CONCLUSION ON PESTICIDE PEER REVIEW

Conclusion regarding the peer review of the pesticide risk assessment of the active substance cyromazine

Issued on 17 September 2008

SUMMARY

Cyromazine is one of the 84 substances of the third stage Part B of the review programme covered by Commission Regulation (EC) No 1490/2002[1]. This Regulation requires the European Food Safety Authority (EFSA) to organise upon request of the EU-Commission a peer review of the initial evaluation, i.e. the draft assessment report (DAR), provided by the designated rapporteur Member State and to provide within six months a conclusion on the risk assessment to the EU-Commission.

Greece being the designated rapporteur Member State submitted the DAR on cyromazine in accordance with the provisions of Article 10(1) of the Regulation (EC) No 1490/2002, which was received by the EFSA on 31 August 2007. The peer review was initiated on 6 November 2007 by dispatching the DAR for consultation of the Member States and the sole applicant Syngenta Ltd. Subsequently, the comments received on the DAR were examined and responded by the rapporteur Member State in the reporting table. This table was evaluated by EFSA to identify the remaining issues. The identified issues as well as further information made available by the applicant upon request were evaluated in a series of scientific meetings with Member State experts in May-June 2008.

A final discussion of the outcome of the consultation of experts took place during a written procedure with the Member States in July - August 2008 leading to the conclusions as laid down in this report.

The conclusion was reached on the basis of the evaluation of the representative uses as insecticide as proposed by the notifier. Full details of the GAP can be found in the attached list of end points.

The representative formulated product for the evaluation was "Trigard® 75 WP", a wettable powder (WP) containing 750 g/kg cyromazine.

[1] OJ No L 224, 21.08.2002, p. 25, as amended by Regulation (EC) No 1095/2007 (OJ L 246, 21.9.2007, p. 19)

Sufficient analytical methods as well as methods and data relating to physical, chemical and technical properties are available to ensure that quality control measurements of the plant protection product are possible. Adequate methods are available to monitor all compounds given in the respective residue definitions in food/feed of plant and animal origin, and environmental matrices.

In the mammalian metabolism studies, cyromazine was rapidly and completely absorbed and excreted after oral administration, metabolism was poor, no potential for bioaccumulation was observed.
Acute toxicity of cyromazine was low either by the oral, dermal or inhalation route; it did neither present eye or skin irritation nor skin sensitization properties according to a Magnusson and Kligman test. The main effect observed upon short term and long term exposure was decreased body weight; the relevant short term NOAEL was the dose level of 5.74 mg/kg bw/day from the one-year dog study and the relevant long term NOAEL was the dose of 6.5 mg/kg bw/day from the oncogenicity study in mice. No evidence of genotoxic or carcinogenic potential was found. Cyromazine did not produce any effect on the reproductive performances or fertility up to the highest dose tested; increased incidence of skeletal malformations and variations were associated with clear maternal toxicity. Two plant/environmental metabolites were assessed for their relevance, 1-methyl-cyromazine and melamine; both metabolites were identified in the rat metabolism studies as well. Based on an open literature review, melamine was considered not relevant for groundwater according to the guidance document on the assessment of the relevance of metabolites in groundwater[2]. The toxicity of the metabolites is covered by the reference values of the parent compound.
The Acceptable Daily Intake (ADI) for cyromazine was 0.06 mg/kg bw/day based on the 1-year dog study, supported by the 2-year study in mice and applying a safety factor of 100; the Acceptable Operator Exposure Level (AOEL) was 0.06 mg/kg bw/day based on the same 1-year dog study and safety factor of 100; and the Acute Reference Dose (ARfD) was 0.1 mg/kg bw based on the maternal effects observed in the developmental toxicity study in rabbit and a safety factor of 100. Dermal absorption was 0.7 % for the concentrate representative formulation and 2 % for the in-use spray dilution. The level of operator exposure calculated for outdoor and glasshouse uses was estimated to be below the AOEL even when no protective personal equipment (PPE) are worn. Worker exposure was calculated to be also below the AOEL without the use of PPE; estimated bystander exposure was negligible.

Metabolism in plants has been investigated using ^{14}C-cyromazine labelled on the triazine ring in celery, lettuce and tomato representing two groups of plants: leafy and fruit crop groups. These studies suggest a simple metabolic transformation leading to the dealkylated product melamine. Taking into account the conclusion of the meeting on mammalian toxicology considering that melamine has the same toxicological profile as the parent, the residue definition for risk assessment was defined as “cyromazine parent compound and melamine expressed as cyromazine” and the

[2] Sanco/221/2000 – rev.10 (25 February 2003): Guidance document on the assessment of the relevance of metabolites in groundwater of substances regulated under Council Directive 91/414/EEC.

residue definition for monitoring was limited to "cyromazine parent only", these residue definitions being set for fruit and leafy crops only. Though it was mentioned that consumer exposure to melamine may be possible through other sources (plastics, colorant, flame retardants, veterinary drugs…), the decision to include the melamine metabolite in the residue definition was taken with regard to the high melamine residue levels observed in the treated crops. After the meeting the RMS proposed conversion factors for leafy and fruit crops in order to take into account the melamine metabolite that was included in the residue definition for risk assessment. These conversion factors have to be considered as provisional since they have not been peer reviewed. Based on the US rotational crop studies performed with unlabelled cyromazine and exaggerated application rates, it was concluded that no significant residues of cyromazine or melamine are expected in practice in rotational crops. A residue definition for animal products was discussed, but the experts were not confident in proposing a residue definition for animal products, since animal dietary burden remains unknown and the validity of the animal metabolism study performed with the parent compound only remains uncertain. The final conclusion was that at this stage, there is no need to propose a residue definition and to set MRLs for animal products based on the intended uses on lettuce and tomato. A residue data set was available to propose MRLs for tomato and lettuce. However, after the meeting and considering the conversion factor for risk assessment and the ARfD value set by the meeting on mammalian toxicology, the initial MRL of 10 mg/kg proposed for lettuce and based on the indoor GAP was shown to be unsafe for the consumer (IESTI 325% of the ARfD). Although it was not discussed during the meeting and it has not been peer reviewed, the EFSA in agreement with the RMS, was of the opinion that an MRL of 3 mg/kg based on the outdoor residue trials would be appropriate for cyromazine on lettuce. Taking into account this proposal, no acute concern is observed, the IESTI using the EFSA model being 94% of the ARfD. It must be pointed out that the consumer exposure was only considered through the representative uses of cyromazine as a plant protection product on lettuce and tomato. However this active substance is also used as a veterinary drug and consumers may additionally be exposed to the melamine metabolite through other sources since this molecule is present in many domestic materials (plastics, colorants, flame retardants….). A potential additional exposure to cyromazine and melamine is then expected.

In soil under aerobic conditions cyromazine exhibits low to moderate persistence. Mineralisation of the [U-^{14}C]-traizine radiolabel to carbon dioxide accounted for 3.7-7.3% AR after 120-121 days. The formation of unextractable residues was a sink, accounting for 7-54 % AR after 120-126 days. The major metabolite melamine was formed up to 74.5% AR after 120 days. This metabolite exhibits low to moderate persistence in soil. Another metabolite, identified as NOA 435343 was measured at max 10.7% at 60d in one soil metabolism study. However, an environmental exposure assessment for this metabolite is not available. The soil exposure assessment (PEC) and plateau concentrations calculation for melamine have not been finalised. Cyromazine exhibits very high to low mobility in soil and there was no indication that adsorption of cyromazine was pH dependant. Melamine can be classified as high to medium mobile in soil, with a clear dependence of adsorption on soil pH.

In dark natural sediment water systems cyromazine partitioned relatively slowly from water to sediment, where it degraded exhibiting high persistence. No metabolite accounted > 2.5% AR at any sampling time. The terminal metabolite, CO_2, was a small sink in the material balance accounting for a maximum of 8 % AR at 103d. Unextracted sediment residues were another sink representing 12-13 % AR at study end. The necessary surface water and sediment exposure assessments at steps 3 and 4 are not available for both cyromazine and melamine.

The potential for groundwater exposure from the applied for intended uses by cyromazine and its metabolites above the parametric drinking water limit of 0.1 µg/L with the appropriate input parameters needs to be finalised.

Based on the estimated photo-oxidative degradation rate in the atmosphere of 4.25 days, a potential for long range aerial transport was identified.

The representative uses of cyromazine are applications to lettuce and tomatoes. The First tier risk assessment resulted in an acute and short-term TER value above the Annex VI trigger values, indicating that acute and short term risk to herbivorous and insectivorous birds was low. However, the TERlt was below the Annex VI trigger value indicating a potential high long term risk to birds.

The long term TER for insectivorous birds was revised considering the Yellow wagtail as a focal species, with a refinement diet PD of 17% small insects and 83% large insects. The resulting TERlt values was 16 which was above the Annex VI trigger value, indicating that long term risk is low for insectivorous birds.

The refinement for the long term risk to medium herbivorous birds was based on the residue decline in plants. A MAF of 1.3 was used for the refined risk assessment for herbivorous birds. The resulting TERlt was above the trigger values indicating the risk was low.

First tier risk assessment for mammals resulted in acute and long-term TER values above the Annex VI trigger values, suggesting a low acute and chronic risk for mammals. The risk to birds and mammals from intake of contaminated drinking water from surface water or puddles was considered to be low.

Based on the information available, cyromazine is proposed to be classified as toxic to aquatic organisms. A potential high risk was indicated with PECsw FOCUS Step 3 values for *Chironomus riparius*. At FOCUS step 4, including a non-spray buffer zone of 10 m, the TER values for all scenarios were above the Annex VI trigger value.

The first tier risk assessment indicated that risk for the relevant soil metabolite melamine was considered to be low for aquatic organisms. Risk mitigation measures were needed to reduce the risk of cyromazine to the aquatic organisms. In case of Annex I inclusion of cyromazine Member States should ask for further refinement of the aquatic risk assessment pertinent to national conditions.

A data gap has been identified for the submission of a new risk assessment for the aquatic organisms based on the agreed PECsw values.

The LD_{50} from acute oral and contact toxicity tests with the preparation were 186 µg a.s. /bee and > 200 µg a.s. /bee, respectively. Hazard Quotients (HQ) were estimated to be 1.6 for the oral exposure

and < 1.5 for the contact exposure. As a conclusion a low risk to bees is expected for the use of cyromazine.

As cyromazine is an insect growth regulator an additional consideration was given to potential on the bee brood as recommended in the SANCO Guideline 10329/2002. Three higher tier studies had been submitted by the applicant, reporting that cyromazine had an effect on the development of eggs and young larvae into adult worker bees following dosing in sucrose provided directly to the hive. The impact of TRIGARD ® 75 WP on bee brood development was further investigated in a semi-field tunnel study and a full-scale field study. The experts agreed that the field study should not be considered in the risk assessment, until the applicant submits a position paper on the melon field study including extrapolation from this study to tomato crops in other Member States. With the available information the risk of cyromazine to bee and the bee brood could be considered to be low for lettuce but not for tomato.

The higher tier risk assessment indicates that a potential risk to some foliar dwelling non-target arthropods, particularly the predatory mites *T. pyri* and *P. persimilis*, was identified based on tier II extended lab studies. A high risk was identified for the in-field areas and the RMS proposes to use the aged residue studies to refine the in-field risk assessment. Experts at the PRAPeR 48 meeting had some concerns regarding the study on *T. pyri* which is used to refine the risk in field. Uncertainty remains with regard to the time needed for recovery. Especially for non-flying insects recovery time might be long. If the cyromazine is included in Annex I, mitigation measures should be considered at Member State level to make sure recolonisation is possible.

The risk to earthworms and soil non-target macro-organisms from cyromazine was expected to be low. However, a data gap has to be set for a risk assessment for the metabolite melamine to earthworms based on the agreed PEC soil values.

Additionally the risk to soil micro-organisms and non target plants was expected to be low. Also the risk of cyromazine to biological methods of sewage treatment is low.

Key words: cyromazine, peer review, risk assessment, pesticide, insecticide

TABLE OF CONTENTS

BACKGROUND

Commission Regulation (EC) No 1490/2002 laying down the detailed rules for the implementation of the third stages of the work program referred to in Article 8(2) of Council Directive 91/414/EEC and amending Regulation (EC) No 451/2000 as amended by Commission Regulation (EC) No 1095/2007, regulates for the European Food Safety Authority (EFSA) the procedure of evaluation of the draft assessment reports provided by the designated rapporteur Member State. Cyromazine is one of the 84 substances of the third stage, part B, covered by the Regulation (EC) No 1490/2002 designating Greece as rapporteur Member State.

In accordance with the provisions of Article 10(1) of the Regulation (EC) No 1490/2002, Greece submitted the report of its initial evaluation of the dossier on cyromazine, hereafter referred to as the draft assessment report, received by EFSA on 31 August 2007. Following an administrative evaluation, the draft assessment report was distributed for consultation in accordance with Article 11(2) of the Regulation (EC) No 1095/2007 on 6 November 2007 to the Member States and the main applicant Syngenta Ltd as identified by the rapporteur Member State.

The comments received on the draft assessment report were evaluated and addressed by the rapporteur Member State. Based on this evaluation, EFSA identified and agreed with Member States on lacking information to be addressed by the notifier as well as issues for further detailed discussion at expert level.

Taking into account the requested information received from the notifier, a scientific discussion took place in expert meetings in May-June 2008. The reports of these meetings have been made available to the Member States electronically.

A final discussion of the outcome of the consultation of experts took place during a written procedure with the Member States in July – August 2008 leading to the conclusions as laid down in this report.

During the peer review of the draft assessment report and the consultation of technical experts no critical issues were identified for consultation of the Scientific Panel on Plant Protection Products and their Residues (PPR).

In accordance with Article 11c(1) of the amended Regulation (EC) No 1490/2002, this conclusion summarises the results of the peer review on the active substance and the representative formulation evaluated as finalised at the end of the examination period provided for by the same Article. A list of the relevant end points for the active substance as well as the formulation is provided in appendix 1.

The documentation developed during the peer review was compiled as a **peer review report** comprising of the documents summarising and addressing the comments received on the initial evaluation provided in the rapporteur Member State's draft assessment report:

- the comments received,
- the resulting reporting table (rev. 1-1 of 4 March 2008)

as well as the documents summarising the follow-up of the issues identified as finalised at the end of the commenting period:

- the reports of the scientific expert consultation,
- the evaluation table (rev. 2-1 of 11 September 2008).

Given the importance of the draft assessment report including its addendum (compiled version of July 2008 containing all individually submitted addenda) and the peer review report with respect to the examination of the active substance, both documents are considered respectively as background documents A and B to this conclusion.

THE ACTIVE SUBSTANCE AND THE FORMULATED PRODUCT

Cyromazine is the ISO common name for *N*-cyclopropyl-1,3,5-triazine-2,4,6-triamine (IUPAC).

Cyromazine belongs to the class of triazine insecticides. Cyromazine is a dipteran moulting disruptor, it inhibits larval growth and development and it prevents the adult emergence from the pupae. Cyromazine is a contact insect growth regulator and also has a good translaminar and root-systemic effect. Cyromazine is used in agriculture to control Dipteran and some Coleopteran insects.

The representative formulated product for the evaluation was "Trigard® 75 WP", a wettable powder (WP) containing 750 g/kg cyromazine, registered under different trade names in Europe.

The representative uses evaluated comprise field and greenhouse foliar spraying, at the first sign of infestation in the crop, to control Dipteran leaf miners in lettuce in all EU countries, and field and greenhouse foliar spraying in tomatoes in Southern Europe and all Europe respectively, at a maximum of 3 treatments in lettuce and maximum of 4 treatments in tomatoes, at maximum application rate per treatment of 300 g a.s./ha, with minimum 7 days interval between applications.

SPECIFIC CONCLUSIONS OF THE EVALUATION

1. Identity, physical/chemical/technical properties and methods of analysis

The minimum purity of cyromazine is 950 g/kg. There is no FAO specification available.

The revised technical specification for the active substance was only partially accepted by the experts at the PRAPeR Meeting 46 (May 2008) and a data gap was proposed for the applicant to provide a new specification for some of the impurities or detailed quality control data for the support of the existing specification. As a consequence the specification for the technical material, as a whole, currently should be regarded as provisional. (September 2008)
The assessment of the data package revealed no issues that need to be included as critical areas of concern with respect to the identity, physical, chemical and technical properties of cyromazine or the respective formulation.
The main data regarding the identity of cyromazine and its physical and chemical properties are given in appendix 1.

Adequate analytical methods are available for the determination of cyromazine in the technical material and in the representative formulation (HPLC-UV) as well as for the determination of the respective impurities in the technical material (HPLC-UV).
Sufficient test methods and data relating to physical, chemical and technical properties are available to ensure that quality control measurements of the plant protection product are possible.

Adequate methods are available to monitor cyromazine residues in food/feed of plant and animal origin. Residues of cyromazine, and also melamine[3], in food of plant origin can be monitored by HPLC-UV with LOQ of 0.05 mg/kg (tomatoes, oranges, beans, potatoes, sunflower seed, oranges). Residues of cyromazine and melamine in food/feed of animal origin can be monitored by HPLC-MS/MS with LOQ of 0.01 mg/kg (bovine milk, chicken egg, ovine kidney and liver and bovine muscle)
The residue definitions for monitoring purposes for soil and water are provisional.
HPLC-MS/MS method is available to monitor residues of cyromazine and its metabolite melamine in soil with LOQ of 0.0025 mg/kg for cyromazine and with LOQ of 0.005 mg/kg for melamine.
Residues of cyromazine in river, ground and drinking water can be determined by HPLC-MS/MS with LOQ of 0.1 µg/L, while melamine residues can be monitored by HPLC-MS/MS with LOQs of 0.1µg/L for drinking water, 9.0 µg/L for river water and 0.5 µg/L for ground water respectively.
Cyromazine residues in air can be monitored by HPLC-MS/MS, with LOQ of 0.0028 mg/m³.
Analytical methods for the determination of residues in body fluids and tissues are not required as cyromazine is not classified as toxic or highly toxic.

[3] melamine: 1,3,5-triazine-2,4,6-triamine

2. Mammalian toxicology

Cyromazine was discussed at the PRAPeR Expert's Meeting on mammalian toxicology (PRAPeR 49) in June 2008.

Although no technical specification had been agreed by the meeting on physical and chemical properties (PRAPeR 46), the meeting on toxicology considered that the batches used in the toxicological studies covered the technical specification as proposed by the applicant in the addendum 1 to volume 4 dated May 2008.

2.1. Absorption, Distribution, Excretion and Metabolism (Toxicokinetics)

Cyromazine was rapidly and completely absorbed and excreted after oral administration, based on urinary recovery of approximately 94-97 % within 24 hours. Distribution of cyromazine into tissues was uniform, although the residues were rapidly eliminated from the tissues; sustained high blood concentrations were observed and highest residues were found in urinary bladder, kidney and liver.

Metabolism of cyromazine was poor as more than 80 % of the administered dose was recovered as parent compound in urine. The predominant metabolic pathway involved biotransformation to hydroxy-cyromazine[4] and 1-methyl-cyromazine[5] and then to melamine[6]. The same pattern of metabolism was observed in faeces. Melamine was found mainly in urine at levels up to 10.7 % of the administered dose; 1-methyl-cyromazine levels in urine corresponded to approximately 2 % of the administered dose.

A single oral dose administered to monkeys presented similar results as found in the rat, except that 94 % of the dose was recovered as parent in urine and the remainder was attributed mainly to melamine.

2.2. Acute toxicity

Cyromazine presented low acute toxicity, either by the oral, dermal or inhalation route; slight skin irritation and no eye irritation were observed. According to a Magnusson and Kligman test, no sensitisation potential was obtained with cyromazine as a 50 % dilution.

2.3. Short term toxicity

The oral short term effects of cyromazine were investigated in a 90-day feeding study in rat and in dog and a 1-year study in dog also by dietary administration. Other routes were tested as a 21-day dermal toxicity study in rabbit and a 28-day inhalation toxicity study in rat.

