CONCLUSION ON PESTICIDE PEER REVIEW

Conclusion on the peer review of the pesticide risk assessment of the active substance cyproconazole[1]

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SUMMARY

Cyproconazole is one of the 84 substances of the third stage part B of the review programme covered by Commission Regulation (EC) No 1490/2002[3], as amended by Commission Regulation (EC) No 1095/2007[4]. In accordance with the Regulation, at the request of the Commission of the European Communities (hereafter referred to as 'the Commission'), the EFSA organised a peer review of the initial evaluation, i.e. the Draft Assessment Report (DAR), provided by Ireland, being the designated rapporteur Member State (RMS). The peer review process was subsequently terminated following the applicant's decision, in accordance with Article 11e, to withdraw support for the inclusion of cyproconazole in Annex I to Council Directive 91/414/EEC.

Following the Commission Decision of 5 December 2008 (2008/934/EC)[5] concerning the non-inclusion of cyproconazole in Annex I to Council Directive 91/414/EEC and the withdrawal of authorisations for plant protection products containing that substance, the applicant Syngenta Crop Protection AG made a resubmission application for the inclusion of cyproconazole in Annex I in accordance with the provisions laid down in Chapter III of Commission Regulation (EC) No. 33/2008[6]. The resubmission dossier included further data in response to the issues identified in the DAR.

In accordance with Article 18 of Commission Regulation (EC) No. 33/2008, Ireland, being the designated RMS, submitted an evaluation of the additional data in the format of an Additional Report. The Additional Report was received by the EFSA on 12 February 2010.

In accordance with Article 19 of Commission Regulation (EC) No. 33/2008, the EFSA distributed the Additional Report to Member States and the applicant for comments on 15 February 2010. The EFSA collated and forwarded all comments received to the Commission on 31 March 2010.

In accordance with Article 20, following consideration of the Additional Report, the comments received, and where necessary the DAR, the Commission requested the EFSA conduct a focused peer review in the areas of mammalian toxicology, environmental fate and behaviour and ecotoxicology, and deliver its conclusions on cyproconazole.

1 On request from the European Commission, Question No EFSA-Q-2010-00824, issued on 8 November 2010.
2 Correspondence: praper@efsa.europa.eu
3 OJ L224, 21.08.2002, p.25
4 OJ L 246, 21.9.2007, p. 19
5 OJ L 333, 11.12.2008, p.11
6 OJ L 15, 18.01.2008, p.5
Suggested citation: European Food Safety Authority; Conclusion on the peer review of the pesticide risk assessment of the active substance cyproconazole. EFSA Journal 2010;8(11):1897. [73 pp.] doi:10.2903/j.efsa.2010.1897. Available online: www.efsa.europa.eu/efsajournal.htm

The conclusions laid down in this report were reached on the basis of the evaluation of the representative uses of cyproconazole as a fungicide on wheat, as proposed by the applicant. Full details of the representative uses can be found in Appendix A to this report.

The preferential metabolism/degradation of each enantiomer in animals, plants and the environment and the possible impact on the toxicity, the consumer risk assessment, worker exposure and the environment was not sufficiently investigated in the studies submitted in the dossier. Nevertheless, regarding the overall worker and consumer exposure, when considering the parent cyproconazole and the representative uses on wheat only, there is a sufficient margin of safety to cover the possible shift to a more toxic isomer. Data gaps are identified to address the impact of the enantiomeric composition of the substance in the environmental compartments.

No critical areas of concern are identified in the physical-chemical section; two data gaps are identified for methods of analysis.

A data gap is identified in the mammalian toxicology section to address the relevance of the impurities present in the technical specification. No critical areas of concern have been identified.

Data gaps are identified in the residue section to address the contribution of the residues of the Triazole Derivate Metabolites present in primary crops, processed products, rotational crops and ruminant matrices to the overall consumer exposure.

The fate and behaviour of cyproconazole was investigated in the different environmental compartments. Cyproconazole is medium to high persistent in soil and only two metabolites are formed at levels that require further consideration (1,2,4-triazol and triazole acetic acid (TAA)). Cyproconazole is expected to be very highly persistent in aquatic systems. For the representative uses assessed contamination of groundwater by cyproconazole or its metabolites above the limit of 0.1 µg/L is not expected. With the available data in the dossier the applicant demonstrated that no consistent preferential diastereomeric degradation is observed. However, no data were available to address the potential enantiomeric conversion or preferential degradation, therefore, a data gap has been identified.

The risk assessment to non-target organisms was conducted without taking into account the impact on the toxicity of the potential enantiomeric conversion or preferential degradation. Therefore a data gap is identified to further address this issue. In addition, a high long-term risk was assessed for herbivorous mammals and therefore a data gap has been identified. This has also been considered to be a critical area of concern. The risk was assessed as low for the other non-target organisms.

KEY WORDS

Cyproconazole, peer review, risk assessment, pesticide, fungicide

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BACKGROUND

Legislative framework

Commission Regulation (EC) No 1490/2002[7], as amended by Commission Regulation (EC) No 1095/2007[8] lays down the detailed rules for the implementation of the third stage of the work programme referred to in Article 8(2) of Council Directive 91/414/EEC. This regulates for the European Food Safety Authority (EFSA) the procedure for organising, upon request of the Commission of the European Communities (hereafter referred to as 'the Commission'), a peer review of the initial evaluation, i.e. the Draft Assessment Report (DAR), provided by the designated rapporteur Member State.

Commission Regulation (EC) No 33/2008[9] lays down the detailed rules for the application of Council Directive 91/414/EEC for a regular and accelerated procedure for the assessment of active substances which were part of the programme of work referred to in Article 8(2) of Council Directive 91/414/EEC but which were not included in Annex I. This regulates for the EFSA the procedure for organising the consultation of Member States and the applicant(s) for comments on the Additional Report provided by the designated RMS, and upon request of the Commission the organisation of a peer review and/or delivery of its conclusions on the active substance.

Peer review conducted in accordance with Commission Regulation (EC) No 1490/2002

Cyproconazole is one of the 84 substances of the third stage part B of the review programme covered by Commission Regulation (EC) No 1490/2002, as amended by Commission Regulation (EC) No 1095/2007. In accordance with the Regulation, at the request of the Commission, the EFSA organised a peer review of the DAR (Ireland, 2006) provided by the designated rapporteur Member State, Ireland, which was received by the EFSA on 2 May 2006.

The peer review was initiated on 11 September 2006 by dispatching the DAR to Member States and the applicant Syngenta Crop Protection AG for consultation and comments. In addition, the EFSA conducted a public consultation on the DAR. The comments received were collated by the EFSA and forwarded to the RMS for compilation and evaluation in the format of a Reporting Table.

The peer review process was subsequently terminated following the applicant's decision, in accordance with Article 11e, to withdraw support for the inclusion of cyproconazole in Annex I to Council Directive 91/414/EEC.

Peer review conducted in accordance with Commission Regulation (EC) No 33/2008

Following the Commission Decision of 5 December 2008 (2008/934/EC)[10] concerning the non-inclusion of cyproconazole in Annex I to Council Directive 91/414/EEC and the withdrawal of authorisations for plant protection products containing that substance, the applicant Syngenta Crop Protection AG made a resubmission application for the inclusion of cyproconazole in Annex I in accordance with the provisions laid down in Chapter III of Commission Regulation (EC) No. 33/2008. The resubmission dossier included further data in response to the issues identified in the DAR.

In accordance with Article 18, Ireland, being the designated RMS, submitted an evaluation of the additional data in the format of an Additional Report (Ireland, 2010a). The Additional Report was received by the EFSA on 12 February 2010.

In accordance with Article 19, the EFSA distributed the Additional Report to Member States and the applicant for comments on 15 February 2010. In addition, the EFSA conducted a public consultation

[7] OJ L224, 21.08.2002, p.25
[8] OJ L246, 21.9.2007, p.19
[9] OJ L 15, 18.01.2008, p.5
[10] OJ L 333, 11.12.2008, p.11

on the Additional Report. The EFSA collated and forwarded all comments received to the Commission on 31 March 2010. At the same time, the collated comments were forwarded to the RMS for compilation in the format of a Reporting Table. The applicant was invited to respond to the comments in column 3 of the Reporting Table. The comments and the applicant's response were evaluated by the RMS in column 3.

In accordance with Article 20, following consideration of the Additional Report, the comments received, and where necessary the DAR, the Commission decided to further consult the EFSA. By written request, received by the EFSA on 3 May 2010, the Commission requested the EFSA to arrange a consultation with Member State experts as appropriate and deliver its conclusions on cyproconazole within 6 months of the date of receipt of the request, subject to an extension of a maximum of 90 days where further information were required to be submitted by the applicant in accordance with Article 20(2).

The scope of the peer review and the necessity for additional information, not concerning new studies, to be submitted by the applicant in accordance with Article 20(2), was considered in a telephone conference between the EFSA, the RMS, and the Commission on 29 April 2010; the applicant was also invited to give its view on the need for additional information. On the basis of the comments received, the applicant's response to the comments, and the RMS' subsequent evaluation thereof, it was concluded that the EFSA should organise a consultation with Member State experts in the areas of mammalian toxicology, environmental fate and behaviour and ecotoxicology, and that further information should be requested from the applicant in the areas of identity, physical-chemical properties, residues, environmental fate and behaviour and ecotoxicology.

The outcome of the telephone conference, together with EFSA's further consideration of the comments is reflected in the conclusions set out in column 4 of the Reporting Table. All points that were identified as unresolved at the end of the comment evaluation phase and which required further consideration, including those issues to be considered in consultation with Member State experts, and the additional information to be submitted by the applicant, were compiled by the EFSA in the format of an Evaluation Table.

The conclusions arising from the consideration by the EFSA, and as appropriate by the RMS, of the points identified in the Evaluation Table, together with the outcome of the expert discussions where these took place, were reported in the final column of the Evaluation Table.

A final consultation on the conclusions arising from the peer review of the risk assessment took place with Member States via a written procedure in October 2010.

This conclusion report summarises the outcome of the peer review of the risk assessment on the active substance and the representative formulation evaluated on the basis of the representative uses as a fungicide on wheat, as proposed by the applicant. A list of the relevant end points for the active substance as well as the formulation is provided in Appendix A. In addition, a key supporting document to this conclusion is the Peer Review Report, which is a compilation of the documentation developed to evaluate and address all issues raised in the peer review, from the initial commenting phase to the conclusion. The Peer Review Report (EFSA, 2010) comprises the following documents:

- the comments received,
- the Reporting Table (revision 1-1; 4 May 2010),
- the Evaluation Table (28 October 2010),
- the report(s) of the scientific consultation with Member State experts (where relevant).

Given the importance of the DAR and the Additional Report including its addendum (compiled version of September 2010 containing all individually submitted addenda) (Ireland, 2010b) and the

Peer Review Report, both documents are considered respectively as background documents A and B to this conclusion.

THE ACTIVE SUBSTANCE AND THE FORMULATED PRODUCT

Cyproconazole is the ISO common name for (2*RS*,3*RS*;2*RS*,3*SR*)-2-(4-chlorophenyl)-3-cyclopropyl-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (IUPAC).

The representative formulated product for the evaluation was 'Alto 100 SL', a soluble concentrate (SL), containing 100 g/L cyproconazole.

The representative uses evaluated comprise outdoor foliar spraying against fungi in wheat. Full details of the representative uses can be found in the list of end points in Appendix A.

CONCLUSIONS OF THE EVALUATION

It must be noted that cyproconazole is a mixture of two diastereoisomers, but the possible preferential metabolism/degradation of each enantiomer in animals, plants and the environment was not sufficiently investigated in the studies submitted in the dossier. Nevertheless, regarding the overall worker and consumer exposure, when considering the parent cyproconazole and the representative uses on wheat only, there is a sufficient margin of safety to cover the possible shift to a more toxic isomer. However, data gaps were identified to address the impact of the enantiomeric composition of the substance in the environmental compartments.

Moreover, the analytical methods used in the studies reported through all sections were not stereo-selective, and all values mentioned as "cyproconazole" have to be considered as "sum of isomers".

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

The minimum purity of the active substance as manufactured should not be less than 940 g/kg. Cyproconazole consists of two diastereoisomers. It is not concluded if there are any relevant impurities (see section 2).

The main data regarding the identity of cyproconazole and its physical and chemical properties are given in Appendix A.

The compounds in the residue definition for plants and animals can be determined with a multi-residue method (DFG S19). A method of analysis for soil was identified as a data gap. The method for water is GC-MSD and for air LC-MS/MS. As the active substance is proposed for classification as toxic, a data gap has been identified for a method of analysis for body fluids and tissues.

2. Mammalian toxicity

Cyproconazole was discussed at the PRAPeR 81 experts' meeting (August - September 2010). The studies performed with the major metabolite 1,2,4-triazole were discussed by Member State experts at the PRAPeR 14 experts' meeting (January 2007).

The new technical specification provided in the addendum to the DAR in July 2010 (Ireland, 2010b) is supported by the batches used in the toxicological tests. The relevance of most of the impurities has not been addressed and therefore a data gap has been identified.

