 6-weeks intervals are suffice. Treatment should be conducted after cleaning out the manure (approximately	- (direct) 0.5 – 1.25 (pouring) 1.25 –5 (spraying)	- (direct) 0.4 - 1 (pouring) 0.1 - 0.4 (spraying)	0.5 (direct) 0.5 (pouring) 0.5 (spraying)	Use dry scattering only in case of very wet or liquid manure. Spraying is used for convenience purposes in case the organic matter is not too dry. In cases

Object and/or situation	Product name	Organisms controlled	Formulation		Application			Applied amount per treatment			Re marks:
			Type (d-f)	Conc. of a.s. (i)	method kind (f-h)	number min max	interval between applications (min)	g a.s./L min max	water L/m^2 min max	g a.s./m^2 min max	
swine, poultry facilities). Also, used for manure outdoors, waste dump sites, waste containers, slurry tanks and manure heaps.					or automatic equipment - or any other suitable spray equipment delivering the spray as a course low-pressure spray onto the fly breeding sites)		within the first 3 days after dung removal) and starting the build up of new breeding material.				when manure is dry only pouring guarantees sufficient penetration of the active ingredient into the organic matter.

(*Novartis* dossier)

Object and/or situation	Product name	Organisms controlled	Formulation		Application			Applied amount per treatment			Re marks:
			Type (d-f)	Conc. of a.s. (i)	method kind (f-h)	number min max	interval between applications (min)	g a.s./L min max	water L/m^2 min max	g a.s./m^2 min max	
Insect Growth Regulator (IGR). Larvicide used in animal housing	Neporex 2SG	Nuisance flies: *Musca domestica,* (Common Housefly), *Fannia canicularis* (Little House Fly), *Drosophila repleta* (Fruit Fly), *Ophyra leucostoma* (Black garbage fly) (*only in case of high (annoying) populations*) Biting flies: *Stomoxys calcitrans* (Stable Fly)	SG (Soluble Granules)	20 g/ Kg (2% w/w)	dry scattering by hand after dilution in water by: spraying (hand pressurized or power-operated sprayer - knapsack or automatic equipment - or any other suitable spray equipment delivering the spray as a course low-pressure	1-5 per year from March/April to October/November	2-3 weeks up to several months The treatment should be repeated within the first 3 days after cleaning (dung removal) but only after the new manure starts to pile up again. Treatment interval depends on management and housing systems as well as on climatic conditions.	- For spraying: 1.25 - 5 (62.5-250 g product) For watering: 0.5 (25 g product)	- 0.1 - 0.4 (spraying) 1 (watering)	0.5 (25 g product/ m^2) 0.5 (25 g product/ m^2)	Applied to manure and other breeding sites for the control of fly larvae in animal housing (e.g. cattle, swine, poultry facilities). Applied by farmers, regarded as professionals. use dry scattering only in case of wet or liquid manure

Object and/or situation	Product name	Organisms controlled	Formulation		Application			Applied amount per treatment			Remarks:
			Type (d-f)	Conc. of a.s. (i)	method kind (f-h)	number min max	interval between applications (min)	g a.s./L min max	water L/m^2 min max	g a.s./m^2 min max	
					spray onto the fly breeding sites) watering (can)						
Insect Growth Regulator (IGR). Larvicide used in animal housing	Neporex 50SP	Nuisance flies: *Musca domestica,* (Common Housefly), *Fannia canicularis* (Little House Fly), *Drosophila repleta* (Fruit Fly) *Ophyra leucostoma* (Black garbage fly) (*only in case of high (annoying) populations*) Biting flies: *Stomoxys*	SP (Soluble Powder)	500 g/ Kg (50% w/w)	after dilution in water by: spraying (hand pressurized or power-operated sprayer - knapsack or automatic equipment - or any other suitable spray equipment delivering the spray as a course low-	3-5 per year from March/April to October/November	2-3 weeks up to several months The treatment should be repeated within the first 3 days after cleaning (dung removal) but only after the new manure starts to pile up again. Treatment interval depends on management	For spraying: 5 (10 g product) For watering: 0.5 (1 g product)	0.1 (spraying) 1 (watering)	0.5 (1 g product/ m^2)	Applied to manure and other breeding sites for the control of fly larvae in animal housing (e.g. cattle, swine, poultry facilities). Applied by farmers, regarded as professionals.

Object and/or situation	Product name	Organisms controlled	Formulation		Application			Applied amount per treatment			Re marks:
			Type (d-f)	Conc. of a.s. (i)	method kind (f-h)	number min max	interval between applications (min)	g a.s./L min max	water L/m^2 min max	g a.s./m^2 min max	
		calcitrans (Stable Fly)			pressure spray onto the fly breeding sites) watering (can)		and housing systems as well as on climatic conditions.				