The most sensitive findings upon short term administration of cyromazine were decreased body weight gain and liver weight in rats and dogs, additionally, haematological, biochemical and

[4] Hydroxy-cyromazine: 4-amino-6-(cyclopropylamino)-1,3,5-triazin-2-ol
[5] 1-methyl cyromazine, *N*-methyl cyromazine: 2,4-diamino-6-(cyclopropylamino)-1-methyl-1,3,5-triazin-1-ium
[6] Melamine: 1,3,5-triazine-2,4,6-triamine

urinalysis changes were seen in dogs together with effects on the heart, kidney and haematopoietic system.

The most relevant short term NOAEL was the dose level of **5.74 mg/kg bw/day** from the 1-year dog study; the 90-day rat NOAEL was the dose level of 23 mg/kg bw/day.

When administered dermally, cyromazine did not produce any adverse effect on rabbits; the dermal NOAEL was the highest dose tested of 2000 mg/kg bw/day.

A revised assessment of the inhalation toxicity study was provided in the addendum1 to Annex B.6. The target organs identified in this study were the liver and pituitary, clinical signs appeared from the lowest dose level on and subsided during the recovery period, therefore the LOAEC was the low dose level of 58 mg/m^3.

2.4. GENOTOXICITY

A comprehensive data package of genotoxicity studies was submitted, including gene mutation and chromosome aberration assays in bacterial, yeast and mammalian cells, and unscheduled DNA synthesis *in vitro*; the *in vivo* genotoxic potential of cyromazine was tested in somatic cells with a nucleus anomaly test in bone marrow cells of Chinese hamsters, a mouse micronucleus test and a mammalian spot test in mouse melanoblasts. A further *in vivo* dominant lethal test in male germinal cells was provided.

All studies gave negative results with cyromazine. The rapporteur Member State noted that the majority of the studies were old and conducted with major deviations from the current guidelines, being some of them not accepted. However the weight of evidence of no genotoxic potential for cyromazine was confirmed by the valid *in vivo* micronucleus test.

2.5. LONG TERM TOXICITY

Long term toxicity of cyromazine was examined in a two-year study in rat and in mouse.

Main effect observed upon long term administration of cyromazine was decreased body weight in the rat; the highest dose level of 156 mg/kg bw/day produced an apparent increase in pituitary and mammary gland tumours, but without a clear dose-response. Historical control data for these tumours were provided by the rapporteur Member State in the evaluation table and in the addendum 2 to Annex B.6 (July 2008). The experts agreed that the results were well within the historical control data and therefore were not treatment related. The NOAEL was the dose level of 14.7 mg/kg bw/day based on decreased body weight, and non-neoplastic lesions in the lungs and kidneys at the highest dose level.

In mice, lower body weight gain was observed at the two highest dose levels. At the mid-dose level of 126 mg/kg bw/day a non-statistically significant decrease of 12 % was observed at the terminal sacrifice, while the decrease was statistically significant at the interim sacrifice. The experts agreed to set the NOAEL at the lowest dose level of **6.5 mg/kg bw/day** based on the body weight effects, which were considered as driving effects for the risk assessment of cyromazine.

EFSA note:

The historical control data for hepatocellular adenomas and carcinomas observed in mice two-year studies were distributed during the meeting and confirmed the conclusion of the rapporteur Member State that cyromazine did not induce an increased incidence of hepatocellular neoplasms in male mice.

No carcinogenic potential was attributed to cyromazine administration in either rats or mice.

2.6. REPRODUCTIVE TOXICITY

Reproductive toxicity of cyromazine was tested in a two-generation reproduction toxicity study in rat, a developmental toxicity study in rat and five developmental toxicity studies in rabbit.

Reproduction toxicity

Main parental effect in the two-generation study consisted of decreased body weight in the two highest doses tested. On this basis, the parental NOAEL was the low dose level of 2 mg/kg bw/day; it was noted that a high interval between doses resulted in a LOAEL of 65 mg/kg bw/day for the parents. No effect on reproductive performance or fertility was observed, therefore, the reproductive NOAEL was the highest dose level of 215 mg/kg bw/day. Reduced pup body weight was observed during lactation at the highest dose level, the offspring's NOAEL was the mid-dose of 65 mg/kg bw/day. Since there was no indication of cyromazine transfer in breast milk (low cyromazine residues in goat milk), classification of cyromazine with the risk phrase R64 "may cause harm to breastfed babies" was not proposed.

Developmental toxicity

Maternal toxicity in the rat developmental toxicity study consisted of decreased body weight, and clinical signs as increased motor activity, red nasal discharge, clear oral discharge and inactivity at the top dose of 600 mg/kg bw/day. Red nasal discharge was also observed at 300 mg/kg bw/day, however it was considered as a marginal effect and the maternal NOAEL was set at 300 mg/kg bw/day. Decreased foetal weight and delayed ossification were observed at the top dose and the same NOAEL of 300 mg/kg bw/day was set for the developmental effects of cyromazine.

The five rabbit studies were examined in detail by the experts, the overall maternal NOAEL was consistently the 10 mg/kg bw/day dose level, based on mortality, decreased body weight, increased post implantation losses and clinical signs of toxicity (decreased defecation and urination). Skeletal malformations and variations were observed in the foetuses at maternal toxic doses: malformed and fused sternebrae, vertebral anomalies with or without associated rib anomalies, 13^{th} rudimentary ribs.

In the draft assessment report, the developmental NOAELs varied from 25, 30, 60, or no developmental toxicity in the different studies, however, looking back at the historical control data, findings at 30 mg/kg bw/day were found to be within the historical control range, while the latter was exceeded at 60 mg/kg bw/day. Therefore the 25 mg/kg bw/day NOAEL could be increased to 30 mg/kg bw/day, which is in line with other studies and the overall developmental NOAEL was set at

30 mg/kg bw/day. As malformations were observed only at the top dose – with marked maternal toxicity, no classification was proposed relating to the developmental toxicity.

2.7. NEUROTOXICITY

No study was provided. Cyromazine does not belong to a chemical group known to induce neurotoxicity, no concern was raised from the other general studies, and therefore no study was required.

2.8. FURTHER STUDIES

Metabolites

Melamine and 1-methyl cyromazine were cyromazine metabolites found in plants and in mammals (see point 2.1).

1-methyl cyromazine

A Derek analysis for toxicological alerts of 1-methyl cyromazine was conducted by the applicant and it revealed the same toxicological alerts as for cyromazine. No toxicity studies were submitted and none were required; studies performed with cyromazine were considered to cover the toxicity of 1-methyl cyromazine.

Melamine

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[7] 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[8].

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.

2.9. MEDICAL DATA

There was no complaint or any sign of adverse effect that could be related to cyromazine exposure reported from the personnel from the manufacturing plants in Europe and the United States.

[7] U.S. Food and Drug Administration (FDA) risk assessment, 2007; European Food Safety Authority (EFSA) statement (2007); and OECD evaluation (OECD SIDS melamine, 1998).

[8] Sanco/221/2000 – rev.10 (25 February 2003): Guidance document on the assessment of the relevance of metabolites in groundwater of substances regulated under Council Directive 91/414/EEC.

2.10. ACCEPTABLE DAILY INTAKE (ADI), ACCEPTABLE OPERATOR EXPOSURE LEVEL (AOEL) AND ACUTE REFERENCE DOSE (ARFD)

ADI

In the draft assessment report the rapporteur Member State proposed an ADI of 0.06 mg/kg bw/day based on the 1-year dog study presenting a NOAEL of 5.74 mg/kg bw/day, a safety factor of 100 and rounding-up 0.0574 to 0.06 mg/kg bw/day. This approach was agreed by the experts at the meeting, which is supported by the oncogenicity study in mice with a NOAEL of 6.5 mg/kg bw/day. The **ADI for cyromazine was established at 0.06 mg/kg bw/day**

AOEL

The approach followed for the ADI was considered applicable to the AOEL setting, the rapporteur Member State proposed an AOEL of 0.06 mg/kg bw/day based on the 1-year dog study and a safety factor of 100, since oral absorption was complete, no correction factor related to the oral absorption was necessary. The approach was agreed by the meeting; it was noted that a lower parental NOAEL was obtained in the two-generation toxicity study, but considering dose spacing, the overall NOAEL for short term rat studies was considered to be the dose level of 23 mg/kg bw/day. **The AOEL was set at 0.06 mg/kg bw/day.**

ARfD

Initially in the draft assessment report, the rapporteur Member State proposed not to set an ARfD based on the toxicological profile of cyromazine and considering that maternal body weight loss is generally not an acute effect.

In the first rabbit developmental study, maternal body weight loss occurred in early gestation (days 6 to 12), then considering that decreased body weight was the critical effect for cyromazine, the experts agreed that an ARfD should be established. **The ARfD was set at 0.1 mg/kg bw**, based on the NOAEL of 10 mg/kg bw/day from the developmental toxicity study in the rabbit and a safety factor of 100. This conclusion is in line with the WHO evaluation of cyromazine from 2006.

2.11. DERMAL ABSORPTION

Dermal absorption of cyromazine was assessed in a rat *in vivo* study and in an *in vitro* comparative dermal penetration study through human and rat skin membranes, both studies were conducted with the representative formulation Trigard® 75 WP.

In the *in vivo* study, the experts agreed to include the amount found in the tape strips as absorbable, due to the unusually aggressive method of tape stripping. In the *in vitro* study, the flux rates were used to compare the dermal absorption between species. The resulting dermal absorption values were 0.7% for the concentrate formulation and 2% for the in-use spray dilution.

2.12. EXPOSURE TO OPERATORS, WORKERS AND BYSTANDERS

The representative plant protection product Trigard® 75 WP is a wettable powder formulation containing 750 g cyromazine/kg. It is an insecticide intended for use on lettuce and tomatoes for both outdoor and greenhouse applications. Trigard® 75 WP is applied by conventional spray equipment at a maximum dose rate of 300 g cyromazine/ha, corresponding to 0.4 kg product/ha in a spray volume of 1000 L/ha. A maximum of four applications are foreseen per year.
Estimation of operator, worker and bystander exposure were recalculated in the addendum 2 to Annex B.6 of July 2008 based on the parameters agreed at the PRAPeR expert meeting.

Operator exposure

The operator exposure estimates were calculated using both the German and the UK POEM models for outdoor applications. For indoor applications the Dutch greenhouse model was used.
According to the German model assumptions, the body weight of operators is 70 kg and 20 ha are treated per day. According to the UK POEM, body weight of operators is 60 kg and 50 ha are treated per day, packaging of 1 kg bag was considered.

Estimated operator exposure presented as % of AOEL (0.06 mg/kg bw/day)

Model / scenario		No PPE	With PPE[(a)] during M/L & application
UK POEM :	tractor-mounted/trailed boom sprayer - hydraulic nozzles	322	277
UK POEM :	hand held application technique outdoor low level target	27	14.4
German model :	tractor-mounted/trailed boom sprayer – hydraulic nozzles	23	15
Dutch model :	greenhouses	36	3.6

[(a)] PPE: gloves for outdoor applications, according to the Dutch greenhouse model: gloves and coverall

According to the UK POEM, estimated exposure of operators applying Trigard® 75 WP by tractor is above the AOEL even considering the use of PPE (gloves during mixing/loading and application); according to the German model, the estimated exposure of operators is below the AOEL even if no PPE are worn. Hand-held applications are estimated to be below the AOEL according to the UK POEM even without the use of PPE; the same conclusion is expected from greenhouse applications according to the Dutch model.

Worker exposure

Estimation of worker exposure was performed according to the model developed by the German BBA (Hoernicke E. *et al.* 1998). A foliar dislodgeable residues (FDR) value of 2 was used to take into account the consecutive applications, transfer factor of 30,000 [cm^2/person/h], default value of 60 kg for worker body weight, dermal absorption of 2 % and penetration through clothing (PPE) of 5 % were used in the calculations.

Estimated worker exposure presented as % of AOEL (0.06 mg/kg bw/day)

Worker exposure	No PPE	With PPE [(a)]
Re-entry activities	80	4

[(a)] PPE: protective gloves, long sleeved shirt and long trousers

Therefore, after the spray solution has dried, the estimated exposure to cyromazine during re-entry operations does not exceed the AOEL, even if no PPE are worn.

Bystander exposure

Estimated bystander exposure was performed by comparison with operator exposure, considering that a bystander is exposed accidentally for 5 min. while an operator is exposed for 6 h. Besides, a 60 kg body weight has been used. The worst case exposure corresponded to **0.25% of the AOEL**, when using the UK POEM via handheld equipment; via tractor, bystander exposure represented 0.10-0.12% of the AOEL.

3. Residues

The active substance was discussed at the PRAPeR experts' meeting for residues (PRAPeR 50, subgroup 1, round 10) in June 2008.

3.1. NATURE AND MAGNITUDE OF RESIDUES IN PLANT

3.1.1. PRIMARY CROPS

Metabolism of cyromazine has been investigated using ^{14}C-cyromazine labelled on the triazine ring in celery, lettuce and tomato representing two groups of plants: leafy and fruit crop groups. The submitted studies suggest a common metabolism pathway in the two plant groups covered with a simple metabolic transformation in leaves and fruits to yield the dealkylated product melamine. No metabolites were identified resulting from further breakdown of the triazine ring over the post-treatment time periods investigated (0 – 14 days).

These metabolism studies have been performed using agricultural practices representative of the intended uses, with a total of 2-6 foliar treatments, application rates up to 1680 g a.s./ha and a sampling at maturity at day 0, 7 or 14. All these studies confirm that parent cyromazine and melamine represent the major part of the TRR, accounting for 37.1-74.0% and 10.9-45.4% respectively. For celery and lettuce, it was pointed out that the part of the uncharacterised/unidentified radioactivity accounting for 7 to 17% of the TRR may represent an absolute residue level up to 0.5 mg/kg, taking into account the high total radioactivity levels observed at certain PHI (5.8 mg/kg in celery stems, 4.05

mg/kg in lettuce leaves). However the RMS confirmed that at GAP application rates, any unidentified fraction contained the individual compound above 0.01 mg/kg.

In addition to the foliar application, a study was performed where ^{14}C-cyromazine was applied as a soil treatment at a rate of 1000 g a.s./ha in order to maximise the potential uptake of the active substance and its potential soil metabolites into rotational crops. Celery plants were grown for 6 or 12 weeks after soil application. A similar metabolic pathway was observed at harvest 12 weeks after planting. Parent cyromazine and melamine metabolite appeared to be the main compounds of concern, accounting for 42.9 and 29.6% of the TRR respectively.

The meeting discussed the additional US studies conducted on celery, lettuce, tomato, carrot and mushrooms with unlabelled material and with exaggerated agricultural practices (up to 19 applications and 5320 g a.s./ha). Only parent cyromazine and melamine were analysed for in the samples collected in these trials. The meeting concluded that the analytical methods used were sufficiently validated and that these studies give additional information on the respective residue levels of cyromazine and melamine observed in crops after foliar treatments. Globally cyromazine residues declined in leafy crops within 14 days after application, this decline being slower for tomato and carrot. Melamine residues were generally of comparable magnitude to those of cyromazine, a slight increase being sometimes observed between 0 and 7 days after application in certain crops due to the degradation from the parent cyromazine.

Taking into account the conclusion of the PRAPeR expert meeting 49 on mammalian toxicology considering that melamine has the same toxicological profile as the parent, the meeting proposed the following residue definitions for fruit and leafy crops:

- For monitoring: cyromazine
- For risk assessment cyromazine, melamine expressed as cyromazine.

Though it was mentioned that consumer exposure to melamine may be possible through other sources (plastics, colorant, flame retardants, veterinary drugs…), **the decision to include melamine metabolite in the residue definition for risk assessment was taken with regard to the high melamine residue levels observed in the treated crops.**

As requested during the meeting of experts, the RMS derived provisional conversion factors (monitoring to risk assessment) for lettuce and tomato, based on the US unlabelled residue studies. It must be noted that these US trials were performed with an exaggerated number of applications (up to 19) leading to an overestimation of the ratio melamine/cyromazine and, to a worst-case conversion factor. **The meeting agreed that these conversion factors are applicable for leafy and fruit crop groups only** and if further uses are envisaged on other plant groups, additional studies/trials in which melamine and cyromazine are individually quantified has to be provided. The conversion factors

submitted by the RMS have to be considered as provisional since these proposals have not been peer reviewed.

Supervised glasshouse and field residue trials have been submitted to propose MRL for the representative uses on tomato and lettuce. In these trials, samples were analysed for cyromazine residues only in accordance with the residue definition for monitoring, but no information was provided on the melamine residue levels. On tomatoes, the residues levels observed in the trials performed under glasshouse conditions were comparable to those from the field trials and the proposed MRL was calculated using the merged data from both growing systems. On lettuce, an initial MRL of 10 mg/kg was proposed by the RMS based on the residue data from the indoor trials, the residue levels measured in the glasshouse trials being significantly higher than those observed in the field trials. However, after the meeting and taking into account the conversion factor for risk assessment and the ARfD value set by the meeting on mammalian toxicology, this proposal was shown to be unsafe for the consumer. Although it was not discussed during the meeting and it has not been peer reviewed, the EFSA in agreement with the RMS, was of the opinion that an MRL of 3 mg/kg would be appropriate for the outdoor uses of cyromazine on lettuce, this proposal being based on the field residue trials performed in Northern and Southern EU (6 in each zone) where the residue levels were in the range of 0.17 to 1.9 mg/kg.

The meeting discussed on the validity of the storage stability studies with regard to the high RSD observed in the recoveries for the field incurred residues in lettuce and celery. These studies were considered not reliable even if cyromazine and melamine residues seem stable over the storage period. However, an additional study provided by the applicant confirms that residue of cyromazine and melamine have to be considered stable under freeze conditions for periods up to 24 months.

Cyromazine is not altered in buffer solution and in standard conditions simulating processing (pasteurisation, baking, boiling, sterilisation…). The meeting discussed if an additional study should now be requested for melamine, metabolite included in the residue definition for risk assessment. Finally the experts agreed that there is no need for a new processing study including melamine since the initial study proves that the parent compound remains stable (recoveries for cyromazine 99.0 to 101.1% depending on conditions) and melamine metabolite denotes a similar chemical structure. Nevertheless, transfer factors in tomato processed fractions have to be reconsidered taking into account the residue definition for RA which include melamine metabolite.

3.1.2. SUCCEEDING AND ROTATIONAL CROPS

Two rotational crop studies performed in the US have been submitted by the applicant. Following multiple applications (12-15) of unlabelled cyromazine on a primary crop (celery or tomato), sweet corn, radish and lettuce were planted as rotational crops at different plant-back intervals of 1 to 8 weeks after the harvest of the primary crop. Due to the high application rates used in these trials, the

meeting was of the opinion that the US data are acceptable and concluded that no significant residues of cyromazine or melamine are expected in practice in rotational crops.

3.2. NATURE AND MAGNITUDE OF RESIDUES IN LIVESTOCK

Though animal metabolism studies are not required to support the representative uses on lettuce and tomato, the expert meeting was asked to consider if the available data and information provided by the applicant allow suggesting a residue definition for animal commodities. The metabolism of cyromazine has been investigated in lactating goat and laying hen.

Two metabolism studies were submitted on goat, but it was proposed to disregard the 1984 study due to the low level of identification in certain fractions and to rely on the 1991 study. Following oral dosing of lactating goats with ^{14}C-triazine labelled cyromazine for four consecutive days at a dose of 91 mg/kg feed, the majority of the administrated radioactivity was excreted in faeces and urine. With regard to the high dose level used in this study, total radioactive residues were close to 1 mg/kg in muscle, pm milk, 3-4 mg/kg in liver and kidney and 0.1-0.2 mg/kg in fat. The unchanged parent compound was the major compound identified in all tissue/organ (muscle, fat, milk, kidney) accounting for 50-87% of the TRR, except in liver where the major compound was the metabolite 1-methyl cyromazine (42% TRR). The melamine metabolite was observed at low level (<6%) except in kidneys (23% TRR). An additional metabolite, hydroxy-cyromazine, was identified in liver but at a very low level (0.17 mg/kg).