Cyproconazole is rapidly absorbed and widely distributed in the body, extensively metabolised, and rapidly eliminated. It has no potential for accumulation. Based on acute oral toxicity in rats, mice and rabbits, classification with R22 "Harmful if swallowed" is proposed. It is of low acute toxicity by the dermal and inhalation routes; no skin or eye irritation, and no skin sensitisation were observed. The main target organ of cyproconazole is the liver upon short-term to long-term exposure. The relevant oral short-term NOAEL is 3.2 mg/kg bw/day observed in the 1-year dog study. A NOAEL of 1.84 mg/kg bw/day was derived based on bodyweight and liver effects from an 18-month study in mice; similar effects were found in a 2-year chronic study in rats, showing a NOAEL of 2.22 mg/kg bw/day. Liver adenomas and carcinomas were observed in the mouse study; despite the mechanistic studies provided, their relevance for humans could not be ruled out and therefore classification as Carc. Cat. 3

R40 "Limited evidence of a carcinogenic effect" is proposed. Cyproconazole is considered unlikely to be genotoxic. In a two-generation study the parental and offspring NOAEL was set at 1.4 and 1.7 mg/kg bw/day in males and females, respectively, based on liver effects in males and litter loss in females; when deriving the reference values, the NOAEL in males was superseded by the long-term/short-term NOAELs for hepatotoxicity seen around 2 mg/kg bw/day. No effects were observed on reproductive performance or fertility. Regarding developmental toxicity studies, the maternal and developmental NOAELs in rabbits were set at 10 mg/kg bw/day and 2 mg/kg bw/day respectively, based on findings of reduced bodyweight in dams and malformations. Based on the occurrence of malformations in both rats and rabbits at doses not causing overt signs of maternal toxicity, classification as T "toxic", Repr. Cat. 2, R61 "May cause harm to the unborn child" is proposed.

Studies were submitted on the metabolites triazole alanine (TA), M21/21a and M36(Z2). An acceptable daily intake (ADI) of 0.1 mg/kg bw/day and an acute reference dose (ARfD) of 0.1 mg/kg bw are derived for the triazole alanine (TA) metabolite, based on the developmental study in rat and applying a safety factor of 1000 to account for developmental effects seen at doses showing no overt signs of maternal toxicity. The reference values of the parent compound are applicable to the metabolite M36(Z2), as well the metabolites M9/M14 (pair of diastereomers) and M38/Z1.

The ADI of cyproconazole is set at 0.02 mg/kg bw/day, based on the NOAEL from the multigeneration study in female rats and from the long-term studies in rats and mice, applying a safety factor (SF) of 100. The acceptable operator exposure level (AOEL) is 0.02 mg/kg bw/day and the ARfD is 0.02 mg/kg bw, derived from the multigeneration study in female rats and the developmental toxicity study in rabbits, with a SF of 100 applied, and no correction for oral absorption required regarding the AOEL.

The estimated operator exposure to 'Alto 100 SL' is below the AOEL without the use of personal protective equipment (PPE) according to the German model. The estimated worker exposure is below the AOEL without the use of PPE. It is noted that the isomer ratio in residues to which workers are exposed and the relative toxicity of each isomer is unknown. However, considering a worst-case scenario where all the residues to which workers are exposed consist of the most toxic isomer, it is assumed that worker exposure would still remain below the AOEL. Estimated bystander exposure is below the AOEL.

3. Residues

The metabolism in plants has been investigated on cereals (wheat), sugar beet (root vegetables), apples and grapes (fruit crops), peanuts (pulses/oilseeds), and coffee, using foliar applications and ^{14}C-cyproconazole, labelled either on the phenyl ring, the triazole moiety, or the alpha carbon position. The triazole labelling was only investigated in cereals, root crops and coffee. In cereals, the parent cyproconazole was recovered as the major compound of the total radioactive residues in straw (36 – 51 % TRR), while in grain the residues were mainly composed of the triazole alanine (TA) metabolite, accounting for up to 77 % of the TRR. Based on the available data, the residue definition for monitoring was limited to the parent cyproconazole (sum of isomers) only. For risk assessment, and considering the significant presence of one Triazole Derivative Metabolite (TDM) in grains, two separate residue definitions were proposed: 1) Parent cyproconazole (sum of isomers) and 2) TDM. This second residue definition is provisional pending finalisation of a global and harmonised approach for all the active substances of the triazole chemical group. In the future, if additional uses are supported, triazole-labelled studies on fruit crops and pulses/oilseeds should be required in order to extend the residue definitions to all categories of crops.

A sufficient number of supervised residue trials have been reported to propose MRL for wheat grain. The storage stability study demonstrated that cyproconazole residues were stable in wheat grain and forage up to 39 months, but it must be highlighted that the storage period of the samples from the supervised trials was not specified. In addition, further residue trials to determine the residue levels of TDM in wheat grain are required to comply with the residue definition for risk assessment proposed for cereals only.

A rotational crop study conducted with an alpha carbon position labelling only showed a metabolism similar to that depicted in the primary crops, where the main detectable residue was parent cyproconazole. The field trials indicated that significant residues (0.097 mg/kg) were only found in leafy crops rotated with wheat at very long plant back intervals (430 days). However, no data were available at shorter plant back intervals. Data to address the magnitude of the residues in rotated leafy crops at the representative plant back interval (120 days) are required, therefore a data gap has been identified. EFSA is of the opinion that it would not be realistic to address the likely residues at a 30 day plant back interval, as no crop failure scenario is expected in view of the representative uses. In addition, no confined rotational crop metabolism study labelled on the triazole moiety was supplied, therefore a data gap was identified.

Cyproconazole is not degraded under standard processing conditions. No processing study was triggered since the residues in grains were below 0.05 mg/kg. Data to address the effect of standard processing conditions on TDM are required, and therefore a data gap has been identified. The magnitude of TDM in processed products may need to be addressed pending the outcome of the residue trials on TDM in grains.

The calculated livestock dietary intake triggered the investigation of the nature of the residues in ruminant matrices (> 0.1 mg/kg diet, DM basis), and metabolism studies on lactating goats and hens were provided. Based on the ruminant metabolism studies, the parent compound was considered as a valid indicator of the total residues, and the definition for enforcement was proposed as cyproconazole (sum of isomers) only. For risk assessment, the following residue definition was proposed: cyproconazole (sum of isomers) and the metabolites M36(Z2), M38(Z1) and M9/M14 (pair of diastereomers), expressed as cyproconazole. A cow feeding study was provided that showed that cyproconazole residue levels below the LOQ are expected in milk, kidney, meat and fat at the calculated dietary burden, except for liver. An MRL of 0.1 mg/kg was proposed for this matrix, and a conversion factor of 3 was derived from the metabolism data. No information was provided concerning the possible intake of TDM and their possible transfer to animal products, while TDM (triazole alanine (TA)) was shown to be the predominant compound of the residues in wheat grain. Further information on TDM in animal matrices (ruminant metabolism study labelled on the triazole ring and feeding studies addressing respectively the nature and the magnitude of TDM present in animal commodities) is required in order to propose a residue definition for risk assessment on TDM in animal products. A data gap was therefore identified. Metabolism studies on poultry were also provided, although the dietary intake was not triggered. The data confirmed a similar metabolic pathway of cyproconazole as in ruminants, although the metabolites M36(Z2) and M38(Z1) were not detected. No MRLs were proposed for poultry products.

No chronic and acute intake concern was identified using the EFSA PRIMo model and the proposed MRL for cyproconazole in wheat, and the MRLs for animal products (3 % of the ADI and 12 % of the ARfD). No concern was identified for the consumer exposure when including the contribution of the leafy crops rotated with wheat (leafy vegetables). It must be highlighted that the consumer risk assessment is limited respectively to the parent cyproconazole (sum of isomers) only for wheat grains and to the parent cyproconazole (sum of isomers) and the relevant non-TDM metabolites M36(Z2), M38(Z1) and M9/M14 (pair of diastereomers) for ruminant matrices, and has to be considered as provisional. The contribution of the TDM present in primary crops, in processed commodities, in ruminant matrices and in rotational crops to the overall consumer exposure has to be demonstrated. Although the preferential degradation/metabolism of each isomer in plants and animals and the subsequent impact on the consumer risk assessment was not addressed, when considering the parent cyproconazole and the representative uses on wheat only, there is a sufficient margin of safety to cover the possible shift to a more toxic isomer.

4. Environmental fate and behaviour

Cyproconazole was discussed at the PRAPeR 82 experts' meeting (September 2010). The studies performed with the major soil metabolite 1,2,4-triazole were discussed by Member State experts at the PRAPeR 12 experts' meeting (January 2007).

The route of degradation of cyproconazole in soil under dark aerobic conditions at 20 – 22 ºC was investigated in three studies with ^{14}C-triazole-labelled cyproconazole (one soil: pH 7.2), ^{14}C-benzyl-labelled cyproconazole (three soils: pH 4.3 – 7.0), and ^{14}C-phenyl-labelled cyproconazole (one soil: pH 7). In all these studies the degradation of cyproconazole was slow, and considerable amounts of radioactivity remained as unmodified cyproconazole at the end of the respective experiments. In the study performed with ^{14}C-triazole-labelled cyproconazole, the metabolite 1,2,4-triazole (max. 17.36 % AR after 140 days, end of the study) was identified as the only major metabolite in soil. Additionally, at the end of the study the metabolite triazole acetic acid (TAA) (max. 6.7 % AR after 140 days) reached levels above 5 % AR and therefore needs to be assessed for potential groundwater contamination. Mineralization of the triazole ring was negligible, and non-extracted radioactivity amounted to 16 % AR at the end of the study (140 days). In the studies performed with the ^{14}C-benzyl and the ^{14}C-phenyl-labelled cyproconazole no major metabolites were identified, and only very minor (< 3 % AR) polar fractions were observed as a consequence of cyproconazole degradation. Substantial mineralization was only observed in two of the experiments performed with cyproconazole ^{14}C labelled in the benzyl position. Non-extracted radioactivity amounted to 13- 23.9 % AR (after 112 days) and 20.8-21.5 % AR (after 140 days) in the experiments performed with the ^{14}C-benzyl and ^{14}C-phenyl-labelled cyproconazole, respectively. In the experiments with the ^{14}C-phenyl-labelled cyproconazole with slightly more harsh extraction steps it was demonstrated that about half of the non-extracted radioactivity was constituted of unmodified cyproconazole. Only slight variations were observed on the diastereomeric ratios during the experiments. These variations are not significant and consistent enough to consider that diastereomeric degradation occurs. However, enantiomeric ratios were not tested during these experiments. Therefore, a data gap was identified to address the impact of the enantiomeric composition of the substance in the environmental compartments.

The degradation of cyproconazole in soil under dark anaerobic conditions showed that cyproconazole is stable under anaerobic conditions. It may be considered that photolysis will not contribute to the environmental dissipation of cyproconazole. The persistence of cyproconazole in soil under dark aerobic conditions was investigated in the route studies and in two additional studies (pH 4.3 – 7.6). At concentrations equivalent to those of the representative uses, cyproconazole may be considered medium to high persistent in soil under dark aerobic conditions. The rate of degradation of the major soil metabolite 1,2,4-triazole under dark aerobic conditions at 20ºC was investigated in one study with three soils. Under these conditions 1,2,4-triazole was low to moderate persistent in soil. The end points from this study were agreed at the experts' meeting PRAPeR 12. The biphasic behaviour and low degradation observed from day 30 in one soil was attributed to the loss of soil biomass (PRAPeR 12). Also, normalization of the half-life values obtained in this study was agreed.

A number of field dissipation studies were submitted (1 in UK (4 sites), 5 in France, and 5 in Germany). However, major deficiencies were identified in some of the trials; the experts at PRAPeR 82 agreed which field trials may be considered reliable (see Appendix A). The kinetic end points have been updated in the resubmission dossier. For some of the field trials the data had to be fitted to DFOP kinetics in order to obtain reliable results. Residues of the major soil metabolite 1,2,4-triazole were not measured in any of the field studies. PEC soil were calculated for cyproconazole and its metabolites 1,2,4-triazole and triazole acetic acid (TAA) according to the representative uses, using worst-case field SFO half-life for cyproconazole, and worst-case laboratory half-life for 1,2,4-triazole and triazole acetic acid (TAA), and assuming the standard FOCUS GW interception factors. The potential for soil accumulation of cyproconazole was calculated using the worst-case field dissipation DFOP end points. Maximum peak concentration was reached after applications at the 12th year.

According to the adsorption / desorption batch equilibrium studies available cyproconazole was low to medium mobile. No obvious pH dependence is observed from the available data. For the metabolite 1,2,4-triazole the PRAPeR 12 meeting of experts agreed that this metabolite may be considered highly to very highly mobile, based on the results of four of the five soils tested. Results for one of the soils were disregarded as it was considered that it does not represent a normal agricultural soil. For the metabolite triazole acetic acid (TAA) the available data show that it may be considered very highly mobile in soil.