The metabolic fate of cyromazine was also investigated in laying hens dosed for seven consecutive days at a rate of 5.0 mg/kg feed with ^{14}C-cyromazine. The majority (99.1%) of the radioactivity was found in the excreta. Egg white and yolk accounted for 0.4% and 0.2% of the applied dose, the recoveries in the other tissues or organs being equal or less than 0.1%. The metabolic profile was incompletely characterised, unchanged cyromazine being the major part of the excreted radioactivity (75%), and melamine being found in eggs.

Based on these studies, the following **provisional** residue definition for animal products was discussed during the meeting:

- Provisional residue definition for monitoring: cyromazine
- Provisional residue definition for risk assessment: cyromazine + 1-methyl cyromazine + melamine, expressed as cyromazine.

However the experts were finally not confident in proposing a residue definition in commodities of animal origin, since animal dietary burden remains unknown. In particular, the validity of the animal metabolism study performed with the parent compound only remains uncertain as the melamine metabolite may be the major residue of concern in the possible crops that might be used for animal feeding. **The final conclusion of these discussions was that there is no need to propose a residue definition and to set MRL for animal products at this stage and based on the intended uses on**

vegetable crops. This point has to be reconsidered if further uses are envisaged on crops fed to animals.

3.3. CONSUMER RISK ASSESSMENT

The consumer risk assessment initially done in the DAR was not accepted by the meeting of experts since it did not include the melamine metabolite. After the meeting the RMS proposed new evaluations taking into account the residue definition for risk assessment including melamine but **these should be considered as provisional and not peer reviewed.**

The chronic assessment, using the EFSA model, the proposed MRLs for lettuce and tomato and the **provisional conversion factors for fruit and leafy crops** (1.83 and 2.33 for lettuce and tomato respectively) showed that the highest Theoretical Maximum Daily Intake (TMDI) is 15% of the ADI (0.06 mg/kg bw/d) for the WHO cluster B diet.

The acute risk assessment was also performed using the EFSA model. For tomato, the International Estimated Short Term Intake (IESTI) calculated with the highest residue level observed in the supervised residue trials (HR: 0.6 mg/kg) and the conversion factor proposed for fruit crops was 81% of the ARfD (0.1 mg/kg bw/d). For lettuce, using the highest value observed in the indoor trials (HR: 6.6 mg/kg) and the conversion factor proposed for leafy crops, the IESTI was 325% of the ARfD. Thus the uses of cyromazine on glasshouse lettuce can not be considered safe for the consumer. On the opposite, taking into account the GAP proposed for outdoor lettuce and the highest residue level of 1.9 mg/kg observed in the field residue trials, the calculated IESTI is 94% of the ARfD. It must be highlighted that these consumer risk assessments have to be considered as provisional since the conversion factor values and the MRL proposed for lettuce and based on outdoor uses of cyromazine were not discussed during the meeting and not peer review.

In addition, the meeting of experts pointed out that the consumer exposure was only considered through the representative uses of cyromazine as a plant protection product on lettuce and tomato. However this active substance is also used as a veterinary drug and a potential additional exposure through the consumption of some specific animal products is expected. Moreover, consumers may additionally be exposed to the melamine metabolite through other sources since this molecule is present in many domestic materials (plastics, colorants, flame retardants….)

3.4. PROPOSED MRLS

Considering the supervised residue trials performed in glasshouses on tomato, the following MRL has been proposed:

- Tomato: 1 mg/kg Glasshouse and field uses (outdoor uses defined for Southern EU only)
- Lettuce: The initial MRL of 10 mg/kg proposed for lettuce and based on the indoor GAP leads to an exceeding of the ARfD. In agreement with the RMS, EFSA was of the opinion that

an MRL of 3 mg/kg based on the outdoor GAP could be proposed provisionally (but this value was not discussed and not peer reviewed).

4. Environmental fate and behaviour

Cyromazine was discussed at the PRAPeR experts' meeting for environmental fate and behaviour in May 2008 (PRAPeR 47) on the basis of the DAR and addendum 1 of May 2008.

The environmental fate of cyromazine was investigated with the test substance radiolabelled only in the triazine ring. The experts from member states confirmed that the cyclopropane ring is a 3-member ring which has the tendency to break, as it is thermodynamically unstable. Therefore further studies to investigate the fate of the cyclopropane ring of cyromazine are considered not necessary.

4.1. FATE AND BEHAVIOUR IN SOIL

4.1.1. ROUTE OF DEGRADATION IN SOIL

The route of degradation of [U-^{14}C]triazine labelled cyromazine was investigated in the laboratory in three studies in the dark (at 20ºC and 75% FC or at 25ºC and 40% maximum water holding capacity (MWHC)). The seven soils covered a range of pH (5.6-8.1), organic carbon content (0.32-5.5%) and clay content (3.5-23.6%). The proposed metabolic pathway of cyromazine in soil involves the initial cleavage of the cyclopropyl ring moiety to form **melamine**[9] (CGA 235129) up to 74.5% AR after 120 days. The formation of bound residues amounted up to 53.9% AR after 126 days. Mineralisation to carbon dioxide accounted for 3.7-7.3% AR after 120-121 days in experiments on 3 of these soils (in the remaining 2 soils the study design did not collect carbon dioxide). Metabolite **NOA 435343**[10] (carboxylic acid of cyromazine) was formed at 10.7% AR after 60 days of incubation in one of the soil metabolism study (Esser, 1995). The applicant excluded this study from the EU evaluation of cyromazine for two reasons: the exaggerated application rate (6772 g cyromazine/ha) and the low organic carbon content of the soil (0.32%). Syngenta therefore concluded that the study was not appropriate to trigger further studies for this degradation product. However, the opinion of the experts from the Member States was that there were no significant evidences to consider the study unacceptable and therefore it was concluded that NOA 435343 should be considered a major metabolite. As a result, a data gap was identified for a complete (soil, groundwater and surface water) environmental exposure assessment for soil metabolite NOA 435343.

Under anaerobic laboratory conditions cyromazine degraded to the major metabolite melamine (max 35.8% AR after 60 days. A number of minor (< 2.2% AR) components were also detected.

Laboratory soil photolysis studies indicated that degradation by photolysis would not be expected to be a process that significantly influences the dissipation of cyromazine in the environment.

[9] CGA 235129 (melamine) = 1,3,5-triazine-2,4,6-triamine
[10] NOA 435343 = *N*-(4,6-diamino-1,3,5-triazin-2-yl)alanine

4.1.2. PERSISTENCE OF THE ACTIVE SUBSTANCE AND THEIR METABOLITES, DEGRADATION OR REACTION PRODUCTS

The rate of degradation of cyromazine in soil was estimated from the results of the studies described in 4.1.1. Two additional studies, one with [U-^{14}C]triazine labelled cyromazine and one with non radiolabelled cyromazine and non radiolabelled melamine, were performed on a total of 4 soils. During the peer review concerns raised over the study design of one of these soil metabolism study (Plücken, 1986/1988), and it was agreed that the degradation rate values for cyromazine and melamine derived from the four soils can not be considered reliable. The available reliable single first order (SFO) DT_{50} values for cyromazine were in the range of 2.9-56 days, indicating that this active substance is low to moderate persistent in soil. In the original DAR, the degradation rate derived from the study by Esser, 1995 was not included in the evaluation of a representative labDT_{50} for cyromazine because the applicant considered the study unrepresentative of normal labelled agricultural use. Following the re-evaluation of the study by the peer review (see section 4.1.1), the RMS was asked to check the validity of degradation rate (= 24 days) reported in the DAR. However, as the details on the kinetic assessment have not been provided, a data gap has been set by the EFSA after the experts meeting. As a consequence, a valid geometric mean labDT_{50} for cyromazine could not be identified.

The metabolite melamine exhibits moderate to high persistence in soil, with SFO DT_{50} ranging from 46 days to 211 days (6 soils tested). It should be noted that the full results of the kinetics modelling and information on the formation fractions calculated in the Aaldeirnk (2003) study were not available to the peer review. For that reason, the DT_{50} values derived from Gartenacher soil, Horst soil and Westmaas soil should be considered with caution.

It was also discussed if and how it might be possible to use the two dissipation studies (bare soil) conducted in Switzerland and in South France to support the applied for intended uses. As a single application was considered in these dissipation trials, it was concluded that they can not be considered as representative in this case.

The accumulation behaviour of cyromazine and melamine in soil was investigated in one trial in Greece, one trial in Spain and 4 trials in USA (California, Nebraska and Florida). During the peer review it was questioned if the US field trials could be considered as representative for the European agro-climatic conditions. Although further information were provided in addendum 1, the experts agreed that the evaluation provided was not sufficient to justify the use of the results to conduct the risk assessment at EU level. Results of the European field soil accumulation studies indicated that no accumulation of cyromazine residues occurred in plots for consecutive years. The melamine residues were observed in all three segments of the 0-30 cm soil layer analysed in the Swiss trials, and several findings slightly above 0.01 mg/kg were detected in 10-30 cm soil depth in Spain. The residues in the 10-20 cm soil layer ranged from < 0.005 to 0.05 mg/kg for melamine in the Greek field conditions with only few samples of the 30-70 cm soil layer containing detectable residues at low levels.

It should be noted that the information on deep freeze stability of residues for both cyromazine and melamine in soil is not available.

Because of the medium-high persistence of melamine in soil, a complete evaluation of the dissipation rates together with PEC (predicted environmental concentration) soil accumulation calculations for this metabolite were required. Some calculations were provided by the applicant but the experts from member states did not accept the input parameters used. As the information is still not available, a data gap for PECsoil and plateau concentrations estimations is identified by EFSA after the experts' meeting.

PEC in soil for cyromazine were re-calculated by RMS and discussed at the meeting of experts. It was agreed that the longest laboratory DT_{50} (normalised to 20ºC and pF2) and that a 50% crop interception factor for tomato use and 25% for lettuce use should be used as input parameters. Although an incorrect crop interception factor was used for lettuce use and the risk for earthworms and soil macro-organisms was not based on the worst case PECmax, it is the opinion of EFSA that in this particular case no new calculations are required for cyromazine to finalize the EU risk assessment as the margin of safety for TER values is quite large.

4.1.3. MOBILITY IN SOIL OF THE ACTIVE SUBSTANCE AND THEIR METABOLITES, DEGRADATION OR REACTION PRODUCTS

Three studies with a total of eleven batch soil adsorption/desorption experiments are available for cyromazine. Ten of these experiments were considered valid. Cyromazine exhibits low to very high mobility in soil with $K_f$oc values in the range 40.2-1784 mL/g (median = 192 mL/g to be used in the modelling) and 1/n values ranging from 0.714 to 0.92 (median = 0.8 to be used in the modelling). Reliable adsorption characteristics of melamine are available for 4 soils. This metabolite is medium to high mobile in soil with $K_f$oc = 54-423 mL/g (1/n = 0.7414-0.83). The meeting of the experts agreed that a clear pH dependency of the adsorption of the parent can not be concluded, whilst a good correlation between the pH and the adsorption coefficient can be observed for melamine. Therefore, it was concluded that this pH dependency should be considered in the FOCUS modelling for melamine.

The leaching characteristics of [U-^{14}]triazine labelled cyromazine were studied in a soil column experiment in four different soils. 32.7% of applied radioactivity was found in the eluate of one of the sand column, while the eluates of the other columns contained < 0.5% of radioactivity.

Results from an aged column leaching study, where 200 mm of water was applied over approximately 16 days, indicated that aged residues containing cyromazine and its metabolite are of low mobility in soil. In another aged residue column leaching study, using an extreme rainfall scenario with precipitation equivalent to 571.5 mm over 45 days, 51% (sandy soil) and <0.15% (silty loam soil) of radioactivity were found in the eluates. The radioactivity in the eluate of the sandy soil consisted of parent (18%) and of melamine (29%). It was concluded form the data that both cyromazine and the metabolite melamine show some potential for leaching in sandy soil under the conditions of this test.

A small scale prospective ground water monitoring study conducted in USA was also available. The relevant information to support a sound evaluation of the study was required during the peer review. Details on the site characteristics, the study design and method of analyses were provided by RMS in

addendum 2 (July 2008). Although the new information has not been peer reviewed, the EFSA agrees with RMS that the experimental design of this study can be considered appropriate to measure leaching into groundwater. Results indicated that the parent compound did not leach from the surface soil into the shallow groundwater and that sporadic detections in the range of 0.10 to 0.21 µg/L of the metabolite melamine were detected. It should also be noted that the application rates and the application time schedule did not reflect the GAP of the representative uses proposed for annex I inclusion at the EU level.

4.2. FATE AND BEHAVIOUR IN WATER

4.2.1. SURFACE WATER AND SEDIMENT

Cyromazine is stable to hydrolysis in buffer solutions (pH 5, 7, 9) at 30, 50 and 70ºC. Cyromazine is stable to photolysis in aqueous solution.

Cyromazine is considered not readily biodegradable.

In the reliable water/sediment study, two different aquatic model systems ($pH_{sediment}$ = 7.2-7.7, pH_{water} = not reported) were investigated at 20ºC. After 103 days of incubation between 23% and 24% of the applied radioactivity were still found in the water phase and between 50 and 52% of the applied radioactivity were extractable from the sediment phase. Cyromazine was adsorbed to the sediment up to 54.2% AR after 56 days. Non-extractable radioactivity assigned for about 13% AR and CO_2 for about 5% to 8% AR. Melamine never exceeded 2.5% of the applied radioactivity in all compartments. No other metabolites exceeded 0.5% of the applied radioactivity.

As the information on the type of kinetics and the compartment model used to calculate DT_{50} values in the water/sediment study were not sufficiently reported in the DAR, further details were included in addendum 1. The experts of the meeting agreed with the kinetic analysis and confirmed that cyromazine dissipates from the water with SFO DT_{50} 14.5-16 days. The half –life for the degradation of cyromazine in the sediment phase was determined to be 142-143 days.

In the original DAR, predicted environmental concentrations (PEC) in surface water were calculated for cyromazine and melamine following the FOCUS SW scheme up to Step 3 and Step 4. Additional Step 4 modelling using a 10 m buffer strip (using standard spray drift reduction values and a 90% reduction in runoff and erosion) was carried out for cyromazine. The meeting of experts discussed the suitability of the modelling exercise and concluded that the application dates window, the $DT_{50\ sed}$ value for cyromazine, the $DT_{50\ water}$ and $DT_{50\ sed}$ for melamine were not appropriate. In addition, in order to evaluate the impact of the two different mitigation measures (spray drift and run-off buffer zones) on PECsw/sed calculations, separate calculations should be provided. At the time of writing the conclusion, the requested information is not available and therefore the surface water exposure assessment for cyromazine and melamine has not been finalised. The EFSA also noted that in the ecotoxicology part of the DAR, the risk from melamine to the aquatic environment was addressed based on FOCUS Step 2 surface water PECs, which were neither reported nor evaluated in the fate section. Considering that the DT_{50} values reported in the DAR differed from the agreed values in

PRAPeR 47, it is the EFSA opinion that these PECs at Step 2 for melamine can not be used in the risk assessment.

4.2.2. POTENTIAL FOR GROUND WATER CONTAMINATION OF THE ACTIVE SUBSTANCE THEIR METABOLITES, DEGRADATION OR REACTION PRODUCTS

The FOCUS ground water modelling study provided by the applicant was not satisfactorily reported in the DAR, particularly in terms of application timings, the degradation scheme assumed and the formation fractions assumed for formation of melamine. Degradation of cyromazine and melamine were simulated using a median labDT_{50} value of 17.6 days and 167 days, respectively (normalised for soil moisture and temperature). In addition, in the original calculations the pH dependence of soil adsorption for melamine was not taken into account and an assessment for metabolite NOA 435343 (see section 4.1.1) was not performed. Finally, it was envisaged to perform a second modelling with FOCUS PEARL model, considering also a multi-compartment approach where melamine is linked to the parent compound according to the soil degradation scheme. All the relevant input parameters for FOCUS GW modelling were discussed at the meeting in order to address the potential for ground water contamination of cyromazine and melamine. At the time of writing the conclusion, the requested information is not available and therefore the ground water exposure assessment for cyromazine and melamine has not been finalised.

4.3. FATE AND BEHAVIOUR IN AIR

Cyromazine has a low vapour pressure of 4.48 x 10^{-7} Pa and a Henry's law constant of 5.8 x 10^{-9} Pa m^3 mol^{-1}. Volatilization studies from soil and plant leaves showed to be insignificant. Assuming an atmospheric hydroxyl radical concentration of 1.5x10^6 radicals cm^{-3}, the photo-oxidative degradation in the atmosphere was calculated to be 102 hours (=4.25 days). Based on this result, the experts from member states agreed that a potential for long range aerial transport has been identified for cyromazine.

5. Ecotoxicology

The intended evaluated uses proposed for the cyromazine is insecticide growth regulator (IGR) with 3 applications in lettuce (max. application rate of 300 g a.s.ha. and with 4 applications in Tomatoes (max. application rate of 300 g a.s./ha).

Cyromazine was discussed by the expert's meeting PRAPeR 48 (subgroup 1) in May 2008.

5.1. RISK TO TERRESTRIAL VERTEBRATES

The risk to birds and mammals was assessed for standard species in accordance with the Guidance Document on Risk Assessment for Birds and Mammals under Council Directive 91/414/EEC (SANCO/4145/2000) using the leafy crops scenario for lettuce and tomatoes.

The first tier risk assessment resulted in acute and short-term TER values above the Annex VI trigger values, indicating that acute and short term risk to herbivorous and insectivorous birds was low. However, the TERlt for insectivorous and herbivorous birds was below the Annex VI trigger value indicating a need for further refinement.

Yellow wagtail was considered as an indicator species for insectivorous birds according to the Ecotoxicology handbook. The diet was refined (PD 17% small and 83% large). The experts agreed on the choice of focal species and the PD refinements. The resulting TERlt value was 16 which is above the Annex VI trigger value, indicating that the long term risk was low for insectivorous birds.

The refinement for the long term risk to medium herbivorous birds was based on residue decline in plants (DT_{50} of 3.3 days). From this DT_{50} a MAF of 1.3 had been used for the refined risk assessment for herbivorous birds. It was discussed at the PRAPeR 48 expert meeting if this degradation rate can be used to represent the whole of Europe, or if these data are only relevant for southern European conditions. Residue experts agreed that Switzerland can be considered as representative for the Northern Member States (Addendum 2 to Annex B). Therefore, the long term risk to medium herbivorous birds had been refined for the Northern and Southern Member States.

In conclusion, the acute, short-term and long-term risk for birds was considered to be low.

The relevant end-point for the long-term exposure for mammals was discussed in the expert meeting. In the development study a NOEL of 30 mg/kg is proposed based on developmental effects. The meeting agreed to use a NOEL of 30 mg/kg in the risk assessment (Addendum 2 to Annex B).

First tier risk assessment for mammals showed acute and long-term TER values above the Annex VI trigger values, indicating a low acute and chronic risk for mammals (Addendum 2 to Annex B).

The risk to birds and mammals from intake of contaminated drinking water from surface water or puddles was considered to be low (Addendum 2 to Annex B)

In conclusion, based on the available information the risk of cyromazine to birds and mammals was considered to be low for the representative uses evaluated.

5.2. RISK TO AQUATIC ORGANISMS

Based on the information available, cyromazine is proposed to be classified as toxic to aquatic organisms.