Hydrolysis of cyproconazole and its metabolite 1,2,4-triazole was investigated in sterile buffer aqueous solutions. In these experiments hydrolysis was negligible, and it is not considered to contribute to the environmental degradation of cyproconazole or its metabolite 1,2,4-triazole. No aqueous photolysis study is available. However, cyproconazole is expected to be stable to direct photolysis in water (at $\lambda > 290$ nm UV adsorption $\varepsilon < 10$ L/mol/cm). Cyproconazole is considered not readily biodegradable in the absence of a biodegradation study.

An aquatic dissipation study in two dark water/sediments at 20°C is available. Degradation in both systems was very slow (DT_{50} >> 1 year). The main dissipation process from the water phase is partition to sediment. Only minor metabolites were found (max. 4.5 % AR after 259 days). Mineralization was negligible, and unextractable radioactivity amounted to 3.8 – 10 % AR after 259 days. The ratio of the cyproconazole diastereoisomers did not change during the course of the study. However, enantiomeric ratios were not checked during these experiments. Therefore, a data gap was identified to address the impact of the enantiomeric composition of the substance in the environmental compartments. Degradation in the biological systems was comparable to the degradation observed in the sterilized systems. This may indicate a low contribution of biologically mediated degradation to the dissipation of cyproconazole. PEC_{SW} and PEC_{SED} were calculated for the representative uses up to FOCUS SW step 3 for cyproconazole, and up to FOCUS SW step 2 for the metabolites 1,2,4-triazole and triazole acetic acid (TAA) (FOCUS, 2001).

The potential groundwater contamination by cyproconazole and its soil metabolites 1,2,4-triazole and triazole acetic acid (TAA) was assessed using FOCUS GW PELMO 3.3.2 and PEARL 3.3.3 models and the corresponding scenarios for the representative uses assessed (FOCUS, 2000; EFSA, 2004)[11]. Annual average 80th percentile concentration at 1 m depth is not expected to exceed the limit of 0.1 µg/L for any of the uses and scenarios simulated.

Photochemical oxidative degradation of cyproconazole and its metabolite 1,2,4-triazole was estimated with the AOPWIN software. The photochemical half-life of cyproconazole in the atmosphere was determined to be around 1 day, and therefore it is not expected to persist in the atmosphere.

5. Ecotoxicology

The risk assessment to non-target organisms was conducted without taking into account the impact on the toxicity of the potential enantiomeric conversion or preferential degradation. Therefore a data gap is identified to further address this issue. For the time being, assuming the worst-case situation where all toxicity would be attributed to one isomer (i.e. by halving the toxicity end points), the risk to omnivorous birds would also be indicated as high (in addition to the long-term risk to herbivorous mammals identified as high in the current risk assessment); while the risk for the other non-target organisms would still be indicated as low. The need for mitigation measures to protect aquatic organisms might need to be extended to other scenarios, however low risk will still be indicated for more than half of them.

The first tier risk assessment for birds and mammals was carried out according to the guidance document (European Commission, 2002). The acute and short-term risk to herbivorous and insectivorous birds via dietary exposure was assessed as low at tier 1 for the representative uses. For the long-term risk assessment it was suggested to use the NOEL of 2.4 mg a.s./kg bw/day from a more recent long-term study with *Anas platyrhynchos*, instead of 1.4 mg a.s./kg bw/day from the older study. Member State experts (PRAPeR 80, September 2010) considered both studies as valid and consistent (i.e. in both studies NOEL was below the LOEL). However, the NOEL of 2.4 mg a.s./kg bw/day was agreed because it was considered more accurate than the NOEL of 1.4 mg a.s./kg bw/day. The long-term risk to herbivorous and insectivorous birds was assessed as high at tier 1 and would need further refinement. However, the experts noted that EFSA (2009) recommends using omnivorous

[11] Simulations utilised a Q10 of 2.2 and Walker Equation coefficient of 0.7

birds as generic focal species both for early and late applications. On this basis, the long-term risk to birds was assessed as low.

The acute risk to insectivorous mammals via dietary exposure was assessed as low at tier 1, but the acute risk to herbivorous mammals was assessed as high. However, the latter was further addressed by assuming that at the time of application of cyproconazole in early growth stage cereals there will only be one application, and therefore the estimated exposure taking into account two applications is likely overestimated. The long-term risk to herbivorous and insectivorous mammals was assessed as high at tier 1 for the representative uses, based on the NOAEL of 1.4 mg a.s./kg bw/day (males). As risk refinement, it was suggested to use the highest tested dose from the two-generation rat study (i.e. NOAEL of 120 ppm, corresponding to an average (F0/F1 and male/female) of 10.59 mg a.s./kg bw/day), instead of the NOAEL of 1.4 mg a.s./kg bw/day. It was considered that no effects on parental survival, food consumption, growth, or reproductive performance were observed at 120 ppm, and therefore it was considered as ecotoxicologically more relevant. However, Member State experts raised concerns regarding apparent effects of 7.6 % on mean postnatal loss. Due to these concerns, it was concluded that the lower dose of 1.7 mg a.s./kg bw/day (females) should be used as the NOAEL for risk assessment. This resulted in a TER of 5.3 for insectivorous mammals, indicating a low risk. However, for herbivorous mammals the risk remained high (TER = 0.27) even when it was estimated according to the EFSA (2009) guidance document (TER = 1.3). After the meeting, a refined long-term risk assessment was provided using a deposition factor of 0.1 from FOCUS (2000) and a foliar DT_{50} of 4.65 from residue trials on cereals (see Addendum dated September 2010, Ireland 2010b). However, the proposed deposition factor of 0.1 is related to a growth stage comparable to a BBCH > 90, while EFSA considers a deposition factor in the range of 0.3 - 0.5, as reported in FOCUS (2000), more appropriate for the representative uses (BBCH 31 - 65 and BBCH 31 - 69). In addition, a concern was also raised over the use of the residue dataset, particularly for the early growth stage. Therefore a data gap was identified to further address the long-term risk to herbivorous mammals.

The risk to earthworm- and fish-eating birds and mammals was assessed as low.

Cyproconazole is very toxic to aquatic organisms. The lowest end point driving the risk assessment is the 21-day NOEC of 0.023 mg/L for *D. magna* (agreed by PRAPeR 80 meeting). The risk to aquatic organisms was assessed as low at $FOCUS_{SW}$ step 1-2, with the exception of the chronic risk to invertebrates and the risk to aquatic plants (southern Europe). At $FOCUS_{SW}$ step 3 the risk to aquatic plants was assessed as low for all scenarios. At $FOCUS_{SW}$ step 3 the long-term risk to *D. magna* was assessed as low for the majority of the scenarios; the TERs were below the Annex VI trigger for the D1-ditch (TER =9.1) and D2-ditch (TER=7.3) scenarios. Risk refinement would be needed for aquatic organisms for these scenarios to quantitatively establish the risk reduction (i.e. mitigation measures). The risk from the relevant metabolite 1,2,4-triazole was assessed as low for aquatic organisms for the representative uses.

Cyproconazole belongs to the triazole group of ergosterol-biosynthesis inhibitors, and thus might cause endocrine disrupting effects. However, the end points from a fish life cycle test and a short-term screening assay study were considered to be sufficient to address such concerns.

The off-field HQ values at tier 1 for both, *T. pyri* and *A. rhopalosiphi* were below the trigger of 2, indicating a low risk for the representative uses on wheat. The in-field risk to these two standard non-target arthropod species was addressed based on higher tier aged-residue studies.

The acute and chronic risk for earthworms and other soil-macro-organisms was assessed as low on the basis of toxicity end points for *Eisenia foetida* and *Folsomia candida*, and PECsoil plateau. Also, the risk for the metabolite 1,2,4-triazole was assessed as low.

The risk to bees, soil micro-organisms, non-target terrestrial plants, and the function of waste water treatment plants was assessed as low for the representative uses.

6. Overview of the risk assessment of compounds listed in residue definitions triggering assessment of effects data for the environmental compartments

6.1. Soil

Compound (name and/or code)	Persistence	Ecotoxicology
cyproconazole	Medium to high (DT_{50} = 72.4 – 347 d)	The overall risk to earthworms and non-target soil macro- and micro-organisms was assessed as low.
1,2,4-triazole	Low to moderate (DT_{50} = 6.3 – 12.3 d)	The risk to earthworms and non-target soil macro- and micro-organisms was assessed as low.

6.2. 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
cyproconazole	low to medium mobile (K_{Foc} = 173 – 711 mL/g)	FOCUS GW: No	yes	yes	Cyproconazole is very toxic to aquatic organisms in surface water. The lowest end point driving the risk assessment is the 21-d NOEC of 0.023 mg a.s./L for *D. magna* (the regulatory concentration with an assessment factor of 10 is 0.0023mg a.s./L).

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
1,2,4-triazole	high to very high mobile (K_{Foc} = 43 – 120 mL/g)	FOCUS GW: No	No data, data not needed	Yes, metabolite classified as R63 "Possible risk of harm to the unborn child"[12].	No
triazole acetic acid (TAA)	very high mobile (K_{doc} = 1.04 - 21 mL/g)	FOCUS GW: No	No data, data not needed	No data, data not needed	No

6.3. Surface water and sediment

Compound (name and/or code)	Ecotoxicology
cyproconazole	Cyproconazole is very toxic to aquatic organisms. The lowest end point driving the risk assessment is the 21-d NOEC of 0.023 mg a.s./L for *D. magna* (the regulatory concentration with an assessment factor of 10 is 0.0023 mg a.s./L). The risk was assessed as low at $FOCUS_{sw}$ step1-3, except for the D1-ditch and D2-ditch scenarios.
1,2,4-triazole	The risk for aquatic organisms was assessed as low.

6.4. Air

Compound (name and/or code)	Toxicology
cyproconazole	Inhalation rat LC_{50} > 5.465 mg/L air/4h, no classification proposed.

[12] according to Annex VI of Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. OJ L 353, 31.12.2008, p. 1

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

- Method of analysis for soil (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see section 1).
- Method of analysis for body fluids and tissues (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see section 1).
- Toxicological information allowing the assessment of the relevance of the impurities present in the technical specification (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see section 2).
- Additional residue trials to determine the level of Triazole Derivative Metabolite (TDM) residues in wheat grain (relevant for the representative uses evaluated; submission date proposed by the applicant: unknown, see section 3).
- Data to address the magnitude of cyproconazole residues in rotational leafy crops at 120 day plant back intervals (relevant for the representative uses evaluated; submission date proposed by the applicant: unknown, see section 3).
- A confined rotational crop metabolism study labelled on the triazole moiety (relevant for the representative uses evaluated; submission date proposed by the applicant: unknown, see section 3).
- Data to address the nature of TDM in processed products under standard hydrolytic conditions (relevant for the representative uses evaluated; submission date proposed by the applicant: unknown, see section 3).
- Data to address the magnitude of TDM in processed products unless residue trial data on TDM in wheat grain indicate these studies are not triggered (relevant for the representative uses evaluated; submission date proposed by the applicant: unknown, see section 3).
- Ruminant metabolism study labelled on the triazole ring and feeding studies addressing respectively the nature and the magnitude of TDM present in animal commodities (relevant for the representative uses evaluated; submission date proposed by the applicant: unknown, see section 3).
- Cyproconazole consists of two diastereoisomers. With the available data in the dossier the applicant demonstrated that no consistent preferential diastereomeric degradation is observed. However, no data were available to address the potential enantiomeric conversion or preferential enantiomeric degradation, and therefore this needs to be addressed (relevant for all representative uses evaluated; data gap identified by EFSA, submission date proposed by the applicant: some published scientific information on the enantio-selective degradation in soil was considered by the RMS in the addendum (July 2010; Ireland, 2010b), but could not be taken into consideration in the peer review in view of the restrictions under Commission Regulation (EC) No. 33/2008; see section 4).
- The impact on the toxicity of the potential enantiomeric conversion or preferential degradation on non-target organisms needs to be addressed (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see section 5).
- The long-term risk to herbivorous mammals needs to be further addressed (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see section 5).

PARTICULAR CONDITIONS PROPOSED TO BE TAKEN INTO ACCOUNT TO MANAGE THE RISK(S) IDENTIFIED

- A high long-term risk for *D. magna* in the scenarios D1-ditch and D2-ditch for the representative uses was indicated (TERs marginally below the Annex VI trigger). Mitigation measures should be considered for these scenarios.

ISSUES THAT COULD NOT BE FINALISED

- The possible impact on the ecotoxicity and the environment of the potential enantio-selective biologically mediated metabolism/degradation or transformation in the environment needs to be addressed in order to address the potential uncertainties in the present risk assessment for non-target organisms.

- The relevance of the impurities present in the technical specification was not addressed.

- The contribution of the residues of the Triazole Derivate Metabolites present in primary crops, processed products, rotational crops and ruminant matrices to the overall consumer exposure was not addressed.

CRITICAL AREAS OF CONCERN

- A high long-term risk was indicated for herbivorous mammals for the representative uses on wheat, based on the data available.

REFERENCES

EFSA (European Food Safety Authority), 2004. Opinion of the Scientific Panel on Plant Health, Plant Protection Products and their Residues on a request of EFSA related to FOCUS groundwater models comparability and the consistency of this risk assessment of groundwater contamination. The EFSA Journal (2004) 93, 1-20.

EFSA (European Food Safety Authority), 2009. Guidance Document on Risk Assessment for Birds & Mammals. EFSA Journal 2009; 7(12):1438.

EFSA (European Food Safety Authority), 2010. Peer Review Report to the conclusion regarding the peer review of the pesticide risk assessment of the active substance cyproconazole.

European Commission, 2002. Guidance Document on Risk Assessment for Birds and Mammals Under Council Directive 91/414/EEC. SANCO/4145/2000.

FOCUS (2000). "FOCUS Groundwater Scenarios in the EU review of active substances". Report of the FOCUS Groundwater Scenarios Workgroup, EC Document Reference SANCO/321/2000-rev.2. 202 pp, as updated by the Generic Guidance for FOCUS groundwater scenarios, version 1.1 dated April 2002.

FOCUS (2001). "FOCUS Surface Water Scenarios in the EU Evaluation Process under 91/414/EEC". Report of the FOCUS Working Group on Surface Water Scenarios, EC Document Reference SANCO/4802/2001-rev.2. 245 pp.

Ireland, 2006. Draft Assessment Report (DAR) on the active substance cyproconazole prepared by the rapporteur Member State Ireland in the framework of Directive 91/414/EEC, February 2006.

Ireland, 2010a. Additional Report to the Draft Assessment Report on the active substance cyproconazole prepared by the rapporteur Member State Ireland in the framework of Commission Regulation (EC) No 33/2008, February 2010.

Ireland, 2010b. Final Addendum to the Draft Assessment Report and Additional Report on cyproconazole, compiled by EFSA, September 2010.

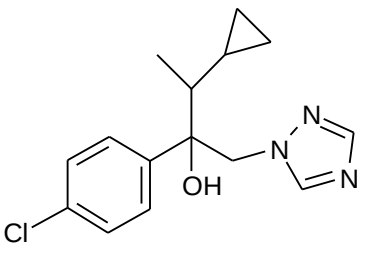
APPENDICES

APPENDIX A – LIST OF END POINTS FOR THE ACTIVE SUBSTANCE AND THE REPRESENTATIVE FORMULATION

Identity, Physical and Chemical Properties, Details of Uses

Common name (ISO)	Cyproconazole
Function	Fungicide
Rapporteur Member State	Ireland

Identity (Annex IIA, point 1)

Chemical name (IUPAC) ‡	(2RS,3RS;2RS,3SR)-2-(4-chlorophenyl)-3-cyclopropyl-1-(1H-1,2,4-triazol-1-yl)butan-2-ol
Chemical name (CA) ‡	alpha-(4-chlorophenyl)-alpha-(1-cyclopropyl-ethyl)-1H-1, 2, 4-triazole-1-ethanol
CIPAC No ‡	600
CAS No ‡	94361-06-5
EC No (EINECS or ELINCS) ‡	Not available
FAO Specification (including year of publication) ‡	No FAO Specification available
Minimum purity of the active substance as manufactured ‡	940 g/kg Cyproconazole has two diastereomers. (Diastereoisomer A: 430 – 500 g/kg, Diastereoisomer B: 470 – 550 g/kg). Diastereomer A: enantiomeric pair, where the 3-hydroxy group and the 2-hydrogen are located on the same side (2S, 3S and 2R, 3R). Diastereomer B: enantiomeric pair, where the 3-hydroxy group and 2-hydrogens are located on opposite sides (2R, 3S and 2S, 3R).
Identity of relevant impurities (of toxicological, ecotoxicological and/or environmental concern) in the active substance as manufactured	Open
Molecular formula ‡	$C_{15}H_{18}ClN_3O$
Molecular mass ‡	291.8 g/mol
Structural formula ‡	

Physical-chemical properties (Annex IIA, point 2)

Melting point (state purity) ‡	106.2 - 106.9°C ± 0.4°C (99.7%)
Boiling point (state purity) ‡	Due to the thermal decomposition of the test substance it was not possible to determine the boiling point under normal pressure (99.7%)
Temperature of decomposition (state purity)	299 °C (99.7%)
Appearance (state purity) ‡	White, fine powder (99.7%)
Vapour pressure (state temperature, state purity) ‡	2.6 x 10^{-5} Pa at 25 °C (99.7%)
Henry's law constant ‡	5.0 x 10^{-5} Pa m^3 mol^{-1}
Solubility in water (state temperature, state purity and pH) ‡	93 mg/L at 22 °C (pH 7.1) (98.9%)
Solubility in organic solvents ‡ (state temperature, state purity)	Solubility (g/L) at 25 °C (96.6%): Acetone: 360 Dichloromethane: 430 Ethyl acetate: 240 Hexane 1.3 Methanol 410 Octanol: 100 Toluene: 100
Surface tension ‡ (state concentration and temperature, state purity)	65.2 mN/m at 20 °C (90 % saturated solution) (96.6%)
Partition co-efficient ‡ (state temperature, pH and purity)	log $P_{O/W}$ = 3.09 at 25 °C (pH 7.2) (99.7%)
Dissociation constant (state purity) ‡	pKa_1 = Cyproconazole will not dissociate in water at environmental pH, therefore no pKa value has been calculated. (98.9%)
UV/VIS absorption (max.) incl. ε ‡ (state purity, pH)	pH 5 solution (99.7 %): λ_{max} 295 (nm); ε = 0.4 ($L.mol^{-1}.cm^{-1}$) pH 7 solution (99.7 %): λ_{max} 295 (nm); ε = 0.7 ($L.mol^{-1}.cm^{-1}$) pH 9 solution (99.7 %): λ_{max} 295 (nm); ε = 0.8 ($L.mol^{-1}.cm^{-1}$)
Flammability ‡ (state purity)	Non-flammable (95%)
Explosive properties ‡ (state purity)	Non-explosive (95.7%)
Oxidising properties ‡ (state purity)	Non-oxidising (95%)

Summary of representative uses evaluated for cyproconazole*

Crop and/ or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Preparation		Application				Application rate per treatment			PHI (days) (m)	Remarks
					Type (d-f)	Conc. of as (i)	method kind (f-h)	growth stage & season (j)	number min/ max (k)	interval between applications (min)	g as/hL min – max (l)	water L/ha min – max	g as/ha min – max (l)		
Wheat	Northern Europe	Alto 100 SL	F	*Erpsiphe graminis, Puccinia spp. Pseudocercosporella herpotrichoides, Septoria spp..*	SL	100 g/L	Foliar spray	BBCH 31 - 69	1 - 2	28 days	0.025 – 0.05	200 - 400	100	35	[1] [2] [3]
Wheat	Southern Europe	Alto 100 SL	F	*Erpsiphe graminis, Puccinia spp. Pseudocercosporella herpotrichoides, Septoria spp..*	SL	100 g/L	Foliar spray	BBCH 31 - 65	1 - 2	28 days	0.025 – 0.05	200 - 400	100	40	[1] [2] [3]

* For uses where the column "Remarks" is marked in grey further consideration is necessary. Uses should be crossed out when the notifier no longer supports this use(s).
(a) For crops, the EU and Codex classifications (both) should be taken into account; where relevant, the use situation should be described (e.g. fumigation of a structure)
(b) Outdoor or field use (F), greenhouse 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 plant- type of equipment used must be indicated
(i) g/kg or g/L. Normally the rate should be given for the active substance (according to ISO) and not for the variant in order to compare the rate for same active substances used in different variants (e.g. fluoroxypyr). **In certain cases, where only one variant is synthesised, it is more appropriate to give the rate for the variant (e.g. benthiavalicarb-isopropyl).**
(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) Indicate the minimum and maximum number of application possible under practical conditions of use
(l) The values should be given in g or kg whatever gives the more manageable number (e.g. 200 kg/ha instead of 200 000 g/ha or 12.5 g/ha instead of 0.0125 kg/ha
(m) PHI - minimum pre-harvest interval

[1] A high long-term risk is indicated for herbivorous mammals
[2] The contribution of the residues of the Triazole Derivate Metabolites present in primary crops, processed products, rotational crops and ruminant matrices to the overall consumer exposure was not addressed.
[3] Possible impact on the ecotoxicity and the environment of the potential enantio-selective biologically mediated metabolism/degradation in the environment was not addressed.

Methods of Analysis

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

Technical as (analytical technique)	Analysis by HPLC with UV detection following dissolution by methanol.
Impurities in technical as (analytical technique)	Analysis by HPLC with UV detection/GC with FID detection following dissolution in methanol.
Plant protection product (analytical technique)	Analysis by HPLC with UV detection following dissolution in methanol.

Analytical methods for residues (Annex IIA, point 4.2)

Food of plant origin		Cyproconazole (sum of isomers)
Food of animal origin		Cyproconazole (sum of isomers)
Soil		Cyproconazole
Water	surface	Cyproconazole
	drinking/ground	Cyproconazole
Air		Cyproconazole
Body fluids and tissues		Cyproconazole

Monitoring/Enforcement methods

Food/feed of plant origin (analytical technique and LOQ for methods for monitoring purposes)	DFG Method S19: Homogenised plant material was extracted with acetone:water (2:1 v/v). The extract was partitioned into acetate/cyclohexane followed by clean up using gel permeation chromatography (GPC). The eluate was analysed using liquid chromatography with mass spectrometric detection (LC-MS-MS). Two transitions were used for quantitation, 291.97 –124.89 m/z and 291.97 – 69.88 m/z. Validation data support a LOQ of 0.01 mg/kg in wheat grain, melons and apples. Acceptable ILV was provided for barley grain and straw.

Food/feed of animal origin (analytical technique and LOQ for methods for monitoring purposes)	DFG Method S19: Beef fat was extracted with ethyl acetate/cyclohexane (1:1 v/v). Muscle, kidney, liver, egg specimens and milk were extracted using n-hexane/acetone (2:1 v/v). The extracts were cleaned up using gel permeation chromatography (GPC). The eluate was analysed using liquid chromatography with mass spectrometric detection (LC-MS-MS). Two transitions were used for quantitation, 291.97 –124.89 m/z and 291.97 – 69.88 m/z. Validation data support a LOQ of 0.01 mg/kg. Acceptable ILV was provided.
Soil (analytical technique and LOQ)	Open
Water (analytical technique and LOQ)	Method REM 200.01 Following the addition of methanol, the water specimen is sucked through a solid phase extraction column for concentration of the analyte. The eluate is evaporated and cyproconazole is quantified in the final extract by GC/MSD using the selected ion mode (SIM). The ion at 292 m/z is used for confirmation and the ions at 139 and 222 m/z are used for quantitation. This method of analysis has proven to be suitable for the determination of cyproconazole in surface water and drinking water with LOQ values of 0.05 µg/L and 0.1 µg/L, respectively.
Air (analytical technique and LOQ)	Method SOP RAM 427/01: Tenax air sampling tubes were fortified with cyproconazole, and air at nominally 35°C and 80% relative humidity was drawn through the tubes for 6 hours. Cyproconazole was removed from the tubes by ultrasonication with acetonitrile. An aliquot was diluted with acetonitrile and ultra pure water and analysed by LC-MS-MS. LOQ = 0.3 ng/L.
Body fluids and tissues (analytical technique and LOQ)	Open

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

	RMS/peer review proposal
Active substance	Cyproconazole and the representative formulation ‘Alto 100 SL’ will not classify from a physical/chemical viewpoint.