Daphnia magna and *Chironomus riparius* are the most sensitive organisms tested. The first tier risk assessment indicated that acute and long-term risk to fish was expected to be low. Also the acute risk to aquatic invertebrates and algae was considered to be low. However, long-term TER values

estimated for aquatic invertebrates and for sediment-dwelling insects, using the PECsw from FOCUS Step 2, were below the Annex VI trigger values. A higher tier risk assessment based on PECsw from FOCUS Step 3, gave TERlt values for *Daphnia magna* above the trigger values. However, long-term TERs estimated for *C. riparius* were below the trigger value for some of the scenarios for both intended uses.

Mitigation measures were needed in order to meet the Annex VI trigger value. When the PECsw from the FOCUS Step 4 with a 10 m non spray buffer zone were applied, then the TERlt values were above the Annex VI trigger values for all scenarios.

The first tier risk assessment indicated that risk for the relevant soil metabolite melamine was considered to be low for aquatic organism.

In conclusion, risk mitigation measures were needed to reduce the risk for cyromazine to the aquatic organisms. In case of Annex I inclusion, risk mitigation options should be decided at Member State level for cyromazine.

The fate experts agreed on a data gap for the submission of the new PECsw calculations.

The submission of a new risk assessment for the aquatic organisms based on the agreed PECsw values is required.

5.3. RISK TO BEES

The LD_{50} from acute oral and contact toxicity tests with the preparation were 186 µg a.s./bee and > 200 µg a.s./bee, respectively. Hazard Quotients (HQ) were estimated to be 1.6 for the oral exposure and < 1.5 for contact exposure.

As cyromazine is an insect growth regulator bee brood was assessed as recommended in the SANCO Guideline 10329/2002.

Three higher tier studies had been submitted by the applicant, Schmitzer (1997) reported that cyromazine had an effect on the development of eggs and young larvae into adult worker bees following dosing in sucrose (provided directly to the hive). The impact of TRIGARD ® 75 WP on bee brood development was further investigated in a semi-field tunnel study and a full-scale field study.

In the tunnel study (Barth M. 1991) bee colonies were placed in a polytunnel containing flowering *Phacelia tanacetifolia* which was then treated with TRIGARD ® 75 WP at 12 or 300 g a.s./ha. From this study it is clear that TRIGARD ® 75 WP applied to flowering *Phacelia tanacetifolia* had no effect on bee mortality, flight, or foraging activity and only had a small effect on colony weight. Therefore a field study (Schur A. 2003) was conducted in which bees are maintained in conditions that more closely resemble those experienced in practice. Melons were used in this study.

The levels of mortality, flight intensity, foraging activity, colony strength, pollen collection and brood development were all comparable to the untreated control, indicating that the application of TRIGARD ® 75 WP at 300 g a.s./ha had no impact on the development of the bee colony.

The experts from the Members States discussed the validity of some of these studies. No clear conclusion could be drawn from the brood development test alone. The experts agreed that the field

study is a higher tier study but concerns were raised since 3 applications are recommended in the GAP while cyromazine was applied only once. Due to high temperature there was only low foraging activity of bees in the field. Extrapolation from this study to northern conditions was considered difficult. Concerns were raised about use and that application can be expected during the whole growth period, which could mean application during flowering. As the field study was done with melons (which have bigger flowers), there were also concerns about the possibility to extrapolate to others crops like tomato.

With the available information, the risk of cyromazine to bees and the brood bee can be considered to be low for lettuce but not for tomatoes.

A new data gap was proposed for the submission of a position paper on the melon field study including extrapolations from this study to tomato crops in other MS

5.4. RISK TO OTHER ARTHROPOD SPECIES

TRIGARD® 75 WP is an insect growth regulator and according to ESCORT 2, the HQ approach and the associated trigger values cannot be used to evaluate the toxicity data for IGR, since such products were not included in the validation exercise. In addition, for such products, sub-lethal endpoints should also be included in the evaluation.

Tier 1 laboratory studies were conducted with *Aphidius rhopalosiphi* mummies, *Coccinella septempunctata* larvae, *Poecillus cupreus* adults and *Aleochara bilineata* adults. Tier II extended laboratory tests with *A. rhopalosiphi, Typhlodromus pyri, C. septempunctata* and *Chrysoperla carnea Encarsia formosa, Phytoseiudus permisilis* and *Folsomia candida* were performed. In addition, three aged residue tests were performed with *T. pyri, E. formosa* and *P. permisilis.*

A tier I risk assessment indicates a low risk to a range of different beneficial organisms when exposure is in different life stages (e.g. *A. rhopalosiphi, C. carnea, C. septempunctata* and *E. formosa* adults and older pupae). The higher tier risk assessment indicates that a potential risk to some foliar dwelling non-target arthropods, particularly the predatory mites *T. pyri* and *P. persimilis,* was identified based on tier II extended laboratory studies. A high risk was identified for the in-field areas and the RMS proposes to use the aged residue studies to refine the in-field risk assessment. Experts at the PRAPeR 48 meeting had some concerns regarding the study on *T. pyri,* which was used to refine in field risk. The experts were of the opinion that there were concerns on recolonisation due to off-field effects and the time needed for recovery. Especially for non-flying insects recovery time might be long.

If cyromazine is included in Annex I, mitigation measures should be considered at Member State level to make sure that recolonisation is possible.

5.5. RISK TO EARTHWORMS

The acute toxicity of cyromazine, Trigard 75 WP and the relevant soil metabolite melamine to earthworms was low. The NOEC for reproductive effects was determined to be 28 day NOEC = 9.6

mg a.s./kg soil for the preparation Trigard 75 WP, and NOEC 56days = 2.5 mg a.s./kg soil for the metabolite melamine.

TER values were estimated for the worst case scenario tomatoes, using the PEC plateau of 0.706 mg/ kg for cyromazine and 0.441 and 0.015 mg /kg for the melamine. The acute TER values for the cyromazine and the metabolite were > 1416 and > 2267, respectively, and the chronic TER values were 472 and 5.6, respectively. All the TER values were above the Annex VI trigger values for acute and chronic effects indicating a low risk to earthworms.

The RMS need to update TER calculations to soil organisms based on the soil PECplateau agreed in the fate meeting, this might lead to a risk to other soil macro-organisms. The applicant did not submit the new PECs estimation and as a consequence the risk assessment for earthworms could not be completed.

EFSA notes that the TER values for the parent have a high safety margin and with the new PECs the TER values are likely to be still higher than the Annex VI trigger values. However the chronic TER for the metabolite based on the new PECsoil values will likely be lower than the Annex VI trigger value.

In conclusion the risk for cyromazine to earthworms is low. However, a data gap has to be set for the submission of a risk assessment for the metabolite melamine to earthworms based on the agreed PEC soil values.

5.6. RISK TO OTHER SOIL NON-TARGET MACRO-ORGANISMS

The soil DT_{50} of the relevant metabolite melamine was 155 days. Therefore the metabolite melamine was tested for effects in a litter bag study. The plant protection product Trigard 75 WP was tested for effects on *Folsomia candida.* The chronic TERs were calculated using the soil $PEC_{soil\ plateau}$ values, and were above the Annex VI trigger values.

The litter bag study of 365 days with the metabolite melamine showed that there were no significant effects on straw decomposition.

The RMS has to update the TER calculations for soil organisms based on the soil PECplateau agreed in the fate meeting. This might lead to a risk for other soil macro-organisms. However, the applicant did not submit the new PECs estimation. EFSA notes that, even taking this into consideration, the TER values for the parent have a high safety margin and even with these new PECs, the TER values probably will be still higher than the Annex VI trigger values.

In conclusion, based on the available data, the risk to other soil non-target macro-organisms was considered to be low for cyromazine and the metabolite melamine.

5.7. RISK TO SOIL NON-TARGET MICRO-ORGANISMS

No effects > 25 % were observed for cyromazine and for CGA 235129 on soil respiration/nitrification at concentrations up to 100 mg /kg soil, and 6.6 mg/kg soil, respectively.

5.8. RISK TO OTHER NON-TARGET-ORGANISMS (FLORA AND FAUNA)

A seedling emergence and vegetative vigour test was done with the preparation Trigard 75 WP. The seedling emergence of 4 species was unaffected up to 300 g a.s./ha and the vegetative vigour of the species was also unaffected at concentration up to 300 g a.s./ha..

The estimated chronic TER values were above the Annex VI trigger values for the proposed uses. In conclusion and based on the available data, the risk for cyromazine was considered to be low

5.9. RISK TO BIOLOGICAL METHODS OF SEWAGE TREATMENT

No inhibitory effects of cyromazine on respiration rates of activated sludge were observed up to doses of 100 mg a.s. /L.
Based on the available data, the risk of cyromazine to biological methods of sewage treatment was considered to be low.

6. Residue definitions

Soil

Definition for risk assessment:	cyromazine, melamine[11], NOA 435343[12]
Definition for monitoring:	cyromazine, melamine, NOA 435343 (provisional, as a data gap for soil exposure assessment has been identified for melamine and NOA 435343)

Water

Ground water

Definition for exposure assessment:	cyromazine, melamine, NOA 435343
Definition for monitoring:	cyromazine, NOA 435343 (provisional, as a data gap for PECgw calculations has been identified for NOA 435343)

Surface water

Water

Definition for risk assessment:	cyromazine; originating from soil via runoff and drainage: melamine, NOA 435343

[11] CGA 235129 (melamine) = 1,3,5-triazine-2,4,6-triamine
[12] NOA 435343 = *N*-(4,6-diamino-1,3,5-triazin-2-yl)alanine

Definition for monitoring: cyromazine, melamine and NOA 435343 (provisional, as a data gap for PECsw calculations has been identified)

Sediment

Definition for risk assessment: cyromazine

Definition for monitoring: cyromazine

Air

Definition for risk assessment: cyromazine

Definitions for monitoring: cyromazine

Food of plant origin (For leafy and fruit crops only)

Definition for risk assessment: cyromazine, melamine expressed as cyromazine

Definition for monitoring: cyromazine

Food of animal origin

Definition for risk assessment: to be reconsidered if further uses are envisaged on crops fed to animals

Definition for monitoring: to be reconsidered if further uses are envisaged on crops fed to animals

Overview of the risk assessment of compounds listed in residue definitions for the environmental compartments

Soil

Compound (name and/or code)	**Persistence**	**Ecotoxicology**
cyromazine	Low to moderate persistence Single first order DT_{50} 2.9-56 days (20°C and pF2 or 470%MWHC soil moisture)	The risk to earthworms and soil micro-organisms was assessed as low
melamine	Moderate to high persistence Single first order DT_{50} 46-211 days (20°C and pF2 or 470%MWHC soil moisture)	Data gap to the Notifier for the submission of a new risk assessment for the melamine to earthworms.
NOA 435343	No data available, data required	No data available

Ground water

Compound (name and/or code)	Mobility in soil	> 0.1 µg / L 1m depth for the representative uses (at least one FOCUS scenario or relevant lysimeter)	Pesticidal activity	Toxicological relevance	Ecotoxicological activity
Cyromazine	Very high to low mobility K_{foc} 40-1784 mL/g	No data available, data required	Yes	Yes	Yes
Melamine	High to medium mobility K_{foc} 54-423 mL/g	No data available, data required	No data was available.	Not relevant; for consumer risk assessment, the reference values of the parent are applicable	Not ecotoxicological relevant.
NOA 435343	No data available, data required	No data available, data required	No data was available.	No data available, not identified in rat metabolism; no conclusion possible on its relevance	No data was available.

Surface water and sediment

Compound (name and/or code)	Ecotoxicology
Cyromazine	The risk was considered to high low for aquatic organism.
Melamine	The risk was considered to be low for aquatic organism.
NOA 435343	No data was available

Air

Compound (name and/or code)	Toxicology
Cyromazine	Rat LC_{50} inhalation > 3.6 mg/L air (maximum attainable concentration)/4 hours (nose only) – no classification is proposed

LIST OF STUDIES TO BE GENERATED, STILL ONGOING OR AVAILABLE BUT NOT PEER REVIEWED

- A revised technical specification (relevant for all representative uses evaluated, data gap identified by PRAPeR 46 meeting (May 2008), date of submission unknown; refer to chapter 1)
- A complete (soil, groundwater and surface water) environmental exposure assessment for soil metabolite NOA 435343 (relevant for all representative uses evaluated; submission date proposed by the notifier: unknown; data gap confirmed by the experts of the PRAPeR 47 meeting, May 2008; refer to point 4.1.1)
- An assessment of the kinetics of the degradation data derived from the study by Esser (1995) and the consequent estimation of the geometric mean labDT_{50} for cyromazine when the DT_{50} value obtained from the Esser study is included in the laboratory degradation rates dataset (relevant for all representative uses evaluated; submission date proposed by the notifier: unknown; data gap identified by EFSA after the PRAPeR 47 meeting, May 2008; refer to point 4.1.2)
- Pending on the results of the potential groundwater contamination of the metabolite NOA 435343, a toxicological assessment on the relevance of this metabolite in groundwater (relevant for all representative uses evaluated; no submission date proposed by the notifier; refer to point 4.1.1)
- Soil exposure assessment (PECsoil) and plateau concentrations estimations for melamine (relevant for all representative uses evaluated; submission date proposed by the notifier: unknown; data gap confirmed by EFSA after the PRAPeR 47 meeting, May 2008; refer to point 4.1.2)
- Aquatic exposure assessment (PEC) for surface water and sediment for cyromazine and melamine up to the FOCUS Step required to finalise the risk to aquatic organisms (relevant for all representative uses evaluated; submission date proposed by the notifier: unknown; data gap confirmed by EFSA after the PRAPeR 47 meeting, May 2008; refer to point 4.2.1)
- An assessment of the potential for groundwater contamination of cyromazine and melamine performed with 2 FOCUS GW models with the agreed (PRAPeR 47) endpoints and taking into account the pH dependency on soil adsorption of melamine (relevant for all representative uses evaluated; submission date proposed by the notifier: unknown; data gap confirmed by EFSA after the PRAPeR 47 meeting, May 2008; refer to point 4.2.2)
- A new risk assessment for the aquatic organisms based on the agreed PECsw values should be required (relevant for all representative uses evaluated; submission date proposed by the notifier: Unknown; refer to point 5.2).
- A position paper on the melon field study to bees , including extrapolation from this study to tomato crops in other MS (relevant for tomato uses; submission date proposed by the notifier: unknown ; refer to point 5.3

- A new risk assessment for melamine to earthworms based on the agreed PEC soil values. (relevant for all representative uses evaluated; submission date proposed by the notifier: unknown; refer to point 5.5

CONCLUSIONS AND RECOMMENDATIONS

Overall conclusions

The conclusion was reached on the basis of the evaluation of the representative uses as insecticide as proposed by the applicant which comprise field and greenhouse foliar spraying for the control Dipteran leaf miners in lettuce in all EU countries, and field and greenhouse foliar spraying in tomatoes in Southern Europe and all Europe respectively, at a maximum of 3 treatments in lettuce and maximum of 4 treatments in tomatoes, at maximum application rate per treatment of 300 g a.s./ha, with minimum 7 days interval between applications.

The representative formulated product for the evaluation was "Trigard® 75 WP", a wettable powder (WP) containing 750 g/kg cyromazine, registered under different trade names in Europe.

Sufficient analytical methods as well as methods and data relating to physical, chemical and technical properties are available to ensure that quality control measurements of the plant protection products is possible.
Adequate methods are available to monitor all compounds given in the respective residue definitions in food/feed of plant and animal origin, and environmental matrices.

In the mammalian metabolism studies, cyromazine was rapidly and completely absorbed and excreted after oral administration, metabolism was poor, no potential for bioaccumulation was observed.
Acute toxicity of cyromazine was low either by the oral, dermal or inhalation route; it did neither present eye or skin irritation nor skin sensitization properties according to a Magnusson and Kligman test. Main effect observed upon short term and long term exposure was decreased body weight. No evidence of genotoxic or carcinogenic potential was found. Cyromazine did not produce any effect on the reproductive performances or fertility up to the highest dose tested; increased incidence of skeletal malformations and variations were associated with clear maternal toxicity. Two plant/environmental metabolites were assessed for their relevance, 1-methyl-cyromazine and melamine; both metabolites were identified in the rat metabolism studies as well. Based on an open literature review, melamine was considered not relevant for groundwater according to the guidance document on the assessment of the relevance of metabolites in groundwater[13]. The toxicity of the metabolites is covered by the reference values of the parent compound.

[13] Sanco/221/2000 – rev.10 (25 February 2003): Guidance document on the assessment of the relevance of metabolites in groundwater of substances regulated under Council Directive 91/414/EEC.

The Acceptable Daily Intake (ADI) for cyromazine was 0.06 mg/kg bw/day, the Acceptable Operator Exposure Level (AOEL) was 0.06 mg/kg bw/day and the Acute Reference Dose (ARfD) was 0.1 mg/kg bw. The level of operator exposure calculated for outdoor and glasshouses' uses was estimated to be below the AOEL even when no protective personal equipment (PPE) are worn. Worker exposure was calculated to be also below the AOEL without the use of PPE; estimated bystander exposure was negligible.

Metabolism in plant has been investigated using ^{14}C-cyromazine labelled on the triazine ring in celery, lettuce and tomato representing two groups of plants: leafy and fruit crop groups. These studies suggest a simple metabolic transformation leading to the dealkylated product melamine. Taking into account the conclusion of the meeting on mammalian toxicology considering that melamine has the same toxicological profile as the parent, the residue for risk assessment was defined as "cyromazine parent compound and melamine expressed as cyromazine" and the residue definition for monitoring was limited to "cyromazine parent only", these residue definitions being set for fruit and leafy crops only. Though it was mentioned that consumer exposure to melamine may be possible through other sources (plastics, colorant, flame retardants, veterinary drugs…), the decision to include melamine metabolite in the residue definition was taken with regard to the high melamine residue levels observed in the treated crops. After the meeting the RMS proposed conversion factors for leafy and fruit crops in order to take into account the melamine metabolite that was included in the residue definition for risk assessment. These conversion factors have to be considered as provisional since they have not been peer reviewed. Based on the US rotational crop studies performed with unlabelled cyromazine and exaggerated application rates, it was concluded that no significant residues of cyromazine or melamine are expected in practice in rotational crops. A residue definition for animal products was discussed, but the experts were not confident in proposing a residue definition for animal products, since animal dietary burden remains unknown and the validity of the animal metabolism study performed with the parent compound only remains uncertain. The final conclusion was that at this stage, there is no need to propose a residue definition and to set MRLs for animal products based on the intended uses on lettuce and tomato. A residue data set was available to propose MRLs for tomato and lettuce. However, after the meeting and considering the conversion factor for risk assessment and the ARfD value set by the meeting on mammalian toxicology, the initial MRL of 10 mg/kg proposed for lettuce and based on the indoor GAP was shown to be unsafe for the consumer (IESTI 325% of the ARfD). Although it was not discussed during the meeting and it has not been peer reviewed, the EFSA in agreement with the RMS, was of the opinion that an MRL of 3 mg/kg based on the outdoor residue trials would be appropriate for cyromazine on lettuce. Taking into account this proposal, no acute concern is observed, the IESTI being 94% of the ARfD. It must be pointed out that the consumer exposure was only considered through the representative uses of cyromazine as plant protection product on lettuce and tomato. However this active substance is also used as a veterinary drug and consumers may additionally be exposed to the melamine metabolite through other sources since this molecule is present in many domestic materials (plastics,

colorants, flame retardants….). A potential additional exposure to cyromazine and melamine is then expected.

Several data gaps need to be addressed before the EU level environmental exposure assessment can be finalised (for details refer to the list of studies to be generated, where 4 data gaps in the area of environmental fate and behaviour are identified). In particular, a full assessment of the major soil metabolite, NOA 435343, needs to be performed. All the relevant input parameters to perform an appropriate exposure assessment (PECs in soil, surface water and groundwater) of cyromazine and its metabolite melamine were discussed at the PRAPeR 47 meeting in order to finalise the risk assessment. However, at the time of writing the conclusions, the required information was not available and therefore it was not possible to carry out an appropriate environmental exposure assessment.