Impact on Human and Animal Health

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

Rate and extent of oral absorption ‡	Rapidly absorbed, > 85 % within 144 hours, based on urinary and biliary excretion and carcass residues
Distribution ‡	Widely distributed, highest residues associated with the organs of elimination (kidney, liver, pancreas)
Potential for accumulation ‡	No evidence of bioaccumulation
Rate and extent of excretion ‡	Major route is biliary excretion for males (75 %) and females (59 %), followed by with renal (26.7 % and 9.5 % respectively); < 5 % faecal excretion
Metabolism in animals ‡	Extensively metabolised (35 metabolites identified)
Toxicologically relevant compounds ‡ (animals and plants)	Cyproconazole
Toxicologically relevant compounds ‡ (environment)	Cyproconazole

Acute toxicity (Annex IIA, point 5.2)

Rat LD_{50} oral ‡	Rat: 350 mg/kg bw Mouse: 200 & 218 mg/kg bw, males & females respectively; 270 mg/kg bw (males) Rabbit: 460 mg/kg bw (females)	**R22**
Rat LD_{50} dermal ‡	Rat: > 2000 mg/kg bw Rabbit: > 2000 mg/kg bw	
Rat LC_{50} inhalation ‡	> 5.465 mg/L, 4 hours, nose-only exposure	
Skin irritation ‡	Non-irritant	
Eye irritation ‡	Non-irritant	
Skin sensitisation ‡	Non-sensitising (M & K)	

Short term toxicity (Annex IIA, point 5.3)

Target / critical effect ‡	Liver toxicity and reduced weight gain in rats, mice and dogs.	
Relevant oral NOAEL ‡	90-day, rat: 6.4 mg/kg bw/day 90-day mouse: 2.2 mg/kg bw/day, LOAEL 43.8 mg/kg bw/day 1-year dog: 3.2 mg/kg bw/day	
Relevant dermal NOAEL ‡	28-day, rat: 10 mg/kg bw/day, based on changes in clinical chemistry.	
Relevant inhalation NOAEL ‡	No data, not required	

Genotoxicity (Annex IIA, point 5.4)

Cyproconazole is unlikely to be genotoxic	

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

Target/critical effect ‡	Reduced body weight gain in male and female rats and mice. Liver: Liver change consistent with adaptive response and hepatotoxicity in rats and mice.	
Relevant NOAEL ‡	1.84 mg/kg bw/day; 18-month mouse 2.22 mg/kg bw/day; 2-year rat	
Carcinogenicity ‡	Liver tumours (adenoma and carcinoma) in mice at 13.17 mg/kg bw/day	**R40**

Reproductive toxicity (Annex IIA, point 5.6)

Reproduction toxicity

Reproduction target / critical effect ‡	Maternal: Increased liver weight. Offspring: Slightly increased pre/peri- and post natal mortality. Reproductive: No effect on reproduction/ fertility	
Relevant parental NOAEL ‡	1.4 mg/kg bw/day (males), based on hepatotoxicity 1.7 mg/kg bw/day (females), based on litter loss	
Relevant reproductive NOAEL ‡	8.3 mg/kg bw/day	
Relevant offspring NOAEL ‡	1.4 mg/kg bw/day (males), based on hepatotoxicity 1.7 mg/kg bw/day (females), based on litter loss	

Developmental toxicity

Developmental target / critical effect ‡	Rabbit: Maternal: ↓mean body weight Developmental: increased post-implantation loss; increased foetal malformations Rat: Maternal: ↓mean body weight gain. Developmental: reduced foetal body weight, teratogenicity (cleft palate, hydrocephaly) at maternally toxic doses.	
Relevant maternal NOAEL ‡	Rabbit: 10 mg/kg bw/day Rat: 12 mg/kg bw/day	

Relevant developmental NOAEL ‡	Rabbit: 2 mg/kg bw/day Rat: 12 mg/kg bw/day	**R61**

Neurotoxicity / Delayed neurotoxicity (Annex IIA, point 5.7)

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

Other toxicological studies (Annex IIA, point 5.8)

Mechanism studies ‡

Liver cell proliferation study in rat: hepatocyte proliferation not induced. Liver cell proliferation study in mouse: transient, early increase in proliferation (LOEL: 2.2 mg/kg bw/day)
Rat and mouse liver enzyme induction: strong induction of phase I and II enzymes in rat. Induction of NCPR, CYP1A, GST and UDPGT in mice

Studies performed on metabolites or impurities ‡

Triazole alanine	
ADME	Rapidly and completely absorbed, rapidly eliminated via the urine mainly unchanged
Rat LD_{50} oral	>5000 mg/kg bw
Mouse oral LD_{50}	>5000 mg/kg bw
28-day oral rat	400 mg/kg bw/day (no clinical findings)
90- day oral rat	370 mg/kg bw/day (reduced bodyweight gain)
90-day oral dog	200 mg/kg bw/day (bodyweight effects)
Genotoxicity	Triazole alanine is unlikely to be genotoxic
Reproductive toxicity	
Reproduction target / critical effect	Maternal (rat): no adverse effect Offspring (rat): reduced neonatal weight Developmental (rat): reduced neonatal weight
Relevant parental NOAEL	500 mg/kg bw/day
Relevant reproductive NOAEL	100 mg/kg bw/day (reduced neonatal weight)
Relevant offspring NOAEL	100 mg/kg bw/day (reduced neonatal weight)
Developmental toxicity	
Developmental target / critical effect	Maternal (rat): adverse effect Developmental (rat): increase in non-ossification of the odontoid process
Relevant maternal NOAEL	1000 mg/kg bw/day
Relevant developmental NOAEL	100 mg/kg bw/day

Reference Values (PRAPeR 14)	Value	Study	Safety factor
ADI ‡	0.1 mg/kg bw/day	Developmental rat	1000
AOEL ‡	If needed should be the same as ADI		
ARfD ‡	0.1 mg/kg bw	Developmental rat	1000

Metabolite M21/21a

Rat LD_{50} oral	> 2000 mg/kg bw, both sexes
Ames test	Negative

Metabolite M36(Z2)

Rat LD_{50} oral	> 2000 mg/kg bw
Mouse LD_{50} oral	> 2000 mg/kg bw
Genotoxicity M36	Metabolite M36(Z2) is unlikely to be genotoxic
28-day oral rat	NOAEL: 155 mg/kg bw/day

Medical data (Annex IIA, point 5.9)

No adverse effects reported.

Summary (Annex IIA, point 5.10)	Value	Study	Safety factor
ADI ‡	0.02 mg/kg bw/day	Rat multigeneration (females) and long-term rat and mouse studies	100
AOEL ‡	0.02 mg/kg bw/day	Rat multigeneration (females) and rabbit developmental studies	100
ARfD ‡	0.02 mg/kg bw	Rat multigeneration (females) and rabbit developmental studies	100

Dermal absorption ‡ (Annex IIIA, point 7.3)

Alto 100 SL	Concentrate: 1 % Spray dilution: 10 % *In vivo* studies in pigs and in rats, *in vitro* comparative human and rat skin (with different preparations)

Exposure scenarios (Annex IIIA, point 7.2)

Operator	Tractor-mounted equipment (application rate 100 g cyproconazole/ha) German model % of AOEL Without PPE 32.6 % With PPE (gloves during M/L; gloves, coverall and sturdy footwear during application) 7.3 % UK POEM % of AOEL Without PPE 217 % With PPE (gloves during M/L and application) 31.5 %
Workers	Re-entry exposure estimate 21 % of the AOEL without PPE.
Bystanders	Up to 58 % of the AOEL

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

	RMS/peer review proposal
Cyproconazole	**T** "Toxic" **Xn, R22** "Harmful if swallowed" **Xn, R40** " Limited evidence of a carcinogenic effect" **T, R61** "May cause harm to the unborn child"

Residues

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

Plant groups covered	-Cereals (wheat):^{14}C-phenyl ring, ^{14}C triazole moiety, ^{14}C alpha carbon; -Fruit crops (grapes, grapevine, apples): ^{14}C alpha carbon; -Root vegetables (sugar beet): ^{14}C Triazole moiety; -Pulses/oilseeds (peanuts): ^{14}C alpha carbon; -Coffee: ^{14}C Triazole moiety.
Rotational crops	Root vegetables (sugar beet, carrots, radishes); leafy vegetables (lettuce), cereals (wheat); oilseeds (oilseed rape); potatoes.
Metabolism in rotational crops similar to metabolism in primary crops?	Rotational crop metabolism was similar to primary crop metabolism for the alpha carbon position labelling. A confined rotational crop metabolism study labelled on the triazole moiety is required.
Processed commodities	Cyproconazole is stable under standard processing conditions. The effect of the standard hydrolytic conditions on Triazole Derivative Metabolites (TDM) in wheat grain is required.
Residue pattern in processed commodities similar to residue pattern in raw commodities?	Open; pending the outcome of TDM in processed products.
Plant residue definition for monitoring	For cereals only: Cyproconazole (sum of isomers).
Plant residue definition for risk assessment	For cereals only: 1) Parent cyproconazole (sum of isomers). 2) TDM. This second residue definition is provisional pending finalisation of a global and harmonised approach for all the active substances of the triazole chemical group regarding the assessment of consumer exposure to TDMs.
Conversion factor (monitoring to risk assessment)	To be determined following the outcome of TDM review.

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

Animals covered	Goat and hen.
Time needed to reach a plateau concentration in milk and eggs	The plateau value was reached in milk for parent cyproconazole and its two main metabolites M_{21a} and M_{36} within 7 days of feeding.
Animal residue definition for monitoring	Cyproconazole (sum of isomers).
Animal residue definition for risk assessment	- Cyproconazole (sum of isomers) and the metabolites M36(Z2), M38(Z1) and M9/M14 (pair of diastereomers) expressed as cyproconazole equivalents. - Open for the TDM (*)
Conversion factor (monitoring to risk assessment)	Liver: 3

Metabolism in rat and ruminant similar (yes/no)	Open; pending the additional data requested on TDM in ruminant matrices.
Fat soluble residue: (yes/no)	Log $P_{o/w}$ = 3.09 Open for the TDM.

(*): The residue definition for risk assessment should be revisited pending the further data requested on TDM in ruminant matrices.

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

Rotational crop field trials indicated that significant residues (0.097 mg/kg at 1N rate) were only found in leafy crops rotated to wheat at very long plant back intervals (430 days). The magnitude of the residues in rotated leafy crops field trials at the representative plant back interval (120 days) should be addressed.

A confined rotational crop metabolism study labelled on the triazole moiety is also required.

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

Stability studies were conducted in sugarbeet, wheat, grapes, apples, nectarines, peaches, peanuts, and in bananas. When stored in a freezer, residues are stable, depending on the study, for between 12 and 42 months.

A storage stability study demonstrated that cyproconazole was stable in wheat grain and forage for up to 39 months. No data were provided on wheat straw.
The storage period of the samples from the residue trials was not provided.

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 level.)	Expected levels are 0.48 /1.2 mg/kg of diet DM (dairy/beef cattle)	0.028 mg/kg diet DM	0.033 mg/kg diet DM
Potential for accumulation (yes/no):	No	No	No
Metabolism studies indicate potential level of residues ≥ 0.01 mg/kg in edible tissues (yes/no)	Yes	No	No metabolism study required as metabolism in rat and ruminants is similar
	Feeding studies (Specify the feeding rate in cattle and poultry studies considered as relevant) Feeding studies in poultry are not required.		

	Feeding level for cows at 20 mg/cow/day was considered as relevant as it corresponds to the calculated dietary burden (17.53 mg/animal/day). Residue levels in matrices: Mean (max) mg/kg		
Overdosing factor	1N		
Muscle	<LOQ(1)	-	-
Liver	0.082	-	-
Kidney	<LOQ(1)	-	-
Fat	<LOQ(1)	-	-
Milk	Cyproconazole= <LOQ(1) M36(Z2)=<LOQ(1) M21/21a: Not detected and not relevant		
Eggs		-	

(1): LOQ of the validated analytical method: 0.01 mg/kg for fat, muscle, kidney, liver and milk.

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)
Wheat grain	Northern	<0.01 x13; 0.01 x3; 0.014; 0.02 x3; 0.024; 0.035 mg/kg		0.05 mg/kg	0.035 mg/kg	<0.01 mg/kg
Wheat straw		0.09; 0.19; 0.19; 0.19; 0.19; 0.21; 0.27; 0.30; 0.32; 0.34; 0.36; 0.46; 0.56; 0.72; 0.87; 0.89; 1.20; 2.0 mg/kg		-	2 mg/kg	0.33 mg/kg
Wheat grain	Southern	n.d.; <0.01; <0.02 x 5; 0.02 mg/kg		0.05 mg/kg	0.02 mg/kg	0.02 mg/kg
Wheat straw		0.20; 0.23; 0.32; 0.37; 0.39; 0.39; 1.60; 1.70; 1.81; 1.83 mg/kg		-	1.83 mg/kg	0.39 mg/kg

(a) Numbers of trials in which particular residue levels were reported
(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

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

ADI	Cyproconazole: 0.02 mg/kg bw/day
TMDI (% ADI) - EFSA PRIMo model Version 2A	**A)** **Plants:** Cyproconazole (sum of isomers). **Animals:** -Cyproconazole (sum of isomers) and the metabolites M36(Z2), M38(Z1), M9/M14. -Highest TMDI= 2.8 % of the ADI -Highest TMDI (including the default highest residue: 0.097 mg/kg in leafy crops rotated to wheat)= 3.3 % of the ADI **B) TDM(*)** Risk assessment not finalised pending the outcome of the TDM review.
IEDI (WHO European Diet) (% ADI)	Not applicable.
NEDI (specify diet) (% ADI)	Not applicable.
Factors included in IEDI and NEDI	Not applicable.
ARfD	Cyproconazole: 0.02 mg/kg bw
IESTI (% ARfD) - EFSA PRIMo model Version 2A	**A)** **Plants:** Cyproconazole (sum of isomers). **Animals:** Cyproconazole (sum of isomers) and the metabolites M36(Z2), M38(Z1), M9/M14. IESTI=12.1% ARfD (milk and milk products) IESTI=43.7% ARfD (scarole broad-leaf) when considering the default value of 0.097 mg/kg for leafy crops rotated with wheat. **B) TDM(*)** Risk assessment not finalised pending the outcome of the TDM review.
NESTI (% ARfD) according to national (to be specified) large portion consumption data	Not applicable.
Factors included in IESTI and NESTI	None.

(*): The overall consumer risk assessment has to be regarded as provisional pending the outcome of the further data on TDM in primary crops, processed products, rotational crops and ruminant matrices.

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	
The effect of standard processing conditions on TDM is required. If it is triggered by the outcome of the residue trials on TDM, the magnitude of TDM residues in processed wheat grain has to be addressed.				

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

Wheat grain	0.05 mg/kg
Ruminant liver	0.1 mg/kg
Milk and other ruminant products	0.01* mg/kg
Leafy rotational crops	0.1 mg/kg (provisional pending the outcome of the required rotated crop field trials at shorter plant back interval -120 days).

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

Fate and Behaviour in the Environment

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

Mineralization after 100 days ‡	0.1 % after 112d, [^{14}C-triazole]-label (n[13]= 1) 26.8-32.9 % after 112d, [^{14}C-benzyl]-label (n= 2) 11.2-48.4 % after 112 d, [^{14}C-phenyl]-label (n= 1) [^{14}C-benzyl= 1], Sterile conditions: not measured
Non-extractable residues after 100 days ‡	13.10 % after 112d, [^{14}C-triazole]-label (n= 1) 16%, day 140 13-23.9 % after 112d, [^{14}C-benzyl]-label (n= 2) 19.4-21.4 % after 112 d, [^{14}C-phenyl]-label (n= 1) 20.8-21.5 % AR, day 140 Sterile conditions: 4.1 % after 112 d (n= 1) [^{14}C-benzyl]
Metabolites requiring further consideration ‡ - name and/or code, % of applied (range and maximum)	1,2,4-triazole (triazole label), 17.36 % at 140 d (n= 1), max. 17.36 %, day 140 Triazole acetic acid (triazole label), 0-6.7 % at 140 d (n= 1).

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

Anaerobic degradation ‡

Mineralization after 100 days	0.1 % after 121 d, [^{14}C-triazole]-label (n= 1 Water-soil system) ND % after 117d, [^{14}C-benzyl]-label (n= 1) 0.1 % after 121 d, [^{14}C-phenyl]-label (n= 1, Water-soil system)
Non-extractable residues after 100 days	0.1 % after 121 d, [^{14}C-triazole]-label (n= 1 Water-soil system). 16.5 % after 117d, [^{14}C-benzyl]-label (n= 1) 0.1 % after 121 d, [^{14}C-phenyl]-label (n= 1, Water-soil system)
Metabolites that may require further consideration for risk assessment - name and/or code, % of applied (range and maximum)	Not applicable.

Soil photolysis ‡

Metabolites that may require further consideration for risk assessment - name and/or code, % of applied (range and maximum)	None identified.

[13] n corresponds to the number of soils.

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

Cyproconazole	Aerobic conditions						
Soil type	X	pH	t. °C / actual soil moisture %	DT_{50} /DT_{90} (d)	DT_{50} (d) 20 °C pF2/10kPa	χ^2	Method of calculation
Loam; Flaach 2/88	----	7.6	22/40	88.9/295	69.8	7.89	SFO
Loam; Flaach 2/89	----	7.6	22/40	72.4/240	72.5	5.45	SFO
Loam; Flaach 2/89	----	7.6	12/40	347/>1000	158	6.25	SFO
Loam; Flaach 2/89	----	7.6	22/20	219/727	135	7.51	SFO
Loam; Flaach 2/89 (low application dose)	----	7.6	22/40	34744.8/149	44.9	6.87	SFO
Sandy loam; Hatzenbühl	----	5.0	22/40	192/638	191	4.57	SFO
Loamy sand; Neuhofen	----	5.0	22/40	132/438	155	7.37	SFO
Silt loam; Louisiana 90	----	4.30	22/75% at 1/3 bar	150.7/500.6	126.1	15.5	SFO
Sandy clay loam; Flaach 2/90	----		22/75% at 1/3 bar	124/412	127	10.0	SFO
Sandy clay loam; Flaach 2/90 (open system)	----		22/40	82.0/272	65.7	5.07	SFO
Sandy clay loam; Flaach 2/90 (closed system)	----		22/40	193/642	155	2.96	SFO
Sandy clay loam; Flaach	----	7.6	20/40	148/491	109	5.40	SFO
Geometric mean/median				**142.3/469.8**	128.6	----	
Comments			The geomeans were calculated in the following way: first the geomean values for sandy clay loam Flaach soils and loam clay soils were calculated, giving two separate values. At the next step these values were combined with the remaining kinetic endpoints to give the final geometric mean values.				

1,2,4-triazole	There are values derived experimentally for 1,2,4-triazole for the purpose of cyproconazole registration. However, in the meantime, at the PRAPeR 12 meeting, the agreed endpoints were derived for 1,2,4 triazole and these were subsequently used in the risk assessment. They are given in the table below. According to the recommendations given during the peer review process these data were removed from the final list of endpoints.

EFSA agreed end point for 1,2,4-triazole

1,2,4-triazole	Aerobic conditions						
Soil type (USDA)	pH ($CaCl_2$)	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
Sandy loam	6.4	20°C / 40 % MWHC	6.32 / 21.0		5.0	0.75	SFO
Loamy sand	5.8	20°C / 40 % MWHC	9.91 / 33.0		9.9	0.81	SFO
Silt loam	6.7	20°C / 40 % MWHC	12.27 / 40.8		8.2	0.95	SFO
Geometric mean					7.4		

Agreed endpoint for calculating PEC soil for EU assessments: 12 days (Not normalised).

Geomean for FOCUS modelling: 7.4 days

Triazole acetic acid (TAA)	Aerobic conditions						
Soil type	pH	t. °C / % MWHC	DT_{50}/ DT_{90} (d)	F.F. k_{dp}/k_f	DT_{50} (d) 20°C pF2/10kPa	χ^2	Method of calculation
Sand	5.2 (0.01M $CaCl_2$)	20°C / 60% (pF=2.5)	9.6/ 31.8		10.9	12.0	SFO
Loamy sand	5.6 (0.01M $CaCl_2$)	20°C / 60% (pF=2.5)	8.4/ 27.8		8.6	14.1	SFO
Sandy loam	6.3 (0.01M $CaCl_2$)	20°C / 60% (pF=2.5)	18.7/ 62.1		16.7	9.5	SFO
Geometric mean/median			DT_{50}: 11.5/ 9.6		11.6 / 10.9		

Field studies

Parent				Aerobic conditions					
Soil type (indicate if bare or cropped soil was used)	Location (country or USA state)	X App. Rate	pH	Depth (cm)	DT_{50} (d) actual	DT_{90}(d) actual	χ^2	DT_{50} (d) Norm.	Method of calculation
Loamy sand (bare) Hernhill	England	80 g a.s./ha x 2	5.3 (KCl)	0-30	107.19	356.08	24.1	62.1	SFO
Clay (bare) Coton 1			7.0 (KCl)	0-30	26.46	841.25	9.99	199.7	DFOP/ slow phase DFOP (norm. value
Sandy soil (bare) Goch Nierswalde	Germany	80 g a.s./ha	5.95	0-30	55.66	>1000	11.2	501.2	DFOP/ slow phase DFOP (norm. value
Sandy loam (bare) Nittenau-Thann			6.6	0-30	92.39	306.92	22.5	67.7	SFO
Silt loam (bare) Hilgermissen			5.1	0-30	141.3	469.5	12.6	84.8	SFO
							Geomean (n = 5)	128.97	

Median (n = 5)	84.8	

PH dependence ‡ (yes / no) (if yes type of dependence)	No
Soil accumulation and plateau concentration ‡	Refer to accumulation calculations in PEC Soil section where the DFOP kinetic fit for Goch-Nierswalde was used as a worst-case example for accumulation.

Laboratory studies‡

Cyproconazole (parent)	Anaerobic conditions.					
Soil type	pH	t. °C / % MWHC	DT_{50} /DT_{90} (d)	DT_{50} (d) 20°C pF2/10kPa	St. (r^2)	Method of calculation
Sandy loam	5.4	24 /3.19 (%w/w) 1/3 bar	Not determined Day 365 parent acc for 95-97 % AR	Not determined		
Loam	7.6 (KCl)	24 °C/40	Poor degradation observed	Not determined		

1,2,4-triazole							
Soil type	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
Silt loam	7.31 (KCl)	20/40	81/291	----	------	0.972	SFO
Geometric mean/median			81/291				

DT_{50} values recommended for modelling calculations

Type of calculations	Substance	DT_{50} [days]	Remarks
PEC_{SOIL}	Cyproconazole – 1-year PEC_{SOIL} calculations	141.3	Longest un-normalised SFO-DT_{50} value from the field studies
	Cyproconazole – accumulation PEC_{SOIL} calculations	DT_{50} 1 = 4.86; DT_{50} 2 = 796.72; g = 0.4753	Worst-case un-normalised DFOP kinetic endpoints from the field studies (site Goch-Nierswalde)
	1,2,4-triazole	12.3	Longest un-normalised value from the laboratory studies; EU EFSA agreed endpoint
	Triazole acetic acid (TAA)	18.7	Longest un-normalised value from the laboratory studies
	Cyproconazole	128.6	Geomean from the laboratory studies normalised for the temperature (using Q_{10} = 2.2) and moisture content
PEC_{GW}	1,2,4-triazole	7.4	Geomean from the laboratory studies normalised for the temperature (using Q_{10} = 2.2) and moisture content; EU EFSA agreed endpoint

	Triazole acetic acid (TAA)	11.5	Geomean from the laboratory studies normalised for the temperature (using Q_{10} = 2.2) and moisture content
	Cyproconazole	128.6	Geomean from the laboratory studies normalised for the temperature (using Q_{10} = 2.2) and moisture content
PEC_{SW}	1,2,4-triazole	7.4	Geomean from the laboratory studies normalised for the temperature (using Q_{10} = 2.2) and moisture content; EU EFSA agreed endpoint
	Triazole acetic acid (TAA)	11.5	Geomean from the laboratory studies normalised for the temperature (using Q_{10} = 2.2) and moisture content

Soil adsorption/desorption (Annex IIA, point 7.1.2)

Parent ‡ Cyproconazole							
Soil Type	OC %	Soil pH	Kd At the initial concentration of 62.5 µg/mL	Koc	Kf	Kfoc	1/n
Gilroy Loam	1.33	6.4	2.2		4.1	309	0.84
Gilroy Sediment	1.33	7.4	3.1		4.9	369	0.86
Keaton Sandy loam	0.76	7.0	0.76		1.3	173	0.87
Briggs Clay	6.63	6.2	12		17	258	0.84
German Loamy sand	2.27	5.1	11		16	711	0.90
Median					4.1	309	0.89
pH dependence, Yes or No			No obvious pH dependence.				

1,2,4-triazole	There are values derived experimentally for 1,2,4-triazole for the purpose of cyproconazole registration. However, in the meantime, at the PRAPeR 12 meeting, the agreed endpoints were derived for the triazoles and these were subsequently used in the risk assessment. They are given in the table below. According to the recommendations given during the peer review process these data were removed from the final list of endpoints.

EFSA agreed end point for 1,2,4-triazole

Metabolite 1,2,4-triazole ‡							
Soil Type	OC %	Soil pH ($CaCl_2$)	Kd (mL/g)	Koc (mL/g)	Kf (mL/g)	Kfoc (mL/g)	1/n
Silty clay	0.70	8.8			0.833	120	0.897
Clay loam	1.74	6.9			0.748	43	0.827
Sand	0.12	4.8			0.234	202	0.885
Silty clay loam	0.70	7.0			0.722	104	0.922
Sandy loam	0.81	6.9			0.720	89	1.016
Arithmetic mean (of 4 values excluding the very low OC sand that was considered not representative of agricultural soils)					0.756	89	0.9155
pH dependence (yes or no)			No				

Agreed endpoint for calculating FOCUS modeling: arithmetic mean Kfoc of 89 mL/g, 1/n 0.92 excluding results of the sand soil.

Metabolite Triazole acetic acid (TAA)‡							
Soil Type	OC %	Soil pH	Kd (mL/g)	Koc (mL/g)	Kf (mL/g)	Kfoc (mL/g)	1/n
Loamy sand	14.42	3.38 (0.01M $CaCl_2$)	0.150	1.04	0.262	1.82	0.903
Clay	0.89	7.55 (0.01M $CaCl_2$)	0.178	20	0.216	24.3	0.911
Silt loam	2.13	5.16 (0.01M $CaCl_2$)	0.448	21	0.402	18.9	0.926
Arithmetic mean					0.293	15.0	0.913
pH dependence (yes or no)			No				

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

Column leaching ‡	Elution (mm): 200 mm Time period (d): 2 d
	‘Alto 100 SL’ (non-radiolabelled 32 µg equivalent to 2 x 80 g a.s./ha) applied to three soil types, namely sand, loamy sand, and sandy loam. Cyproconazole was not detected in the leachate. [LOD 1.6 % of the applied test substance]
Aged residues leaching ‡	Not required as a result of Annex IIA, point 7.1.2
Lysimeter/ field leaching studies ‡	Not required.