Acute, short term risk and long-term risk to birds and mammals was assessed as low. The risk to birds and mammals from intake of contaminated drinking water from surface water or puddles was considered to be low.

Based on the information available cyromazine is proposed to be classified as toxic to aquatic organisms. At FOCUS step 4, including a non-spray buffer zone of 10m, the TER values for all scenarios were above the Annex VI trigger value. The first tier risk assessment indicated that risk for the relevant soil metabolite melamine was assessed to be low for aquatic organisms. Risk mitigation measures were needed to reduce the risk of cyromazine to the aquatic organisms. In case of Annex I inclusion of cyromazine, Member States should ask for further refinement of the aquatic risk assessment pertinent to national conditions. A data gap has been identified for the submission of a new risk assessment for the aquatic organisms based on the agreed PECsw values.
Risk assessment based on higher tier studies provide sufficient evidence to conclude that the risk to bees is low for lettuce but not for the use in tomatoes. The applicant should submit a position paper on the melon field study including extrapolation from this study to tomato crops in other MS.
Uncertainty remains with regard to the recovery time. Especially for non-flying insects recovery time might be long. If cyromazine is included in Annex I, mitigation measures should be considered at Member State level to make sure that recolonisation is possible.
The risk of cyromazine to earthworms and soil non-target macro-organisms was assessed to be low. However, the RMS needs to update TER calculations to soil macro-organisms based on the soil $PEC_{plateau}$ as agreed in the fate meeting. This might lead to a risk for other soil macro-organisms. The applicant did not submit the new PECs estimation and as a consequence the risk assessment for earthworms could not be completed. A data gap has to be set for the submission of a risk assessment for the metabolite melamine to earthworms based on the agreed PEC soil values.
EFSA notes that the TER values for the parent have a high safety margin and with the new PECs the TER values are likely to be still higher than the Annex VI trigger values. However the chronic TER

for the metabolite based on the new PECsoil values will likely be lower than the Annex VI trigger value. In conclusion the risk for cyromazine to soil macro-organisms is low. However, a data gap has to be set to the Notifier to submit a risk assessment for the metabolite to earthworms based on the agreed PEC soil values.
Additionally the risk to soil micro-organisms and non target plants was expected to be low. Also the risk of cyromazine to biological methods of sewage treatment is low.

Particular conditions proposed to be taken into account to manage the risk(s) identified

- A non-spray buffer zone of 10 m for aquatic organisms (refer to point 5.2) is necessary.
- Mitigation measures should be considered at Member State level to make sure recolonisation of non-target arthropods is possible. (refer to point 5.4)

Critical areas of concern

- No peer reviewed consumer risk assessments are available. The acute risk assessment carried out by the RMS indicate that the **indoor** use of cyromazine on lettuce following the critical GAP as defined in the DAR (3 applications, 300 g a.s./ha, PHI 14 days) leads to an exceedence of the ARfD.
- A complete (soil, groundwater and surface water) environmental exposure assessment for soil metabolite NOA 435343 is necessary
- No reliable assessment of PEC soil, $PEC_{SW/SED}$ and PEC_{GW} for cyromazine and its metabolite melamine. Environmental risk assessment has not been finalised.
- A new risk assessment for aquatic organisms based on the agreed PECsw values should be required.
- A refinement of the long term risk for melamine to earthworms.

APPENDIX 1 – LIST OF ENDPOINTS FOR THE ACTIVE SUBSTANCE AND THE REPRESENTATIVE FORMULATION

(Abbreviations used in this list are explained in appendix 2)

Identity, Physical and Chemical Properties, Details of Uses, Further Information

Active substance (ISO Common Name) ‡	Cyromazine
Function (*e.g.* fungicide)	Insecticide

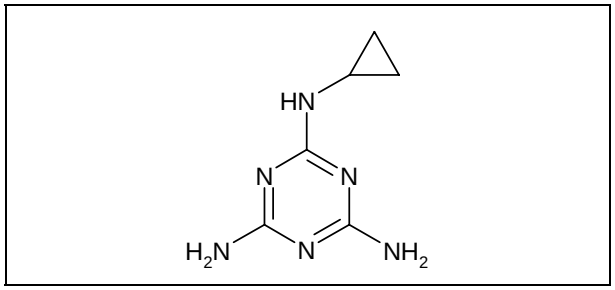
Rapporteur Member State	Greece
Co-rapporteur Member State	-

Identity (Annex IIA, point 1)

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
CIPAC No ‡	420
CAS No ‡	66215-27-8
EC No (EINECS or ELINCS) ‡	266-257-8
FAO Specification (including year of publication) ‡	-
Minimum purity of the active substance as manufactured ‡	950 g/kg
Identity of relevant impurities (of toxicological, ecotoxicological and/or environmental concern) in the active substance as manufactured	none
Molecular formula ‡	$C_6H_{10}N_6$
Molecular mass ‡	166.2 g/mol

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Structural formula ‡



‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Physical and chemical properties (Annex IIA, point 2)

Melting point (state purity) ‡	223.2°C (99.2%)
Boiling point (state purity) ‡	No boiling point due to thermal decomposition (99.2%) (decomposition starts immediately after melting)
Temperature of decomposition (state purity)	decomposition starts immediately after melting
Appearance (state purity) ‡	Pure a.s. (99.2%): white powder with no odour
	Technical a.s. (97.5%): off-white powder with no odour
Vapour pressure (state temperature, state purity) ‡	$4.48 \cdot 10^{-7}$ Pa at 25 °C (99.3% pure)
Henry's law constant ‡	Calculated values at 25°C: $5.8 \cdot 10^{-9}$ Pa · m³ / mol
Solubility in water (state temperature, state purity and pH) ‡	Pure a.s. (99.2%): at 25 °C and 8.0g/l at pH 5.3 13g/l at pH 7.1 13g/l at pH 9.0
Solubility in organic solvents ‡ (state temperature, state purity)	At 25°C (97.5% technical): acetone: 1.4g / l hexane: < 1mg / l ethyl acetate: 660mg / l octanol: 1.5g / l toluene: 11mg / l dichloromethane: 210mg / l methanol: 17g / l
Surface tension ‡ (state concentration and temperature, state purity)	At 20°C (97.5% technical): σ = 59.0 mN / m at 1g/l aqueous solution
Partition co-efficient ‡ (state temperature, pH and purity)	At 25 °C: pH 5: log P_{ow}: - 0.36 ± (0.012) pH 7: log P_{ow}: - 0.069 ± (0.009) pH 9: log P_{ow}: - 0.039 ± (0.009) Chemical purity of Cyromazine: = 99.6%
Dissociation constant (state purity) ‡	pK_a = 5.22 at 20°C (99.6% technical)

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

UV/VIS absorption (max.) incl. ε ‡ (state purity, pH)	**UV/vis –spectrum** **UV Absorption Characteristics (99.2% purity):** The molar extinction were determined to be: Solution Wavelength [nm] neutral 208.0 acidic 215.5 241.3 basic 230.0 solution Molar extinction coefficient [l / mol · cm] neutral 39070 acidic 29540 17340 basic 11540 No absorption maximum between 340 nm and 750 nm was observed.
Flammability ‡ (state purity)	Not highly flammable (97.5%, technical) Cyromazine has no self-ignition temperature (97.5% technical)
Explosive properties ‡ (state purity)	Cyromazine is not expected to have explosive properties (97.5% technical)
Oxidising properties ‡ (state purity)	Cyromazine is not expected to have oxidizing properties (97.5% technical)

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Summary of representative uses evaluated (*cyromazine*)

Crop and/ or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks: (m)
					Type (d-f)	Conc. of a.s. (i)	method kind (f-h)	growth stage & season (j)	number min max (k)	interval between applications (min)	g a.s./hL min max	water L/ha min max	g as/ha min max		
Lettuce, cos lettuce, head lettuce	N & S Europe	TRIGARD® 75 WP	F	Leaf miners	WP	750 g/kg	Foliar	At the first sign of infestation in the crop	3	7 days	30	1000	300	7	[1] [3]
Lettuce, cos lettuce, head lettuce	N & S Europe	TRIGARD® 75 WP	G	Leaf miners	WP	750 g/kg	Foliar	At the first sign of infestation in the crop	3	7 days	30	1000	300	14	[1] [2]
Tomato	N & S Europe	TRIGARD® 75 WP	G	Leaf miners	WP	750 g/kg	Foliar	At the first sign of infestation in the crop	4	7 days	30	1000	300	3	[1]
Tomato	S Europe	TRIGARD® 75 WP	F	Leaf miners	WP	750 g/kg	Foliar	At the first sign of infestation in the crop	4	7 days	30	1000	300	3	[1]

[1] A complete environmental exposure assessment has not been finalised (data gaps identified in section B.8)
[2] After the meeting and considering the ARfD value and the provisional conversion factor for risk assessment, the indoor use on lettuce was considered as not safe for the consumer since an exceeding of the ARfD was observed.
[3] A provisional MRL based on the outdoor GAP has been proposed after he PRAPeR meeting on residues by EFSA in agreement with the RMS but not discussed and not peer reviewed

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Remarks:

(a) For crops, the EU and Codex classifications (both) should be used; where relevant, the use situation should be described (*e.g.* fumigation of a structure)
(b) Outdoor or field use (F), glasshouse application (G) or indoor application (I)
(c) e.g. biting and suckling insects, soil born insects, foliar fungi, weeds
(d) e.g. wettable powder (WP), emulsifiable concentrate (EC), granule (GR)
(e) GCPF Codes - GIFAP Technical Monograph No 2, 1989
(f) All abbreviations used must be explained
(g) Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench
(h) Kind, e.g. overall, broadcast, aerial spraying, row, individual plant, between the plants - type of equipment used must be indicated
(i) g/kg or g/l
(j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application
(k) The minimum and maximum number of application possible under practical conditions of use must be provided
(l) PHI - minimum pre-harvest interval
(m) Remarks may include: Extent of use/economic importance/restrictions

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Methods of Analysis

Analytical methods for the active substance (Annex IIA, point 4.1)

Technical as (analytical technique)	-**HPLC/UV**:
Impurities in technical as (analytical technique)	- **HPLC-UV** for impurities in cyromazine technical.
Plant protection product (analytical technique)	**HPLC-UV**

Analytical methods for residues (Annex IIA, point 4.2)

Analytical methods for residues (Annex IIA, point 4.2)

Residue definitions for monitoring purposes

Food of plant origin		Cyromazine
Food of animal origin		Cyromazine
Soil		Cyromazine, melamine (provisional)
Water	surface	Cyromazine (provisional)
	drinking/ground	Cyromazine (provisional)
Air		Cyromazine
Blood		-

Food/feed of plant origin (analytical technique and LOQ for methods for monitoring purposes)	**Doc No.: REM 174.02** Substrates: tomatoes, oranges, beans, potatoes, sunflower seed, oranges Analysis: HPLC/UV Determined analyte: cyromazine, melamine LOQ: 0.05mg/kg **Doc No.: 02-S104:** ILV study Substrates: tomatoes, sunflower seed Analysis: HPLC/UV Determined analyte: cyromazine, melamine

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	LOQ: 0.05mg/kg **Doc No.: REM 4/86** Substrates: cucumber, zucchini, green peppers, tomatoes, sugar beet, onions, lettuce, celery, grapes, melons, chilli peppers, peas, mushrooms, grass, barley (grain and straw). Analysis: HPLC/UV Determined analyte: cyromazine, melamine LOQ: 0.1mg/kg
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)	**Doc No.: RJ3369B** Substrates: bovine milk, chicken egg, ovine kidney and liver and bovine muscle Analysis: LC/MS/MS Determined analyte: cyromazine, melamine LOQ: 0.01mg/kg **Doc No.: CEMR-2172**: ILV study Substrates: bovine muscle, bovine milk, chicken egg Analysis: LC/MS/MS Determined analyte: cyromazine, melamine LOQ: 0.01mg/kg
Soil (principle of method and LOQ)	**Doc No: TMJ4943B**: Substrates: soil Analysis: LC/MS/MS Determined analyte: cyromazine, melamine LOQ for cyromazine: 0.0025mg/kg LOQ for melamine: 0.005mg/kg
Water (principle of method and LOQ)	**Doc No: RJ3401B:** Substrates: river, ground and drinking water Analysis: LC/MS/MS Determined analyte: cyromazine, melamine LOQ for cyromazine = 0.1µg/L (river, ground and drinking water) LOQ for melamine = 0.1µg/L (drinking water) LOQ for melamine = 9.0µg/L (river water) LOQ for melamine = 0.5µg/L (ground water)

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Air (principle of method and LOQ)	**Doc No:** TMJ4861B**:** Substrates: air Analysis: LC/MS/MS Determined analyte: cyromazine LOQ: 0.0028mg/m^3
Body fluids and tissues (principle of method and LOQ)	No method required

Classification and proposed labelling with regard to physical and chemical data (Annex IIA, point 10)

	RMS/peer review proposal
Active substance	None

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Impact on Human and Animal Health

Absorption, distribution, excretion and metabolism (toxicokinetics) (Annex IIA, point 5.1)

Rate and extent of absorption ‡	Quantitatively adsorbed (greater than 97 % of the dose within 72 hours) and rapid (94-97 % of the total urinary excreted radioactivity within 24 hours) for the single low dose level.
Distribution ‡	Widely and uniformly distributed.
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. No radioactivity was detected in the expired air. Total radioactivity recoveries were > 97 % of the administered dose.
Metabolism in animals ‡	The major part of the excreted radioactivity was attributed to the parent compound (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.
Toxicologically relevant compounds ‡ (animals and plants)	Parent compound.
Toxicologically relevant compounds ‡ (environment)	Parent compound.

Acute toxicity (Annex IIA, point 5.2)

Rat LD_{50} oral ‡	3387 mg/kg bw	
Rabbit LD_{50} dermal ‡	> 3100 mg/kg bw	
Rat LC_{50} inhalation ‡	> 3.6 mg/L air/4 h. nose only, maximum attainable concentration	
Skin irritation ‡	Slightly irritant	
Eye irritation ‡	Non-irritant	
Skin sensitisation ‡	Non-sensitizer (M&K test)	

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Short term toxicity (Annex IIA, point 5.3)

Target / critical effect ‡	Oral: Decreased body weight gain, 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 ‡	5.74 mg/kg bw/day, 1-year dog 23 mg/kg bw/day, 90-day rat
Relevant dermal NOAEL ‡	> 2000 mg/kg bw/day, 21-day rabbit
Relevant inhalation NOAEC ‡	LOAEC = 58 mg/m^3, 28-day rat

Genotoxicity ‡ (Annex IIA, point 5.4)

No genotoxic potential	

Long term toxicity and carcinogenicity (Annex IIA, point 5.5)

Target/critical effect ‡	Decreased body weight gain (rat, mouse)	
Relevant NOAEL ‡	14.7 mg/kg bw/day, 2-year rat 6.5 mg/kg bw/day, 2-year mouse	
Carcinogenicity ‡	No carcinogenic risk to humans	-

Reproductive toxicity (Annex IIA, point 5.6)

Reproduction toxicity

Reproduction target / critical effect ‡	No adverse effects on reproductive performance or fertility; decreased offspring body weight during lactation at doses showing maternal toxicity (decreased body weight)
Relevant parental NOAEL ‡	2 mg/kg bw/day; LOAEL = 65 mg/kg bw/day
Relevant reproductive NOAEL ‡	215 mg/kg bw/day
Relevant offspring NOAEL ‡	65 mg/kg bw/day

Developmental toxicity

Developmental target / critical effect ‡	foetal toxicity (rats and rabbits) in the presence of substantial maternal toxicity (body weight loss)
Relevant maternal NOAEL ‡	Rat: 300 mg/kg bw/day Rabbit: 10 mg/kg bw/day
Relevant developmental NOAEL ‡	Rat: 300 mg/kg bw/day Rabbit: 30 mg/kg bw/day

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Neurotoxicity (Annex IIA, point 5.7)

Acute neurotoxicity ‡	No data available - not required
Repeated neurotoxicity ‡	No data available - not required
Delayed neurotoxicity ‡	No data available - not required

Other toxicological studies (Annex IIA, point 5.8)

Mechanism studies ‡	No data available - not required
Studies performed on metabolites or impurities ‡	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‡ (Annex IIA, point 5.9)

No complaint or sign of adverse effect that can be related to the exposure to cyromazine have been reported in personnel from manufacturing plants in Europe and the United States

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Summary (Annex IIA, point 5.10)	Value	Study	Safety factor
ADI ‡	0.06 mg/kg bw/day	1-year dog study supported by 2-year mouse study	100
AOEL ‡	0.06 mg/kg bw/day	1-year dog study	100
ARfD ‡	0.1 mg/kg bw	Developmental study in rabbit	100

Dermal absorption‡ (Annex IIIA, point 7.3)

Formulation: TRIGARD® 75 WP (A-6808 A)	2 % for the dilution and 0.7 % for the concentrate based on an *in vivo* rat study & an *in vitro* comparative dermal penetration study in rat and human skin membranes.

Exposure scenarios (Annex IIIA, point 7.2)

Operator	FIELD application (outdoor) The estimated exposure levels are lower than the AOEL for the intended uses of TRIGARD® 75 WP at a maximum dose of 300 g cyromazine/ha even when no PPE is considered. German model: (tractor-mounted) % of AOEL No PPE 23 % With PPE (gloves during mix/load & applic) 15 % UK POEM: (tractor-mounted) No PPE 322 % With PPE (gloves during mix/load & applic) 277 % UK POEM: (hand-held) No PPE 27 % With PPE (gloves during mix/load & applic) 14.4 % Greenhouse application (indoor) The estimated exposure levels using the Dutch greenhouse model are lower than the AOEL even when no PPE is considered. Dutch model: % of AOEL No PPE 36 % With PPE (gloves & coverall) 3.6 %
Workers	Worker exposure levels were estimated to be lower than the AOEL when no PPE is used. Hoernicke *et. al* : % of AOEL No PPE 80 % With PPE (gloves, long sleeved shirt & long

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Bystanders	trousers) 4 % Bystander exposure levels were calculated to account for less than 1 % of the AOEL based on the estimated operator exposure levels and considering that a bystander will be exposed accidentally for 5 min to the spray (worst case assumption).

Classification and proposed labelling with regard to toxicological data (Annex IIA, point 10)

	RMS/peer review proposal
Cyromazine	None

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Metabolism in plants (Annex IIA, point 6.1 and 6.7, Annex IIIA, point 8.1 and 8.6)

Plant groups covered	Leafy crops (L) (lettuce, celery), Fruits (F) (tomato)
Rotational crops	
Metabolism in rotational crops similar to metabolism in primary crops?	Yes
Processed commodities	Not applicable
Residue pattern in processed commodities similar to residue pattern in raw commodities?	Not applicable
Plant residue definition for monitoring	Cyromazine (for leafy crops and fruit crops only)
Plant residue definition for risk assessment	Cyromazine plus melamine metabolite, expressed as cyromazine (leafy crops, fruits)
Conversion factor (monitoring to risk assessment)	**No peer reviewed conversion factor available** After the meeting the RMS proposed a provisional conversion factors 1.83 and 2.33 for leafy crops and fruit crops respectively, derived from the US residue trials data base, but these values were not discussed and not peer reviewed

Metabolism in livestock (Annex IIA, point 6.2 and 6.7, Annex IIIA, point 8.1 and 8.6)

Animals covered	Lactating goats, laying hens
Time needed to reach a plateau concentration in milk and eggs	
Animal residue definition for monitoring	Not necessary at that stage. To be reconsidered if further uses are envisaged on crops fed to animals.
Animal residue definition for risk assessment	Not necessary at that stage. To be reconsidered if further uses are envisaged on crops fed to animals.
Conversion factor (monitoring to risk assessment)	Not discussed
Metabolism in rat and ruminant similar (yes/no)	Not Relevant
Fat soluble residue: (yes/no)	Not Relevant

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Residues in succeeding crops (Annex IIA, point 6.6, Annex IIIA, point 8.5)

TRR at harvest in rotational crops following application of ^{14}C-cyromazine (1009 g/ha) to a celery crop (plant-back interval 84 days) were:

Sweetcorn:	0.02 mg eq/kg
Radish tops:	0.02 mg eq/kg
Radish root:	0.01 mg eq/kg

Following treatment of a tomato crop (total 1680 g/ha) TRR in rotational crop at maturity were:

Lettuce:	<0.01 mg/kg
Sugar beet:	0.01 mg/kg
Wheat grain	<0.01 mg/kg
Soybeans:	0.03 mg/kg
Carrot tops:	0.05 mg/kg
Carrot roots:	<0.02 mg/kg

Following multiple applications of cyromazine (980 to 3640 g a.s./ha) on tomatoes grown as a primary crop, residues in winter wheat, winter barley, sweetcorn, sorghum, sugar beet, sweet potatoes, radish and cabbage grown as succeeding were <0.05 mg/kg, the plant-back intervals being 5 to 44 weeks

Following multiple applications of cyromazine (1680 to 22500 g a.s./ha) on celery grown as a primary crop, maximum residues were 006 mg/kg in sweet corn ears, 0.11 mg/kg in radish roots and 0.08 mg/kg in lettuce.