PEC (soil) (Annex IIIA, point 9.1.3)

Parent – **Cyproconazole** Method of calculation	**1 Year PEC Soil** DT_{50} (d): 141.3 days Kinetics: SFO Field or Lab: Longest unnormalised SFO DT_{50} value from the field studies Tool: ESCAPE v. 2.0 **Accumulation PEC Soil** DT_{50} (d): DT_{50} 1 = 4.86; DT_{50} 2 = 796.72; (g = 0.4753) Kinetics: DFOP Field or Lab: Worst-case unnormalised DFOP kinetic endpoints from the field studies Tool: ESCAPE v. 2.0
Application data	Crop: cereals – spring and winter, Depth of soil layer (1 Year PEC Soil Calculation): 5 cm Depth of soil layer (Accumulation PEC_{SOIL} calculations): 20 cm (tillage depth) Soil bulk density: 1.5 g/cm^3 % plant interception: 70% for the first application, 90% for the second application Number of applications: 1 or 2 Interval (d): 28 days Application rate(s): 100 g as /ha per application

Single application				Double application			
1-year PEC_{SOIL} values (SFO kinetics)	**DAT**	**$PEC_{s,actual}$ (mg/kg)**	**$PEC_{s,twa}$ (mg/kg)**	**1-year PEC_{SOIL} values (SFO kinetics)**	**DAT**	**$PEC_{s,actual}$ (mg/kg)**	**$PEC_{s,twa}$ (mg/kg)**
	0	0.0400	----		0	0.0484	----
	1	0.0398	0.0399		1	0.0481	0.0483
	2	0.0396	0.0398		2	0.0479	0.0481
	4	0.0392	0.0396		4	0.0474	0.0479
	7	0.0386	0.0393		7	0.0467	0.0476
	14	0.0373	0.0387		14	0.0452	0.0467
	21	0.0361	0.0380		21	0.0436	0.0460
	28	0.0349	0.0374		28	0.0422	0.0452
	42	0.0326	0.0361		42	0.0394	0.0438
	50	0.0313	0.0355		50	0.0378	0.0430
	100	0.0245	0.0316		100	0.0296	0.0399
Background concentration (DFOP kinetics)	Final background concentration in 20 cm layer [mg/kg]		0.0135	**Background concentration (DFOP kinetics)**	Final background concentration in 20 cm layer [mg/kg]		0.0181
	Occurring after [years]		12		Occurring after [years]		12
Accumulation PEC_{SOIL} (DFOP kinetics)	**DAT**	**$PEC_{s,actual}$ (mg/kg)**	**$PEC_{s,twa}$ (mg/kg)**	**Accumulation PEC_{SOIL}**	**DAT**	**$PEC_{s,actual}$ (mg/kg)**	**$PEC_{s,twa}$ (mg/kg)**
	0	0.0535	----		0	0.0581	----
	1	0.0510	0.0522		1	0.0556	0.0568
	2	0.0487	0.0510		2	0.0534	0.0556
	4	0.0452	0.0490		4	0.0498	0.0536
	7	0.0414	0.0465		7	0.0460	0.0511
	14	0.0368	0.0426		14	0.0414	0.0484
	21	0.0351	0.0403		21	0.0397	0.0475
	28	0.0343	0.0389		28	0.0514	0.0470
	42	0.0338	0.0373		42	0.0460	0.0463
	50	0.0336	0.0367		50	0.0453	0.0460
	100	0.0327	0.0349		100	0.0439	0.0450
Plateau Concentration (Single application)				Final background concentration in 20 cm layer is 0.0135 mg/kg (reached after 12 years)			
				0.0535 mg/kg is peak concentration in 5cm layer for a further year of application on top of the final background concentration.			

Plateau Concentration (Double application)	Final background concentration in 20 cm layer is 0.0181 mg/kg (reached after 12 years)
	0.0581 mg/kg is peak concentration in 5cm layer for a further year of application on top of the final background concentration.

Metabolite – 1,2,4-triazole Method of calculation	Molecular weight relative to the parent: 0.237 (69.1/291.8) DT_{50} (d): 12.3 Kinetics: SFO Field or Lab: Longest un-normalised laboratory value; The INI PEC was calculated by the conversion from the max. PEC obtained from the parent compound, either 1-year or accumulation.
Application data	Application rate assumed: 100 g a.s. /ha (assumed 1,2,4-triazole is formed at a maximum of 17.36 % of the applied dose).

Single application				Double application			
Calculated using max. 1-year PEC_{SOIL} for Cyproconazole as a starting value	DAT	$PEC_{s,actual}$ (mg/kg)	$PEC_{s,twa}$ (mg/kg)	Calculated using max. 1-year PEC_{SOIL} for Cyproconazole as a starting value	DAT	$PEC_{s,actual}$ (mg/kg)	$PEC_{s,twa}$ (mg/kg)
	0	0.002	----		0	0.002	----
	1	0.002	0.002		1	0.002	0.002
	2	0.001	0.002		2	0.002	0.002
	4	0.001	0.001		4	0.002	0.002
	7	0.001	0.001		7	0.001	0.002
	14	0.001	0.001		14	0.001	0.001
	21	0.001	0.001		21	0.001	0.001
	28	0.000	0.001		28	0.000	0.001
	42	0.000	0.001		42	0.000	0.001
	50	0.000	0.001		50	0.000	0.001
	100	0.000	0.001		100	0.000	0.000
Calculated using max. accumulation PEC_{SOIL} for Cyproconazole as a starting value	DAT	$PEC_{s,actual}$ (mg/kg)	$PEC_{s,twa}$ (mg/kg)	Calculated using max. accumulation PEC_{SOIL} for Cyproconazole as a starting value	DAT	$PEC_{s,actual}$ (mg/kg)	$PEC_{s,twa}$ (mg/kg)
	0	0.002	----		0	0.002	----
	1	0.002	0.002		1	0.002	0.002
	2	0.002	0.002		2	0.002	0.002
	4	0.002	0.002		4	0.002	0.002
	7	0.001	0.002		7	0.002	0.002
	14	0.001	0.002		14	0.001	0.002
	21	0.001	0.001		21	0.001	0.001
	28	0.000	0.001		28	0.000	0.001
	42	0.000	0.001		42	0.000	0.001
	50	0.000	0.001		50	0.000	0.001
	100	0.000	0.001		100	0.000	0.000
Plateau concentration				Not determined			

Metabolite – Triazole acetic acid (TAA)	
Method of calculation	Molecular weight relative to the parent: 0.436 (127.1/291.8) DT_{50} (d): 18.7 Kinetics: SFO Field or Lab: Longest un-normalised laboratory value; The PEC INI was calculated by the conversion from the max. PEC obtained from the parent compound, either 1-year or accumulation.
Application data	Application rate assumed: 100 g as /ha (assumed triazole acetic acid (TAA) is formed at a maximum of 7.00 % of the applied dose).

Single application				Double application			
Calculated using max. 1-year PEC_{SOIL} for Cyproconazole as a starting value	DAT	$PEC_{s,actual}$ (mg/kg)	$PEC_{s,twa}$ (mg/kg)	Calculated using max. 1-year PEC_{SOIL} for Cyproconazole as a starting value	DAT	$PEC_{s,actual}$ (mg/kg)	$PEC_{s,twa}$ (mg/kg)
	0	0.001	----		0	0.002	----
	1	0.001	0.001		1	0.001	0.001
	2	0.001	0.001		2	0.001	0.001
	4	0.001	0.001		4	0.001	0.001
	7	0.001	0.001		7	0.001	0.001
	14	0.001	0.001		14	0.001	0.001
	21	0.001	0.001		21	0.001	0.001
	28	0.000	0.001		28	0.001	0.001
	42	0.000	0.001		42	0.000	0.001
	50	0.000	0.001		50	0.000	0.001
	100	0.000	0.000		100	0.000	0.000
Calculated using max. accumulation PEC_{SOIL} for Cyproconazole as a starting value	DAT	$PEC_{s,actual}$ (mg/kg)	$PEC_{s,twa}$ (mg/kg)	Calculated using max. accumulation PEC_{SOIL} for Cyproconazole as a starting value	DAT	$PEC_{s,actual}$ (mg/kg)	$PEC_{s,twa}$ (mg/kg)
	0	0.002	----		0	0.002	----
	1	0.002	0.002		1	0.002	0.002
	2	0.001	0.002		2	0.002	0.002
	4	0.001	0.001		4	0.001	0.002
	7	0.001	0.001		7	0.001	0.001
	14	0.001	0.001		14	0.001	0.001
	21	0.001	0.001		21	0.001	0.001
	28	0.001	0.001		28	0.001	0.001
	42	0.000	0.001		42	0.000	0.001
	50	0.000	0.001		50	0.000	0.001
	100	0.000	0.000		100	0.000	0.000
Plateau concentration				Not determined			

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

Hydrolytic degradation of the active substance and metabolites > 10 % ‡	pH 4, 50 °C, 5 days, no degradation observed. No metabolites observed.
	pH 5, 50 °C, 5 days, no degradation observed. No metabolites observed.
	pH 7, 50 °C, 5 days, no degradation observed. No metabolites observed.
	pH 9, 50 °C, 5 days, no degradation observed. No metabolites observed.
Photolytic degradation of active substance and metabolites above 10 % ‡	At pH 7, molar absorption coefficients (ε) of the active substance are observed to be less than < 10 L/mol/cm at wavelengths ≥ 290 nm.
Quantum yield of direct phototransformation in water at Σ > 290 nm	Not determined, not required.
Readily biodegradable ‡ (yes/no)	No.

Degradation in water / sediment

Cypro-conazole	Distribution River: max in water *95.8 % AR* at *0* d, (16.1 % after 105 day), Max. sed 76.2% after *63*d Pond: maximum in water *96.7 % AR* after *7*d. (6.4 % after 105 day), Max. sed 80.9 % after *63*d)									
Water / sediment system	pH water phase	pH sed	t. °C	DT_{50}/DT_{90} whole sys.	χ^2	DT_{50}/DT_{90} water	χ^2	DT_{50}/DT_{90} sed	χ^2	Method of calculation
River	Surface 7.64-8.05 5 cm above sediment 7.64	7.3 (6.9)	20	980days / >1000 days	1.06	not calculated		not calculated		SFO
Pond	Surface 7.45-7.96 5 cm above sediment 7.64	7.7	20	>1000 days / >1000 days	1.06	not calculated		not calculated		SFO
Geometric mean/median				1000 days						

Metabolite

Several unknown metabolites (< 10 %) were observed.

	River system					Pond system			
Meatbolite	Max in water phase	Day	Max in sediment phase	Day		Max in water phase	Day	Max in sediment phase	Day
U0	1.5	7/154	2.2	28/105		2.6	0	3.2	154
U1	1.3	259	1.0	259		1.7	259	2.8	259
U2	0.6	259	0.6	154		0.1	105/154	0.8	210/259
U3	0.3	259	2.0	210		0.3	259	0.2	259
U4	0.1	210	-			0.1	210	0.3	210
U5	-	-	-			0.4	210	0.4	210

Mineralization and non extractable residues

Water / sediment system	pH w	pH sed	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	Surface 7.64-8.05 5 cm above sed. 7.64	Surface 7.64-8.05 5 cm above sediment 7.64	0.4 % after 259 d	3.8 % after 259 d	3.8 % after 259 d
Pond	Surface 7.45-7.96 5 cm above sed. 7.64	Surface 7.45-7.96 5 cm above sediment 7.64	0.3 % after 259 d	10.0 % after 259 d	10.0 % after 259 d