Therefore, no significant residues of cyromazine and melamine are expected in rotational /succeeding crops when cyromazine is used following the intended GAPs.

Stability of residues (Annex IIA, point 6 introduction, Annex IIIA, point 8 Introduction)

Cyromazine and melamine residues are stable in plant tissues for a minimum of 9.5–24 months under freezer storage conditions.

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Residues from livestock feeding studies (Annex IIA, point 6.4, Annex IIIA, point 8.3)

	Ruminant:	Poultry:	Pig:
	Conditions of requirement of feeding studies		
Expected intakes by livestock ≥ 0.1 mg/kg diet (dry weight basis) (yes/no - If yes, specify the evel)	No	No	No
Metabolism studies indicate potential level of residues ≥ 0.01 mg/kg in edible tissues (yes/no)	Not Required	Not Required	Not Required
	Feeding studies (Specify the feeding rate in cattle and poultry studies considered as relevant) Residue levels in matrices : Mean (max) mg/kg		
Muscle	-	-	-
Liver	-	-	-
Kidney	-	-	-
Fat	-	-	-
Milk	-		
Eggs		-	

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Summary of residues data according to the representative uses on raw agricultural commodities and feedingstuffs (Annex IIA, point 6.3, Annex IIIA, point 8.2)

Crop	Northern or Mediterranean Region, field or glasshouse, and any other useful information	Trials results relevant to the representative uses (a)	Recommendation/comments	MRL estimated from trials according to the representative use	HR (c)	STMR (b)
Lettuce	Glasshouse (EU N, S)	1.2, 2.16, 2.94, 3.0, 3.39, 4.16, 4.91, 5.9 and 6.6 mg/kg	The MRL proposal of 10 mg/kg based on indoor trials **leads to an exceeding of the ARfD**	10 mg/kg	6.6 mg/kg	3.4 mg/kg
	Field (EU N, S)	**N-EU:** 0.27, 0.28, 0.31, 0.94, 1.24, 1.82 **S-EU:** 0.17, 0.18, 0.34, 1.4, 1.8, 1.9		No peer reviewed MRL proposed(d)	1.9 mg/kg	0.64 mg/kg
Tomatoes	Glasshouse, (EU N, S)	0.05, 0.10, 0.13, 0.15, 0.16, 0.18, 0.19, 0.21, 0.22 and 0.30 mg/kg	No significant difference between the median residues produced by glasshouse and field conditions. Thus the residue populations for field-grown and glasshouse tomatoes are merged and used to propose an MRL based on the residue data from both growing systems	1 mg/kg	0.6 mg/kg	0.17 mg/kg
	Field (EU S)	**(S-EU):** 0.10, 0.11, 2x 0.15, 0.19, 0.23, 0.45 and 0.60 mg/kg				

(a) Numbers of trials in which particular residue levels were reported *e.g.* 3 x <0.01, 1 x 0.01, 6 x 0.02, 1 x 0.04, 1 x 0.08, 2 x 0.1, 2 x 0.15, 1 x 0.17
(b) Supervised Trials Median Residue *i.e.* the median residue level estimated on the basis of supervised trials relating to the representative use
(c) Highest residue

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(d) After the meeting and in agreement with the RMS, EFSA was of the opinion that an MRL of 3 mg/kg could be provisionally proposed on lettuce, based on the outdoor residue trials submitted by the applicant and presented in the DAR.

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Consumer risk assessment (Annex IIA, point 6.9, Annex IIIA, point 8.8)

ADI	0.06 mg/kg b.w./day
TMDI (% ADI) according to WHO European diet	16.2% (taking into account an MRL of 10 mg/kg for lettuce)
TMDI (% ADI) according to national (to be specified) diets	Up to 23% (EFSA model, WHO Cluster B diet) (taking into account an MRL of 10 mg/kg for lettuce)
IEDI (WHO European Diet) (% ADI)	Not assessed
NEDI (specify diet) (% ADI)	Not assessed
Factors included in IEDI and NEDI	The provisional conversion factor for risk assessment proposed by the RMS for leafy and fruit crops have been included in the calculation, these factors being not peer reviewed.
ARfD	0.1mg/kg bw
IESTI (% ARfD)	**Acute assessment not peer reviewed** 325% (for lettuce, using an HR value of 6.6 mg/kg from indoor residue trials) 81.4% (for tomato, using an HR value of 0.6 mg/kg)
NESTI (% ARfD) according to national (to be specified) large portion consumption data	Not relevant
Factors included in IESTI and NESTI	The provisional conversion factor for risk assessment proposed by the RMS for leafy and fruit crops have been included in the calculation, these factors being not peer reviewed.

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Processing factors (Annex IIA, point 6.5, Annex IIIA, point 8.4)

Crop/ process/ processed product	Number of studies	Processing factors		Amount transferred (%) (Optional)
		Transfer factor	Yield factor	
To be reconsidered for tomato taking into account the residue definition proposed for risk assessment that include the melamine metabolite				

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Proposed MRLs (Annex IIA, point 6.7, Annex IIIA, point 8.6)

Lettuce (Indoor GAPs)	10 mg/kg **This MRL was considered as unsafe** for the consumer, the acute risk assessment performed by the RMS after the meeting showing an exceeding of the ARfD.
Lettuce (Outdoor GAPs)	**No peer reviewed MRL available**(1).
Tomato	1 mg/kg
.....	
.....	

When the MRL is proposed at the LOQ, this should be annotated by an asterisk after the figure

(1): After the meeting and in agreement with the RMS, EFSA was of the opinion that an MRL of 3 mg/kg could be provisionally proposed on lettuce, based on the outdoor residue trials submitted by the applicant. Using the HR value of 1.9 mg/kg observed in the field trials, the IESTI is 94% of the ARfD.

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Route of degradation (aerobic) in soil (Annex IIA, point 7.1.1.1.1)

Mineralization after 100 days ‡	3.7-7.3 % AR after 120-121 d, [U-^{14}C]triazine-labelled cyromazine (n = 3)
Non-extractable residues after 100 days ‡	7.2-53.9 % AR at 120-126 d [U-^{14}C]triazine-labelled cyromazine (n = ~~8~~ 7)
Metabolites requiring further consideration ‡ - name and/or code, % of applied (range and maximum)	Melamine 74.5% AR at 120 (n= 3) [U-^{14}C]triazine-labelled cyromazine

Route of degradation in soil - Supplemental studies (Annex IIA, point 7.1.1.1.2)

Anaerobic degradation ‡ Mineralization after 100 days	*1.6*% after 6*0* d, [U-^{14}C]triazine-labelled cyromazine] (n= 1)
Non-extractable residues after 100 days	*4.6* % after *60* d, [U-^{14}C]triazine-labelled cyromazine] (n= *1*)
Metabolites that may require further consideration for risk assessment - name and/or code, % of applied (range and maximum)	Melamine – *35.8* % at 6*0* d (n= *1*)
Soil photolysis ‡ Metabolites that may require further consideration for risk assessment - name and/or code, % of applied (range and maximum)	Melamine – 54.0% at 240 hrs (irradiated, moist soil) [U-^{14}C]triazine-labelled cyromazine] (n= *1*) 14.7 % at 240 hrs (irradiated, dry soil) [U-^{14}C]triazine-labelled cyromazine] (n = 1)

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Rate of degradation in soil (Annex IIA, point 7.1.1.2, Annex IIIA, point 9.1.1)

Laboratory studies ‡

Cyromazine	Aerobic conditions						
Soil type	X [14]	pH ~~in 0.01M CaCl2~~	t. °C / % MWHC	DT_{50} /DT_{90} (d)	DT_{50} (d) 20 °C pF2/10kPa	St. (r^2)	Method of calculation
Gartenacker loam/silt loam	-	7.3 (KCl)	20 °C / 40% MWC	2.9 / 9.6	1.8	0.976	SFO
Gartenacker loam/silt loam	-	7.3 (KCl)	10 °C / 40% MWC	5.6 / 18.5	**	0.979	SFO
Horst loamy sand	-	5.7 ($CaCl_2$)	20 °C / pF 2	46 / 153	46	0.969	SFO
Westmaas loam	-	7.5 ($CaCl_2$)	20 °C / pF 2	15 / 50	15	0.992	SFO
Naaldwijk loamy sand	-	6.8 ($CaCl_2$)	20 °C / pF 2	56 / 186	56	0.990	SFO
Marsillarues silty clay loam	-	8.1 (H_2O)	20 °C / 40% MWC	38.2 / 127	22.1	0.997	SFO
18 Acres sandy clay loam	-	5.6 (KCl)	20 °C / pF 2	49.6 / 165	49.6	0.971	SFO
Fresno California sandy loam*	-	6.7 (KCl)	25 °C / 75% FC	Data gap			
Geometric mean/median			-	Data gap			

* from Esser (1995)
** not included in the statistical analysis

Melamine	Aerobic conditions							
Soil type	X [1]	pH	t. °C / % MWHC	DT_{50}/ DT_{90} (d)	f. f. k_{dp}/ k_f	DT_{50} (d) 20 °C pF2/10kPa	St. (r^2)	Method of calculation
Gartenacker loam/silt loam		7.3 (KCl)	20 °C / 40% MWC	125*	*	na	0.976	SFO
Horst loamy sand		5.7 ($CaCl_2$)	20 °C / pF 2	88*	*	na	0.969	SFO
Westmaas loam		7.5 ($CaCl_2$)	20 °C / pF 2	211*	*	na	0.992	SFO

[14] X This column is reserved for any other property that is considered to have a particular impact on the degradation rate.

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Melamine	Aerobic conditions							
Soil type	X [1]	pH	t. °C / % MWHC	DT_{50}/ DT_{90} (d)	f. f. k_{dp}/ k_f	DT_{50} (d) 20 °C pF2/10kPa	St. (r^2)	Method of calculation
Naaldwijk loamy sand		6.8 ($CaCl_2$)	20 °C / pF 2	120	**	na	na	SFO
Marsillarues silty clay loam		8.1 (H_2O)	20 °C / 40% MWC	75	**	na	na	SFO
18 Acres sandy clay loam		5.6 (KCl)	20 °C / pF 2	46	**	na	na	SFO
Geometric mean/median				155				

(n.a.): not available
* The full results of the kinetics modelling and information on the formation fractions calculated in the Aaldeirnk (2003) study were not available to the peer review. For that reason, these DT_{50} values should be considered with caution.
** Clarifications were required to the RMS.

Field studies ‡
No reliable data available

pH dependence ‡ (yes / no) (if yes type of dependence)	No
Soil accumulation and plateau concentration ‡	3 accumulation trials (CH, SP, GR) showed that there was no increase of cyromazine levels in soil over time.

Laboratory studies ‡

Cyromazine	Anaerobic conditions						
Soil type	X[15]	pH	t. °C / % MWHC	DT_{50} / DT_{90} (d)	DT_{50} (d) 20 °C pF2/10kPa	St. (r^2)	Method of calculation
Sandy loam		6.7	25 °C / 75% FC	97.6 / -	-	0.966	SFO

[15] X This column is reserved for any other property that is considered to have a particular impact on the degradation rate.

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Soil adsorption/desorption (Annex IIA, point 7.1.2)

Cyromazine ‡							
Soil Type	OC %	Soil pH (H_2O)	Kd (mL/g)	Koc (mL/g)	Kf (mL/g)	Kfoc (mL/g)	1/n
Loamy sand	1.3	5.9	-	-	6.77	521	0.92
Loam	1.5	7.5	-	-	1.44	96	0.73
Loamy sand	1.8	6.8	-	-	3.6	200	0.87
Clay	2.8	5.9	-	-	50.38	1784	0.73
Sand	0.5	6.5	-	-	1.09	207	0.714
Silt loam	0.6	7.5	-	-	5.62	910	0.769
Sandy loam	0.8	7.8	-	-	0.61	79	0.909
Sand	1.3	7.8			0.52	40.2	0.83
Loamy sand	3.3	6.7			2.37	71.9	0.85
Silt loam	2.1	6.1			3.87	183	0.77
Sandy loam			-	-			
Arithmetic mean/median						409/192	0.8/0.8
pH dependence, Yes or No			no				

Metabolite melamine ‡							
Soil Type	OC %	Soil pH (H_2O)	Kd (mL/g)	Koc (mL/g)	Kf (mL/g)	Kfoc (mL/g)	1/n
Loamy sand	1.3	5.9			5.50	423	0.80
Loam	1.5	7.5			1.45	97	0.80
Loamy sand	1.8	6.8			2.77	154	0.83
Loamy sand	1.5	4.2			5.57	371	0.715
Silt loam	1.8	7.3			0.9638	54	0.7414
Arithmetic mean/median							

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

pH dependence (yes or no)	Yes (for FOCUS modelling specific Kfoc and 1/n values should be calculated for scenarios with acidic and alkaline soils to take into consideration the pH dependency)

Mobility in soil (Annex IIA, point 7.1.3, Annex IIIA, point 9.1.2)

Column leaching ‡	Eluation: 200 mm equivalent water precipitation Time period (d): 2 d Leachate: 32.7 % of applied radioactivity in the eluate of 1 sandy soil, < 0.5% of radioactivity in the eluates of the 2 other soils.
Aged residues leaching ‡	Aged for (d): 28 d and 30 d Eluation (mm): 200 mm of water over approximately 16 days and 571.5 mm over approximately 45 days.
	Leachate: 0.06-0.37 % of applied radioactivity in leachate after application of 200 mm rainfall in 16 days. <0.10-51% of radioactivity in the leachates after application of 571.5 mm in 45 days.
Lysimeter/ field leaching studies ‡	Groundwater monitoring study in the USA: cyromazine was not detected below 15 cm soil depth, no detectable residues > 0.10 µg/L in groundwater. There were sporadic detections of melamine from samples collected from the deep wells during 5 sampling intervals, which were close to the detection limit All other sample intervals had no detections of melamine.

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

PEC (soil) (Annex IIIA, point 9.1.3)

Cyromazine Method of calculation	Risk assessment for earthworms and soil macro-organisms based on PECini
Application data	Crop: lettuce 3 x 300 gr/ha, tomatoes 4 x 300 gr/ha Depth of soil layer: 5cm Soil bulk density: 1.5g/cm^3 % plant interception: 50% Number of applications: 3 (lettuce) / 4 (tomatoes) Interval (d): 7 (lettuce) / 7 (tomatoes) Application rate(s): 3 x 300 gr/ha (lettuce) / 4 x 300 gr/ha (tomatoes)

PEC$_{(s)}$ (mg/kg) **(Lettuce)**	Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial			0.548	
Plateau concentration	-			

PEC$_{(s)}$ (mg/kg) **(Tomatoes)**	Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial			0.440	
Plateau concentration	-			

Metabolite melamine Method of calculation	Data gap

Route and rate of degradation in water (Annex IIA, point 7.2.1)

Hydrolytic degradation of the active substance and metabolites > 10 % ‡	Hydrolytically stable at pH: 5, 7 and 9at 30, 50 and 70 °C

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Photolytic degradation of active substance and metabolites above 10 % ‡	Stable
Quantum yield of direct phototransformation in water at Σ > 290 nm	-
Readily biodegradable ‡ (yes/no)	No

Degradation in water / sediment

Cyromazine	Distribution (max in water 95.98 % at 0 d. Max. sed 54.21 % after 56d)									
Water / sediment system	pH water phase	pH sed (H_2O)	t. °C	DT_{50}-DT_{90} whole sys.	St. (r^2)	DT_{50}-DT_{90} water*	St. (r^2)	DT_{50}-DT_{90} sed	St. (r^2)	Method of calculation
River system (Rhine at Möhlin, CH)	8.12	7.7	20.4	211 / -	-	16 / -	-	143 / -	-	SFO
Pond system (Rotenfluh at Möhlin, CH)	7.84	7.24	15.0	244 / -	-	14.5 / -	-	142 /-	-	SFO
Geometric mean/median			-	228		15		143		-

Mineralization and non extractable residues					
Water / sediment system	pH water phase	pH sed (H_2O)	Mineralization x % after n d. (end of the study).	Non-extractable residues in sed. max x % after n d	Non-extractable residues in sed. max x % after n d (end of the study)
River system (Rhine at Möhlin, CH)	8.12	7.7	7.59% after 103 d	12.14% after 103 d	12.14% after 103 d
Pond system (Rotenfluh at Möhlin, CH)	7.84	7.24	5.25% after 103 d	12.86% after 100 d	12.86% after 100 d

*The DT50 value in water refers to dissipation time for the parent

Melamine never exceeded 3.5% AR in all compartments

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

PEC (surface water) and PEC sediment (Annex IIIA, point 9.2.3)

Data gap for FOCUS PECsw for cyromazine and melamine

PEC (ground water) (Annex IIIA, point 9.2.1)

Data gap for FOCUS PECgw for cyromazine and melamine

Fate and behaviour in air (Annex IIA, point 7.2.2, Annex III, point 9.3)

Direct photolysis in air ‡	-
Quantum yield of direct phototransformation	Molar adsorption coefficient < 10 (I/mol*cm) at 290 nm
Photochemical oxidative degradation in air ‡	Half-life of 102 hours for hydroxyl reactions (Atkinson method) – (assumes OH radical concentration of $1.5*10^6$ molecules / cm^3 over a 12 hour day) A potential for aerial long range transport for cyromazine was identified at PRAPeR 47
Volatilisation ‡	From plant surfaces: cyromazine is non-volatile with a vapour pressure of 4.48×10^{-7} Pa No volatilization of cyromazine from soil was observed after 24 hrs of exposure at an air flow of 1 m/s.
Metabolites	-

PEC (air)

Method of calculation	Estimation based on compound properties

$PEC_{(a)}$

Maximum concentration	Negligible

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Residues requiring further assessment

Environmental occurring metabolite requiring further assessment by other disciplines (toxicology and ecotoxicology).	Soil: cyromazine, melamine, NOA 435343 Surface Water: cyromazine, originating from soil via runoff and drainage: melamine, NOA 435343 Sediment: cyromazine Ground water: cyromazine, melamine, NOA 435343 Air: cyromazine

Monitoring data, if available (Annex IIA, point 7.4)

Soil (indicate location and type of study)	-
Surface water (indicate location and type of study)	-
Ground water (indicate location and type of study)	USA, small – scale study, it represents typical practices for tomato production and for use of the test substance in an extreme worst – case environment with respect to potential for groundwater contamination. Cyromazine was not detected below 15 cm soil depth, no detectable residues > 0.10 µg/L in groundwater.
Air (indicate location and type of study)	-

Points pertinent to the classification and proposed labelling with regard to fate and behaviour data

Possible candidate for R53

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Effects on Non-target Species

Effects on terrestrial vertebrates (Annex IIA, point 8.1; Annex IIIA, points 10.1 and 10.3)

Acute toxicity to mammals	Rat LD_{50} 3387 mg a.s./kg bw
Acute toxicity to birds	LD_{50} (Peking duck) >1000 mg a.s./kg LD_{50} (Japanese quail) =2338 mg a.s./kg LD_{50} (mallard duck) > 2510 mg a.s./kg LD_{50} (Bobwhite quail) = 1785 mg a.s./kg
Dietary toxicity to birds	LC_{50} (Mallard duck) >526 mg a.s./kg bw/day LC_{50} (Japanese quail) >683 mg a.s./kg bw/day LC_{50} (Peking duck) >1115 mg a.s./kg bw/day LC_{50} (Bobwhite quail) >1370 mg a.s./kg bw/day
Reproductive toxicity to birds	NOEL (Mallard duck) 38.3 mg a.s./kg bw/day NOEL (Bobwhite quail) 110 mg a.s./kg bw/day
Reproductive/long term toxicity to mammals	Rat $NOAEL_{(offspring)}$ 30 mg a.s./kg bw/day

Toxicity/exposure ratios for terrestrial vertebrates (Annex IIIA, points 10.1 and 10.3)

Exposure period	Crop, use pattern	Category (*e.g.*, insectivorous bird)	Toxicity endpoint	ETE [mg a.s./kg bw/day]	TER	TER risk trigger (from Annex VI)
Acute	Field tomato: 4 x 300 g (7 day interval)	Medium herbivore bird	LD_{50} > 1000 mg a.s./kg	35.7	>28	≤ 10
		Small insectivore bird		16.2	>62	≤ 10
	Field lettuce: 3 x 300 g (7 day interval)	Medium herbivore bird		33.72	>30	≤ 10
		Small insectivore bird		16.2	>62	≤ 10
		Drinking water for birds		16.18	>61.8	≤ 10
Short-term	Field tomato: 4 x 300 g (7 day interval)	Medium herbivore bird	LD_{50} >526 mg a.s./kg bw/day	20.1	>26	≤ 10
		Small insectivore bird		9.1	>58	≤ 10
	Field lettuce: 3 x	Medium herbivore bird		18.24	>29	≤ 10

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

	300 g (7 day interval)	Small insectivore bird		9.1	>58	≤ 10
Long-term	Field tomato: 4 x 300 g (7 day interval)	Medium herbivore bird	NOEL 38.3 mg a.s./kg bw/day	3.15 [a]	**3.6** Refine 6.1	≤ 5
		Small insectivore bird		4.52 [b]	**4.2** Refine 16	≤ 5
	Field lettuce: 3 x 300 g (7 day interval)	Medium herbivore bird		3.15 [a]	**3.9** Refine 6.1	≤ 5
		Small insectivore bird		4.52 [b]	**4.2** Refine 16	≤ 5
Acute	Field tomato: 4 x 300 g (7 day interval)	Medium herbivore mammal	LD_{50} 3387 mg a.s./kg bw	13.2 [c]	257	≤ 10
		Drinking water for mammals		9.41	360	≤ 10
Long-term [b]	Field tomato: 4 x 300 g (7 day interval)	Medium herbivore mammal	$NOAEL_{(offspring)}$ 30 mg a.s./kg bw/day	3.9 [c]	7.7	≤ 5

[a] The ETE is calculated using a refined MAF based on a measured foliar DT_{50} of 3.3 days for cyromazine (rather than the default value of 10 days)
[b] The ETE is calculated using the yellow wagtail as the relevant small insectivore focal species.
[c] In each case the field tomato represents the worst case compared to the use in field lettuce, so only values for the tomato scenario are presented

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Toxicity data for aquatic species (most sensitive species of each group) (Annex IIA, point 8.2, Annex IIIA, point 10.2)

Treatment	Species	Study Type	LC_{50} /EC_{50} [mg a.s./L]	LC_0 /NOEC [mg a.s./L]
Technical cyromazine	Rainbow trout	96-hour static	>100	<1
	Common Carp	96-hour static	>100	<10
	Common Carp	96-hour static	>100	>100
	Channel catfish	96-hour static	>100	>100
	Fathead minnow (*Pimephales promelas*)	32-day flow-through (ELS)	N.A.	14
	Daphnia magna	48-hour static	>100	10
	Daphnia magna	48-hour static	>100	4.6
	Chironomus riparius	48-hour semi static	>120	120
	Daphnia magna	21-day flow-through	N.A.	0.31 (reproduction and length)
	Scenedesmus subspicatus	5-day static test	124	-
	Chironomus riparius	26-d chronic (water/sediment)		0.025
TRIGARD 75 WP	Rainbow trout	96-h static	>100 (>75 mg a.s/l)	32 (24 mg a.s/l)
	Daphnia magna	48-h static	90 (68 mg a.s/l)	18 (13.5 mg a.s/l)
	Selenastrum capricornutum	72-h static	110 (82.5 mg a.s/l)	18 (13.5 mg a.s/l)
CGA 235129	Rainbow trout	96-hour static	>120	120
	Daphnia magna	48-h acute (static)	>2000	<180
	Daphnia magna	48-h acute (static)	60	6.25
	Daphnia magna	14-day static test		
	Selenastrum capricornutum	72-h acute (static)	>100 [a]	100 [a]
	Scenedesmus pannonicus	96-h static	940	320

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Toxicity/exposure ratios for the most sensitive aquatic organisms (Annex IIIA, point 10.2)

FOCUS Step-2 modeling

Organism	Test substance	Toxicity Endpoint	PEC (µg/L)	TER [a]	TER risk trigger value (from 91/414/EEC)
Fish	TRIGARD® 75 WP	96-h LC_{50} >75 mg/L	44.88	>1671	<100
	Cyromazine	32-day NOEC 14 mg/L	44.88	310	<10
Aquatic Invertebrate	TRIGARD® 75 WP	48-h EC_{50} =68 mg/L	44.88	1515	<100
	Cyromazine	21-d NOEC 0.31 mg/L	44.88	**6.9**	<10
Algae	TRIGARD® 75 WP	72-h E_rC_{50} =82.5 mg/L	44.88	1838	<10
Aquatic insects	Cyromazine	48-h EC_{50} >120 mg/L	44.88	**>**2700	<100
	Cyromazine	26-d NOEC 25µg/L	44.88	**0.56**	<10

a Figures in bold are below the trigger value and indicate potential risk

FOCUS Step-3 modeling

Scenario Water body	Max PEC (tomatoes)				Max PEC (lettuce)			
	Aquatic inverts (*D .magna*)		Aquatic insects (*C. riparius*)		Aquatic inverts (*D. magna*)		Aquatic insects (*C. riparius*)	
	SW (µg/L)	TER_{LT}	SW (µg/L)	TER_{LT}	SW (µg/L)	TER_{LT}	SW (µg/L)	TER_{LT}
D3 Ditch	n.a	n.a	n.a	n.a	1.39	223	1.39	18
D4 Pond	n.a	n.a	n.a	n.a	0.114	2700	0.124	220
D4 Stream	n.a	n.a	n.a	n.a	1.05	295	1.05	24
D6 Ditch	1.27	250	1.26	19.8	2.09	150	2.09	12
R1 Pond	n.a	n.a	n.a	n.a	0.447	694	0.447	56
R1 Stream	n.a	n.a	n.a	n.a	5.54	56	5.54	**4.5**
R2 Stream	6.95	45	6.95	**3.6**	3.83	64	3.83	**6.5**
R3 Stream	16.2	19	16.2	**1.5**	13.7	23	13.7	**1.8**
R4 Stream	14.3	22	14.3	**1.7**	11.7	26	11.7	**2.1**

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

FOCUS Step-4 modeling (inclusion of 5m buffer) for *C. riparius*

Scenario Water body	Max PEC (tomatoes)		Max PEC (lettuce)	
	SW (µg/L)	TER	SW (µg/L)	TER
D3 Ditch	n.a	n.a	0.369	68
D4 Pond	n.a	n.a	0.100	250
D4 Stream	n.a	n.a	0.378	66
D6 Ditch	0.34	74	2.09	12
R1 Pond	n.a	n.a	0.361	69
R1 Stream	n.a	n.a	3.54	**7.1**
R2 Stream	2.98	**8.4**	2.45	10
R3 Stream	7.51	**3.3**	6.88	**3.6**
R4 Stream	6.75	**3.7**	5.84	**4.3**

Figures in bold are below the trigger value and indicate potential risk

FOCUS Step-4 modeling (inclusion of 10m buffer) for *C. riparius*

Scenario Water body	Max PEC (tomatoes)		Max PEC (lettuce)	
	SW (µg/L)	TER	SW (µg/L)	TER
R1 Stream	n.a	n.a	0.706	35
R2 Stream	0.598	42	n.a	n.a
R3 Stream	1.50	17	1.37	18
R4 Stream	1.35	19	0.797	31

Bioconcentration

Bioconcentration factor (BCF)	The BCF for edible, non-edible and whole fish is < 1
Annex VI Trigger for the bioconcentration factor	BCF = 100 (for plant protection products containing active substances that are not readily biodegradable)
Clearance time (CT_{50}) (CT_{90})	Not applicable since BCF <1
Level of residues (%) in organisms after the 14 day depuration phase	Not applicable since BCF <1

Effects on honeybees (Annex IIA, point 8.3.1, Annex IIIA, point 10.4)

Acute oral toxicity	186 µg a.s./bee
Acute contact toxicity	>200 µg a.s./bee

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Hazard quotients for honey bees (Annex IIIA, point 10.4)

Test substance	Exposure route	Endpoint	Maximum single application rate	Hazard quotient	Annex VI trigger
TRIGARD ® 75 WP (A-6808 A)	Oral	186 µg a.s./bee	300 g a.s./ha	1.6	>50
TRIGARD ® 75 WP (A-6808 A)	Contact	>200 µg a.s./bee	300 g a.s./ha	<1.5	>50

Field or semi-field tests
Cyromazine is an insect growth regulator and therefore additional consideration was given to potential effects on the bee brood as recommended in SANCO/10329/2002.

Toxicity of TRIGARD ® 75 WP (A-6808 A) to honeybees (Apis mellifera) under semi field and field conditions

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Test design	Application rate (formulation/ha)	Duration of exposure (days)	Observations
Ready to feed syrup amended with cyromazine was provided to a bee colony with few natural nectar sources	0.225 g a.s./L . Added to one litre of a ready-to-use sugar solution was compared to an untreated sugar solution control and a toxic reference treatment in 1L of ready-to –use syrup).	1. The total duration of the study was 3 weeks, which is equivalent to the normal time, taken for honeybee brood development	Assessments of brood development took place half a day prior to application and one, two and three weeks after application, allowing for one complete development period of the honeybees to elapse. In the test treatment the lack of young larvae and round maggots observed after one week means that many of the eggs, young larvae and round maggots did not develop successfully. Two weeks after treatment malformations were found in the newly hatched worker bees in the A-6808A treatment. These bees had stunted wings and demonstrated movement/co-ordination problems. These malformed workers were transferred to the dead bee traps. The increase of eggs after 2 weeks is due to the queen laying new eggs in the empty brood cells. Round maggots and closed brood at the time of treatment were unaffected. Treatment with cyromazine did not appear to have an effect on the total size of the colonies relative to the control. Feeding the brood with food contaminated with the toxic reference resulted in high levels of larval mortality which triggered the queen to lay increasing amounts of new eggs. The larval mortality led ultimately to low amounts of closed brood. A decrease in hive size was noted in the toxic reference treatment.
Semi field (Tunnel test) Application to flowering *Phacelia* in a tunnel.	16 or 400	11	Three replicate hives per treatment were established for the purpose of this study. The beehives were removed from the tunnels 11 days after application and carefully placed on the same longitudinal axis they were on in the tunnel, and within 1m of the position they were in the tunnel. Each tunnel was closed again to prevent foraging of bees on *Phacelia* treated with other treatments. **Mortality**: Over the period of the study no significant difference in mortality between the test treatments and the control was observed. No abnormal behaviour of the bees around the hive or at the entrance of the hive was observed. **Flight / foraging activity:** At the assessments 0.5, 1 and 2 hours after application no decrease in the number of foraging bees was observed in the control or 16g A-6808 A/ha treatment. At these timepoints significant reductions in foraging activity was observed in the higher test substance and toxic standard treatments. Foraging activity in the toxic standard treatment was similar to control 4 hours after treatment whilst in the 400 g A-6808. A treatment 4 h after treatment foraging remained reduced. The differences in the number of foraging bees / m^2 observed between the control and test treatments on day +1 to day +11 were not significantly different and were within the normal range of biological variation. After the beehives had been removed from the polytunnel a pollen trap was placed outside each

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

			hive on day 13 and 15 to record the type of pollen the bees were collecting. There was no significant difference in the pollen collected by the bees in each hive, with 85 – 86% of the collected pollen coming from untreated *Phacelia tanacetifolia* plants. **Frame assessments:** There was a slight reduction in the weight of the 400 g A-6808 A /ha and Dimilin treated colonies when recorded 20 days after treatment in comparison to their pre-treatment weights. But no significant decrease or increase in the weight development of the control or either A-6808 A treatment exposed colonies when comparing their weights 3 days before and 20 days after treatment were noted. **Brood assessments:** In the control treatment 87.2 % of eggs developed into adults compared to 44.1 % (as an average of **0**, 53.3 and 79.1%) in the 16g A-8606 A treatment, 61.7% (as an average of 70.3, **17.2** and 97.6%) for the 400g A-8606 A treatment and 51.6% in the toxic reference treatment. The results for the A-6808 A treatments should be treated with caution as the variability (as you can see above) between replicates in the egg development is high. With the 400g A-6808 A treatment apparently having less effect on brood development than the 16g A-6808 A treatment. For the development of larvae into adults there is less variation between replicates in the A-6808 A treatments, with the percentage development for both of the A-6808 A treatments is in the same range as the control treatment. The development from larvae to adult was significantly lower in the toxic reference treatment compared to the control. **Conclusions:** Exposure of bees to CGA 72662 75 WP (A-6808 A) applied once at 16g or 400g/ha to flowering *Phacelia* in tunnel tests resulted in no increases in adult mortality. At the higher treatment level foraging levels were reduced and foraging behaviour affected but only for a short period after application. The successful development of eggs into adults was slightly affected in both treatments but the development of larval stages into adults was unaffected..
Field Test Application to flowering sweet melon plants whilst bees were actively foraging in the field	300 g a.s./ha	28	Subsequent observations, over a 28-day period detected NO treatment related effects on flight activity, condition or development of the colony and brood or in the behaviour of the bees was observed

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Effects on other arthropod species (Annex IIA, point 8.3.2, Annex IIIA, point 10.5)

Test	Test species	Summary of design	Endpoints
Lab study	*Aphidius rhopalosiphi*	Direct application to mummies (wasp pupae in host aphids) (2D application scenario)	LR_{50} (adult emergence & immediate survival) = >891 g a.s. /ha ER_{50} (based on fecundity) = > 891 g a.s./ha
Lab study	*Coccinella septempunctata*	Exposure of larvae to dried residues on glass plates (2D application scenario)	LR_{50} > 900 g a.s./ha NOEC 900 g a.s./ha
Lab study	*Poecilus cupreus*	Direct application to adult beetles and subsequent exposure to treated sand (2D application scenario)	LR_{50}>900 g a.s./ha
Lab study	*Aleochara bilineata*	Exposure to fresh residues on quartz sand (2D application scenario)	LR_{50} > 900 g a.s./ha ER_{50} (based on fecundity) 900 g a.s./ha
Extd. lab	*Aphidius rhopalosiphi*	Exposure of adults to residues on barley seedlings (3D application scenario)	48-h LR_{50} > 891g a.s./ha
			$EC_{50\ (reproduction)}$ >891g a.s./ha`
Extd. lab	*Typhlodromus pyri*	Exposure of protonymphs to residues on excised bean leaves (2D application)	LR_{50} (based on mort escape) 47 g a.s. /ha Highest rate resulting in <50% effects on reproduction = 1.36 g a.s./ha [a]
Extd. lab		Direct application to eggs and exposure of hatched protonymphs to spray residues on bean leaves (2D application scenario): eggs<24h	LR_{50} (egg hatch) = >30g a.s./ha
			$LR_{50\ (total\ mortality)}$ 2.42g a.s./ha
Extd. Lab.: Field aged residues		4 x 10.065 g a.s./ha (7 day interval)	Time to <50% effect 0/14-d (mortality/fecundity)
		3 x 3.015 g a.s./ha (7 day interval)	Time to <50% effect 0/14-d (mortality/fecundity)
		4 x 300 g a.s./ha (7 day interval)	Time to <50% effect on mortality35d fecundity phase not conducted

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

		3 x 300 g a.s./ha (7 day interval)	Time to <50% effect on mortality 28d fecundity phase not conducted
Extd. lab	*Chrysoperla carnea*	Exposure of larvae to residues on excised bean leaves (3D application)	LR_{50} > 33 g a.s./hL (330 g a.s./ha) when applied four times on a seven day schedule/ No harmful effects on reproduction were observed in this treatment
Extd. lab		Direct application to eggs followed by exposure of subsequent hatched larvae to residues on bean leaves (3D application scenario)	1 application to eggs, hatched larve exposed to 4 applications at upto 33 g a.s./hL (330 g a.s./ha) on a seven day schedule produces <50% effects on egg hatch, survival of larvae or pre-imaginal mortality , reproductive ability of surviving adults was unaffected
Extd. lab		Direct application to pupae and subsequent exposure to dried residues on bean leaves (3 D application scenario)	4 applications at upto 33 g a.s./hL (330 g a.s./ha) on a seven day schedule produces <50% effects on adult emergence from the pupae and adult survival $NOEC_{(fecundity)}$ 4 applications at upto 33 g a.s./hL (330 g a.s./ha) on a seven day
Extd. Lab	*Coccinella septempunctata*	Exposure of four day old second instars to dried residues on bean leaves (2D application scenario)	$NOER_{(based\ on\ fecundity)}$ 891 g a.s./ha (the highest rate tested) LR_{50} >891 g a.s. /ha
Extd. Lab		Direct application to eggs with subsequent exposure to dried residues on bean leaves (2D application scenario)	LR_{50} (total pre-imaginal mortality) >891 g a.s./ha ER_{50} (egg hatch) >891 g a.s./ha
Extd. Lab Field aged residues	*Encarsia formosa*	Exposure of adults to dried residues on tomato leaves (3D application scenario)	<50 % effects on mortality and fecundity following four applications at 33 g a.s. /hL (330 g a.s./ha) on a seven day schedule

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Extd. Lab		Direct application of parasitised whitefly scales (larvae/pupae) (3D application scenario)	When applied three times on a seven day schedule: <50% effects on pupal development from pre-imaginal development and fecundity with 2.28 g a.s./hL (22.8 g a.s./ha) <50% effects on adult emergence form 33 g a.s./hL (330 g a.s./ha) [b]
Extd. Lab		Direct application to parasitised whitefly scales (pupae) (3 D application scenario)	When applied two times on a seven day schedule at up to 33 g a.s./hL (330 g a.s./ha) < 50% effects on pupal development or fecundity of emerged adults was observed
Extd. lab	*Phytoseiulus persimilis*	Exposure of 24-h old protonymphs to dried residues on bean leaves (2D application scenario)	LR_{50} mort escape 7.690 g a.s./ha LR_{50} (mort) 10.830 g a.s./ha < 50% effects on fecundity at 13.58 g a.s./ha
Extd. Lab with field aged residues		Protonymphs, less than 24h-old were exposed to field aged residues on sweet pepper leaves (3D application scenario)	3 applications on a seven day schedule to the point of run-off at up to 10 g a.s./hl (100 g a.s./ha) resulted in < 50% effects on pre-imaginal mortality and fecundity when exposed just after the last application
Extd. lab		Direct treatment of eggs on bean leaves (2D application scenario)	LR_{50} (egg hatch) >600 g a.s./ha LR_{50} (post hatch and pre-imaginal mortality) 30.49 g a.s./ha
Extd. lab	*Folsomia Candida*	Exposure of 10-12 day old juveniles to amended soil (2D application scenario)	EC_{50} 54.4 mg a.s./kg dry weight soil NOEC 9.6 mg a.s./kg dry weight of soil

[a] In higher treatments with <50% mortality-escape after 7-days, the development of immature organisms into adult was delayed in most replicates. This will have impacted the fecundity, although in reality this is an effect on juvenile development rather than on reproduction itself.
[b] Results should be interpreted with care, since the test substance related effects on whitefly host *T. vaporariorum* were observed and may have influenced the results.
n.a. fecundity phase was not conducted since insufficient adults were available

However, as TRIGARD® 75 WP (A-6808 A) is an insect growth regulator the HQ approach and the associated trigger values cannot be used to evaluate the toxicity data for IGR', since such products were not included in the validation exercise.

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

In-field

Comparison of Tier I laboratory toxicity endpoints with the in-field PER values following application of TRIGARD® 75 WP (A-6808 A)

Species (reference)	Application scenario	Toxicity endpoint [g a.s./ha]		Limit rate tested resulting in <50% effects [a] at ≥ PER (in-field)		
				Lettuce and tomato foliar PER (390 g a.s./ha)	Lettuce soil PER (420 g a.s./ha)	Tomato soil PER (525 g a.s./ha)
A. rhopalosiphi	2D	LR_{50}	>891	Yes	Yes	Yes
		ER_{50}	>891	Yes	Yes	Yes
C. septempunctata	2D	LR_{50}	>900	Yes	Yes	Yes
		NOER	900	Yes	Yes	Yes
P. cupreus adults	2D	LR_{50}	>900	Yes	Yes	Yes
		ER_{50}	>900	Yes	Yes	Yes
A. bilineata adults	2D	LR_{50}	>900	Yes	Yes	Yes
		ER_{50}	>900	Yes	Yes	Yes

[a] In the case of *C. septempunctata*, in accordance with test guidelines the reproductive performance of treatment groups is compared against historical data in a semi-quantitative manner, rather than detecting effects 50% different form the control

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Comparison of Tier II extended toxicity endpoints for foliar dwelling organisms with the in-field PER values following application of TRIGARD® 75 WP (A-6808 A)

Species (reference)	Application scenario	Toxicity endpoint [g a.s./ha]		Limit rate tested resulting in <50% effects a at ≥ PER (in-field) b		
				Lettuce and tomato foliar PER (390 g a.s./ha)	Lettuce soil PER (420 g a.s./ha)	Tomato soil PER (525 g a.s./ha)
A. rhopalosiphi adults	3D	LR50 (adults)	>891	Yes	Yes	Yes
		ER50	>891	Yes	Yes	Yes
T. pyri protonymphs	2D	LR50	47	No	No	No
		Highest rate <50% effect on fecundity	1.36	No	No	No
T. pyri eggs	2D	LR50 (egg hatch)	>30	No	No	No
		LR50 (overall mortality) c	2.42	No	No	No
C. septempunctata larvae	2D	LR50 (pre-imaginal mortality of larvae)	>891	Yes	Yes	Yes
		NOER	891 (highest rate tested)	Yes	Yes	Yes
C. septempunctata eggs	2D	LR50 (egg hatch only)	>891	Yes	Yes	Yes
		LR50 (overall pre-imaginal mortality including egg hatch)	>891	Yes	Yes	Yes

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Phytoseiulus persimilis protonymphs	2D	LR50	7.69	No	No	No
		Highest rate <50% effect on fecundity	13.58	No	No	No
P. persimilis eggs	2D	LR50 (egg hatch only)	>450	Yes	Yes	Yes
		LR50 (post-hatch pre-imaginal mortality)	30.49	No	No	No

[a] In the case of *C. septempunctata*, in accordance with test guidelines the reproductive performance of treatment groups is compared against historical data in a semi-quantitative manner, rather than detecting effects 50% different form the control.
[b] In cases in which the toxicity value is based on the highest rate tested (i.e. > values) and this is below the PER value, the real toxicity endpoint resulting in 50% effects may or may not be above the PER value. However, insufficiently high rates have been tested to determine this.
[c] LR_{50} (overall mortality) includes deaths during egg hatch, and dead and escaped mites during the pre-imaginal development of hatched mites.

In-field foliar risk assessment for foliar dwelling non-target arthropods incorporating dissipation of residues over time, assuming 1st order degradation kinetics.

Species/ developmental stage	Toxicity endpoint (g a.s./ha)	Time to <50% effects (days after last application)	
		Lettuce [a]	Tomato [b]
Typhlodromus pyri (protonymphs)	Highest rate resulting in, 50% effects on fecundity [c] 1.36	27	27
Typhlodromus pyri (eggs)	LR_{50} > 30 (egg hatch)	13	13
	LR_{50} 2.42 (overall mortality) [d]	25	25
Phytoseiulus persimilis (protonymphs)	LR_{50} 7.69	19	19
	Highest rate with < 50% effects on fecundity = 13.58	16	16
Phytoseiulus persimilis (eggs)	LR_{50} (egg hatch) >600	0	0
	LR_{50} (post-hatch and pre-imaginal mort-escape) = 30.49	13	13

[a] based on 3 x 300 g a.s./ha, 7-day interval DT_{50} (foliage) 3.3 days
[b] based on 4 x 300 g a.s./ha, 7-day interval DT_{50} (foliage) 3.3 days
[c] In higher treatments with < 50% mortality-escape after 7-days, the development of immature organisms into adults was delayed in most replicates. This will have an impact on fecundity although in reality this is an effect on juvenile development rather than on reproduction itself.
[d] Overall mortality includes mortalities during egg hatch and pre-imaginal mortality-escape

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Off-field

Comparison of Tier I laboratory toxicity endpoints with the off-field PER values following application of TRIGARD® 75 WP (A-6808 A)

Species (reference)	Application scenario	Toxicity endpoint [g a.s./ha]		Limit rate tested resulting in <50% effects [a] at ≥ PER (off-field)	
				Lettuce foliar PER (2D)	Lettuce foliar PER (2D)
A. rhopalosiphi (Reber, 2002a)	2D	LR_{50}	>891	Yes	Yes
		ER_{50}	>891	Yes	Yes
C. septempunctata (Reber, 1997a)	2D	LR_{50}	>900	Yes	Yes
		NOER	900	Yes	Yes
P. cupreus adults (Reber, 1997b)	2D	LR_{50}	>900	Yes	Yes
		ER_{50}	>900	Yes	Yes
A. bilineata adults (Reber, 1997c)	2D	LR_{50}	>900	Yes	Yes
		ER_{50}	>900	Yes	Yes

[a] In the case of *C. septempunctata*, in accordance with test guidelines the reproductive performance of treatment groups is compared against historical data in a semi-quantitative manner, rather than detecting effects 50% different form the control

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Comparison of Tier II extended toxicity endpoints with the off-field PER values following application of TRIGARD® 75 WP (A-6808 A)

Species (reference)	Application scenario	Toxicity endpoint [g a.s./ha]		Limit rate tested resulting in <50% effects a at ≥ PER (in-field) b when considering an uncertainty factor of 5			
				Lettuce off-field PER for comparison to 2-D higher tier studies	Lettuce off-field PER for comparison to 2-D higher tier studies	Lettuce off-field PER for comparison to 2-D higher tier studies	Lettuce off-field PER for comparison to 2-D higher tier studies
A. rhopalosiphi adults (Reber, 2002b)	3D	LR50 (adults)	>891	-	Yes	-	Yes
		ER50	>891	-	Yes	-	Yes
T. pyri protonymphs (Bruhl, 2002)	2D	LR50	47	Yes	-	Yes	-
		Highest rate <50% effect on fecundity	1.36	No	-	No	-
T. pyri eggs (Bruhl, 2001)	2D	LR50 (egg hatch)	>30	Yes	-	Yes	-
		LR50 (overall mortality) c	2.42	No	-	No	-
C. septempunctata larvae (Zenz,2002)	2D	LR50 (pre-imaginal mortality of larvae)	>891	Yes	-	Yes	-
		NOER	891 (highest rate tested)	Yes	-	Yes	-
C. septempunctata eggs (Halsall, 2002)	2D	LR50 (egg hatch only)	>891	Yes	-	Yes	-
		LR50 (overall pre-imaginal mortality including egg hatch)	>891	Yes	-	Yes	-
Phytoseiulus persimilis protonymphs (Bargen, 2002a)	2D	LR50	7.69	Yes	-	No	-
		Highest rate <50% effect on fecundity	13.58	Yes	-	Yes	-
P. persimilis eggs (Bargen, 2002c)	2D	LR50 (egg hatch only)	>450	Yes	-	Yes	-
		LR50 (post-hatch pre-imaginal mortality)	30.49	Yes	-	Yes	-

[a] In the case of *C. septempunctata*, in accordance with test guidelines the reproductive performance of treatment groups is compared against historical data in a semi-quantitative manner, rather than detecting effects 50% different form the control.
[b] In cases in which the toxicity value is based on the highest rate tested (i.e. > values) and this is below the PER value, the real toxicity endpoint resulting in 50% effects may or may not be above the PER value. However, insufficiently high rates have been tested to determine this.
[c] LR_{50} (overall mortality) includes deaths during egg hatch, and dead and escaped mites during the pre-imaginal development of hatched mites.
[d] Off-field PER including vegetation dilution factor of 10
[e] Off-field PER not including vegetation distribution factor of 10

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Higher tier extended laboratory field-aged residue data with *T. pyri* with simulated off-field PER values following application of TRIGARD® 75 WP (A-6808 A)

Species	Drift scenario scenario					Summary of results
	Crop	Overall 90th %ile drift rate [c]	Vegetation distribution factor [d]	Uncertainty factor [e]	Resulting drift rate at each application	
T. pyri protonymphs	Lettuce [a]	2.01% for 3 applications to vegetables < 50 cm tall at 1 m from crop	10	5	3 x 3.015 g a.s./ha	No unacceptable risk (i.e. < 50% effects) to non-target arthropods in off field situations, even when organisms are exposed just after the last of the three applications.
	Tomato [b]	6.71% for 4 applications to vegetables > 50 cm tall at 3 m from crop	10	5	4 x 10.065 g a.s./ha	May have transient effect on some non-target arthropods (based on data with the representative species *T. pyri*). However, soon after the last application (14 days) residues are not expected to pose an unacceptable risk (<50% effects) to non-target arthropods in off field situations

[a] field rate is 3 x 300 g a.s./ha, 7-day interval
[b] field rate is 4 x 300 g a.s./ha, 7-day interval
[c] drift values as recommended in ESCORT 2
[d] Before each of the applications on the whole bean plants the leaves were fixed in an approximate horizontal position using a rod system. This resulted in an application of the test item with a track sprayer to a two dimensional intact leaf. Thus since the mites were exposed to these excised leaves the application scenario was 2D, even though applied to whole plants. Therefore it is considered appropriate to include the vegetation distribution factor as recommended by ESCORT 2
[e] uncertainty factor of 5 included to cover extrapolation to other off-field non-target arthropods (as recommended by ESCORT 2)

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Effects on earthworms, other soil macro-organisms (Annex IIA, points 8.4 and 8.5, Annex IIIA, points 10.6)

Acute toxicity	Technical 14-day LD_{50} > 1000 mg a.s./kg CGA 235129 (metabolite of cyromazine) 14-day LC_{50} >1000 mg/kg
Chronic and reproductive toxicity	Technical 56-d NOEC 333 mg a.s./kg soil CGA 235129 56-d NOER 1875 g/ha (NOEC 2.50 mg/kg) [a]
Field studies A litter bag test was conducted with the metabolite CGA 235129 on the decomposition of straw under field conditions. The target concentration was 218 µg CGA 235129 /kg soil. The test item did not have a significant adverse effect on organic matter decomposition.	

[a] Chronic metabolite endpoint in terms of NOEC calculated from NOER used in the study assuming 5 cm soil depth and soil bulk density of 1.5 g/cm^3.

Toxicity/exposure ratios for earthworms (Annex IIIA, point 10.6)

Risk to earthworms following application of TRIGARD® 75 WP (A-6808 A) in lettuce and tomato

Test substance	Use pattern [a]	Test type	Endpoint	PEC max (mg/kg)	TER	Annex VI trigger
Cyromazine	Tomato	Acute	14-day LD_{50} > 1000 mg a.s./kg	0.706	>1416	<10
CGA 235129	Tomato	Acute	14-day LC_{50} > 1000 mg/kg	0.441	>2267	<10
Cyromazine	Tomato	Chronic	56-d NOEC 333 mg a.s./kg	0.706	472	<5
CGA 235129	Tomato	Chronic	56-d NOEC 2.50 mg/kg	0.441	5.6	<5

[a] The field tomato scenario of 4 x 300 g a.s./ha with a 7 day spray interval, is the worst-case compared to the field lettuce scenario of 3 x 300 g a.s./ha with a 7 day spray interval and is therefore the only value presented

Risk to other soil macro-organisms following application of TRIGARD® 75 WP (A-6808 A) in lettuce and tomato

Test substance	Application schedule	PEC max (mg/kg)	28-day NOEC [a]	TER collembola	Annex VI trigger
TRIGARD® 75 WP	Tomato (4 x 300 g a.s./ha)	0.706	9.6 mg/kg	13.6	<5
	Lettuce (3 x 300 g a.s./ha)	0.552	9.6 mg/kg	17.4	<5

[a] calculated from the NOEC of the study with TRIGARD® 75 WP (A-6808 A) assuming a nominal 75% cyromazine content

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Effects on soil micro-organisms (Annex IIA, point 8.5, Annex IIIA, point 10.7)

Risk to soil micro-organsisms following application of TRIGARD® 75 WP (A-6808 A) in lettuce and tomato

Test substance	Exposure period	Parameters observed	Endpoint	PECs [a] (µg/kg)	Safety factor of NOEC above PECs
Cyromazine	28 days	Microbial soil respiration & nitrification	NOEC 100 mg/kg	706	141
CGA 235129	28 days	Carbon mineralisation & nitrification	NOEC 6.33 mg/kg NOEC 6.33 mg/kg	441	14.4

[a] The field tomato scenario of 4 x 300 g a.s./ha with a 7 day spray interval, is the worst-case compared to the field lettuce scenario
of 3 x 300 g a.s./ha with a 7 day spray interval and is therefore the only value presented

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Assessment of Potential for Effects on Other Non-target Organisms (Flora and Fauna) (Annex IIA, point 8.6, Annex IIIA, point 10.8).

Risk of TRIGARD® 75 WP (A-6808 A) to non-target plants at a 1 m distance from a lettuce crop and 3 m distance from a tomato crop (> 50 cm high)

Crop	Seedling emergence ED_{50} [a]	Worst-case PER (off-field)	TER Non-target plants
Tomato	> 300 g a.s./ha	26.17	> 11
Lettuce	> 300 g a.s./ha	7.84	> 38

[a] actually the highest rate at which < 50% effects on vegetative vigour were observed

Effects on biological methods for sewage treatment (Annex IIA, point 8.7)

Test type/organism	endpoint
Activated sludge	Cyromazine (as): EC_{50} > 100 mg as/Kg

Ecotoxicologically relevant metabolites

Environmental occurring metabolite ecotoxicologically relevant.	Soil: melamine (CGA 235129) Surface Water: melamine (CGA 235129) Sediment: -

Points pertinent to the classification and proposed labelling with regard to ecotoxicological data

None

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

APPENDIX 2 – ABBREVIATIONS USED IN THE LIST OF ENDPOINTS

ADI	acceptable daily intake
AF	assessment factor
AOEL	acceptable operator exposure level
AR	applied radioactivity
ARfD	acute reference dose
a.s.	active substance
AV	avoidance factor
BCF	bioconcentration factor
bw	body weight
CA	Chemical Abstract
CAS	Chemical Abstract Service
CIPAC	Collaborative International Pesticide Analytical Council Limited
d	day
DAR	draft assessment report
DM	dry matter
DT_{50}	period required for 50 percent dissipation (define method of estimation)
DT_{90}	period required for 90 percent dissipation (define method of estimation)
dw	dry weight
ε	decadic molar extinction coefficient
EC_{50}	effective concentration
EbC_{50}	effective concentration (biomass)
ErC_{50}	effective concentration (growth rate)
EEC	European Economic Community
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINKS	European List of New Chemical Substances
EMDI	estimated maximum daily intake
ER50	emergence rate, median
EU	European Union
FAO	Food and Agriculture Organisation of the United Nations
FIR	food intake rate
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
f(twa)	Time weighted average factor
g	gram
GAP	good agricultural practice
GCPF	Global Crop Protection Federation (formerly known as GIFAP)

Appendix 2 – abbreviations used in the list of endpoints

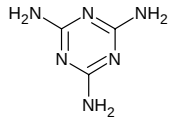
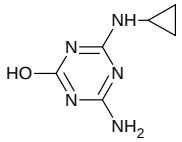
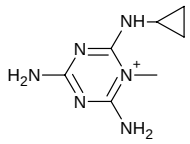
GS	growth stage
h	hour(s)
ha	hectare
hL	hectolitre
HPLC	high pressure liquid chromatography or high performance liquid chromatography
HQ	hazard quotient
IGR	insect growth regulator
ISO	International Organisation for Standardisation
IUPAC	International Union of Pure and Applied Chemistry
K_{oc}	organic carbon adsorption coefficient
kg	kilogram
L	litre
LC	liquid chromatography
LC-MS	liquid chromatography-mass spectrometry
LC-MS-MS	liquid chromatography with tandem mass spectrometry
LC_{50}	lethal concentration, median
LD_{50}	lethal dose, median; dosis letalis media
LOAEC	lowest observable adverse effect concentration
LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOQ	limit of quantification (determination)
m	metre
MAF	multiple application factor
µg	microgram
mg	milligram
ml	millilitre
mN	milli-Newton
MRL	maximum residue limit or level
MS	mass spectrometry
NESTI	national estimated short term intake
NIR	near-infrared-(spectroscopy)
ng	nanogram
nm	nanometer
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level

Appendix 2 – abbreviations used in the list of endpoints

PD	proportion of different food types
PEC	predicted environmental concentration
PEC_A	predicted environmental concentration in air
PEC_S	predicted environmental concentration in soil
PEC_{SW}	predicted environmental concentration in surface water
PEC_{SED}	predicted environmental concentration in sediment
PEC_{GW}	predicted environmental concentration in ground water
pH	pH-value
PHI	pre-harvest interval
pK_a	negative logarithm (to the base 10) of the dissociation constant
P_{OW}	partition coefficient between n-octanol and water
PPE	personal protective equipment
ppm	parts per million (10^{-6})
ppp	plant protection product
PT	proportion of diet obtained in the treated area
r^2	coefficient of determination
RMS	rapporteur member state
RPE	respiratory protective equipment
RUD	residue per unit dose
SD	standard deviation
SSD	species sensitivity distribution
STMR	supervised trials median residue
TER	toxicity exposure ratio
TER_A	toxicity exposure ratio for acute exposure
TER_{ST}	toxicity exposure ratio following repeated (short-term) exposure
TER_{LT}	toxicity exposure ratio following chronic (long-term) exposure
TMDI	theoretical maximum daily intake
TWA	time weighted average
UV	ultraviolet
WHO	World Health Organisation
WG	water dispersible granule
yr	year

Appendix 3 – used compound code(s)

APPENDIX 3 – USED COMPOUND CODE(S)

Code/Trivial name	Chemical name	Structural formula
Melamine CGA 235129	1,3,5-triazine-2,4,6-triamine	
hydroxy-cyromazine	4-amino-6-(cyclopropylamino)-1,3,5-triazin-2-ol	
1-methyl cyromazine	2,4-diamino-6-(cyclopropylamino)-1-methyl-1,3,5-triazin-1-ium	
NOA 435343	*N*-(4,6-diamino-1,3,5-triazin-2-yl)alanine