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

Parent – **Cyproconazole** Parameters used in FOCUSsw step 1 and 2	Version control no. of FOCUS calculator: ver. 1.1 Molecular weight (g/mol): 291.8 Water solubility (mg/L): 93 K_{fOC} (L/kg): 309 (median value) DT_{50} soil (d): 142 days (Lab geomean normalised value. In accordance with FOCUS, SFO) **Praper 82** proposed that the correct DT_{50} Soil (d) for use in modelling is 128.6 days. However, the figure used (142 days) is more conservative and therefore the calculations were not revised. DT_{50} water/sediment system (d): 1000 days DT_{50} water (d): 1000 DT_{50} sediment (d): 1000 Crop interception (%): 70%
Parameters used in FOCUSsw step 3 (if performed)	Version control no.'s of FOCUS software: SWASH v. 2.1 Vapour pressure: 2.6 E-5 Pa at 25°C K_{FOC}: 309 L/kg (median value) 1/n: 0.86
Application rate	Crop: spring cereals Crop interception: 70 % Number of applications: 1 or 2 Interval (d): 28 Application rate(s): 100 g a.s./ha Application window: Step 1& Step 2 – March - May; Step 3: a) for a single application: D1: 01 June – 01 July D3: 02 May – 01 June; D4: 23 May – 22 June; D5: 12 April – 12 May; R4: 12 April – 12 May; b) for a multiple application: D1: 01 June – 29 July; D3: 02 May – 29 June; D4: 23 May – 22 June; D5: 12 April – 09 June; R4: 12 April – 09 June; Crop: winter cereals Crop interception: 70 % Number of applications: 1 or 2 Interval (d): 28 Application rate(s): 100 g a.s./ha Application window: Step 1& Step 2 – March - May; Step 3:

	a) for a single application: D1: 15 May – 14 June; D2: 15 April – 15 May; D3: 09 May – 08 June; D4: 01 April – 01 May; D5: 01 April – 01 May; D6: 15 March – 14 April; R1: 15 April – 15 May; R3: 22 March – 21 April; R4: 01 April – 01 May; b) for a multiple application: D1: 15 May – 12 July; D2: 15 April – 12 June; D3: 09 May – 12 June; D4: 01 April – 06 July; D5: 01 April – 29 May; D6: 15 March – 12 May; R1: 15 April – 12 June; R3: 22 March – 19 May; R4: 01 April – 29 May;
1,2,4-triazole Parameters used in FOCUSsw step 1 and 2	Molecular weight: 69.1 Water solubility (mg/L): 7 x 10^5 (20°C) Soil or water metabolite: soil metabolite K_{foc} (L/kg): 89 DT_{50} soil (d): 7.4 days (Laboratory normalised geomean value. In accordance with FOCUS, SFO) DT_{50} water/sediment system (d): 1000 days DT_{50} water (d): 1000 days DT_{50} sediment (d): 1000days Crop interception (%):cereals - 70% Maximum occurrence observed (% molar basis with respect to the parent) Soil: 17.36 Water/sediment system: 1% (conservative assumption)
Parameters used in FOCUSsw step 3 (if performed)	Calculations not performed

Application rate	Crop: winter cereals Crop interception: 70% Number of applications: 1 or 2 Interval (d): 28 Application rate(s): 100 g a.s./ha Application window: Step 1& Step 2 – March - May; Crop: spring cereals Crop interception: 70% Number of applications: 1 or 2 Interval (d): 28 Application rate(s): 100 g a.s./ha Application window: Step 1& Step 2 – March - May;
Main routes of entry	Standard FOCUS Step1 & Step 2 assumptions
Triazole acetic acid (TAA) Parameters used in FOCUSsw step 1 and 2	Molecular weight: 127.1 Water solubility (mg/L):7 x 10^5 (20°C) Soil or water metabolite: soil metabolite K_{fOC} (L/kg): 15 DT_{50} soil (d): 11.5 days (Laboratory normalised geomean value. In accordance with FOCUS, SFO) DT_{50} water/sediment system (d): 1000 days DT_{50} water (d): 1000 days DT_{50} sediment (d): 1000days Crop interception (%):cereals - 70%; Maximum occurrence observed (% molar basis with respect to the parent) Soil: 7.00 Water/sediment system: 1% (conservative assumption)
Parameters used in FOCUSsw step 3 (if performed)	Calculations not performed

Application rate	Crop: winter cereals Crop interception: 70% Number of applications: 1 or 2 Interval (d): 28 Application rate(s): 100 g a.s./ha Application window: Step 1& Step 2 – March - May; Crop: spring cereals Crop interception: 70% Number of applications: 1 or 2 Interval (d): 28 Application rate(s): 100 g a.s./ha Application window: Step 1& Step 2 – March - May;
Main routes of entry	Standard FOCUS Step1 & Step 2 assumptions

Results of Step 1 & Step 2 calculations for cyproconazole, 1,2,4-triazole and triazole acetic acid (TAA) (only max. values used in aquatic risk assessment reported):

Substance	Single application at 100 g a.s./ha						Multiple applications at 2 x 100 g a.s./ha					
	STEP 1		STEP 2				STEP 1		STEP 2			
			North Europe		South Europe				North Europe		South Europe	
	PEC_{sw} [µg/L]	PEC_{sed} [µg/kg dry sediment]	PEC_{sw} [µg/L]	PEC_{sed} [µg/kg dry sediment]	PEC_{sw} [µg/L]	PEC_{sed} [µg/kg dry sediment]	PEC_{sw} [µg/L]	PEC_{sed} [µg/kg dry sediment]	PEC_{sw} [µg/L]	PEC_{sed} [µg/kg dry sediment]	PEC_{sw} [µg/L]	PEC_{sed} [µg/kg dry sediment]
Cyproconazole	24.527	72.946	2.109	6.295	3.498	10.584	49.054	145.892	3.860	11.541	6.461	19.571
1,2,4-triazole	1.227	1.090	0.053	0.047	0.103	0.092	2.454	2.180	0.058	0.051	0.112	0.099
triazole acetic acid (TAA)	1.000	0.150	0.051	0.008	0.098	0.015	2.001	0.299	0.063	0.009	0.118	0.018

Results of STEP 3 calculations for cyproconazole (only global max. values used in aquatic risk assessment reported):

a) use in spring cereals:

FOCUS Scenario	Single application at 100 g a.s./ha				Multiple applications at 2 x 100 g a.s./ha			
	PEC_{sw} [µg/L]	PEC_{sw} [µg/L] including substance adsorbed to the suspended particles	PEC_{sed} [µg/kg dry sediment]	Migration route	PEC_{sw} [µg/L]	PEC_{sw} [µg/L] including substance adsorbed to the suspended particles	PEC_{sed} [µg/kg dry sediment]	Migration route
D1 - ditch	1.848	1.849	11.466	Drainage	2.531	2.533	15.435	Drainage
D1 - stream	1.153	1.154	6.294	Drainage	1.579	1.580	8.410	Drainage
D3 – ditch	0.633	0.634	0.282	Spray drift	0.555	0.556	0.354	Spray drift
D4 – pond	0.279	0.279	1.794	Drainage	0.458	0.459	2.831	Drainage
D4 – stream	0.527	0.527	0.637	Spray drift	0.535	0.535	1.006	Drainage
D5 – pond	0.170	0.170	1.480	Drainage	0.234	0.234	2.064	Drainage
D5 – stream	0.545	0.546	0.330	Spray drift	0.511	0.512	0.453	Spray drift
R1 - stream	0.803	0.804	0.680	Runoff	0.803	0.804	0.678	Runoff

b) use in winter cereals:

FOCUS Scenario	Single application at 100 g a.s./ha				Multiple applications at 2 x 100 g a.s./ha			
	PEC_{sw} [µg/L]	PEC_{sw} [µg/L] including substance adsorbed to the suspended particles	PEC_{sed} [µg/kg dry sediment]	Migration route	PEC_{sw} [µg/L]	PEC_{sw} [µg/L] including substance adsorbed to the suspended particles	PEC_{sed} [µg/kg dry sediment]	Migration route
D1 – ditch	1.273	1.274	8.962	Drainage	1.983	1.984	13.355	Drainage
D1 – stream	0.796	0.797	4.893	Drainage	1.240	1.241	7.223	Drainage
D2 – ditch	1.735	1.736	7.860	Drainage	3.170	3.171	14.479	Drainage
D2 – stream	1.080	1.080	4.601	Drainage	1.973	1.974	8.529	Drainage
D3 – ditch	0.633	0.634	0.283	Spray drift	0.554	0.555	0.322	Spray drift
D4 – pond	0.222	0.222	1.479	Drainage	0.376	0.376	2.392	Drainage
D4 – stream	0.540	0.540	0.538	Spray drift	0.474	0.474	0.871	Spray drift
D5 – pond	0.162	0.162	1.428	Drainage	0.245	0.245	2.112	Drainage
D5 – stream	0.526	0.526	0.316	Spray drift	0.513	0.513	0.468	Spray drift
D6 – ditch	0.641	0.641	0.623	Spray drift	0.562	0.562	0.972	Spray drift
R1 – pond	0.061	0.061	0.385	Runoff	0.118	0.118	0.705	Runoff
R1 – stream	0.485	0.485	0.226	Runoff	0.624	0.624	0.501	Runoff
R3 - stream	0.636	0.636	0.385	Runoff	0.911	0.912	0.439	Runoff
R4 - stream	0.632	0.633	0.526	Runoff	0.632	0.633	0.525	Runoff

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

Method of calculation and type of study (*e.g.* modelling, field leaching, lysimeter)	For FOCUS GW modelling, values used – Modelling using FOCUS models, with appropriate FOCUSgw scenarios, according to FOCUS guidance. Model(s) used: FOCUS PEARL ver. 3.3.3 and FOCUS PELMO ver. 3.3.2. Scenarios: Chateaudun, Hamburg, Jokioinen, Kremsmunster, Okehampton, Piacenza, Porto, Sevilla, Thiva Crop: Winter Cereals, Spring Cereals, Q_{10} = 2.2 Substance-specific input parameters: **Cyproconazole:** M = 291.8 g/mol; S_{H2O} = 93 mg/L (20°C); p = 0 Pa(20°C); DT_{50} = 142 days (geomean, lab studies, normalisation to pF2, 20^0C with Q_{10} = 2.2) **Praper 82** proposed that the correct DT_{50} Soil (d) for use in modelling is 128.6 days. However, the figure used (142 days) is more conservative and therefore the calculations were not revised. K_{fOC} = 309 mL/g; K_{fOM} = 179 mL/g; 1/n = 0.86 (all values medians). **1,2,4-triazole :** M = 61.9 g/mol; S_{H2O} = 7 x 10^5 mg/L (20°C); p = 0 Pa(20°C); DT_{50} = 7.4 days (geomean, lab studies, normalisation to pF2, 20°C with Q_{10} = 2.2; EFSA agreed endpoint) K_{fOC} = 89 mL/g; K_{fOM} = 51.6 mL/g; 1/n = 0.92 (all values arithmetic means; EFSA agreed endpoint). Transformation parent --> 1,2,4-triazole *ff* = 1; **Triazole acetic acid (TAA):** M = 127.1 g/mol; S_{H2O} = 7 x 10^5 mg/L (20°C); p = 0 Pa(20°C); DT_{50} = 11.5 days (geomean, lab studies, normalisation to pF2, 20°C with Q_{10} = 2.2) K_{fOC} = 15 mL/g; K_{fOM} = 8.7 mL/g; 1/n = 0.913 (all values arithmetic means). Transformation 1,2,4-triazole --> Triazole acetic acid (TAA) *ff* = 1;
Application rate	Application rate: 2 x 100 g a. s./ha;

Crop interception: 70% for the first application, 90% for the second application; No. of applications: 2 Interval between the application: 28 days Time of application: winter cereals – early spring (exact dates depend on the scenario), spring cereals – early spring (exact dates depend on the scenario);

PEC(gw) - FOCUS modelling results (80th percentile annual average concentration at 1m); after two applications

a) spring cereals:

Scenario	Model: FOCUS-PEARL 3.3.3.			Model: FOCUS-PELMO 3.3.2.		
	80th percentile PEC_{GW} values [µg/L] for:			80th percentile PEC_{GW} values [µg/L] for:		
	Cyproconazole	1,2,4-triazole	Triazole acetic acid (TAA)	Cyproconazole	1,2,4-triazole	Triazole acetic acid (TAA)
Châteaudun	< 0.0001	< 0.0001	<0.0001	< 0.001	< 0.001	< 0.001
Hamburg	0.0028	0.0002	0.0081	< 0.001	< 0.001	0.037
Jokioinen	< 0.0001	< 0.0001	0.0003	< 0.001	< 0.001	0.009
Kremsmünster	0.0015	0.0001	0.0037	< 0.001	< 0.001	0.008
Okehampton	0.0028	0.0003	0.0089	< 0.001	< 0.001	0.021
Porto	< 0.0001	< 0.0001	<0.0001	< 0.001	< 0.001	< 0.001

b) winter cereals:

Scenario	Model: FOCUS-PEARL 3.3.3.			Model: FOCUS-PELMO 3.3.2.		
	80th percentile PEC_{GW} values [µg/L] for:			80th percentile PEC_{GW} values [µg/L] for:		
	Cyproconazole	1,2,4-triazole	Triazole acetic acid (TAA)	Cyproconazole	1,2,4-triazole	Triazole acetic acid (TAA)
Châteaudun	< 0.0001	< 0.0001	0.0001	< 0.001	< 0.001	0.003
Hamburg	0.0025	0.0002	0.0075	< 0.001	< 0.001	0.052
Jokioinen	< 0.0001	< 0.0001	0.0002	< 0.001	< 0.001	0.025
Kremsmünster	0.0017	0.0001	0.0004	< 0.001	< 0.001	0.01
Okehampton	0.0036	0.0003	0.0099	< 0.001	< 0.001	0.048
Piacenza	0.0149	0.0010	0.0195	0.003	< 0.001	0.086
Porto	< 0.0001	< 0.0001	<0.0001	< 0.001	< 0.001	< 0.001
Sevilla	< 0.0001	< 0.0001	0.0005	< 0.001	< 0.001	0.002
Thiva	< 0.0001	< 0.0001	0.0002	< 0.001	< 0.001	0.004

$PEC_{(gw)}$ From lysimeter / field studies: No data submitted.

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

Direct photolysis in air ‡	Not studied.
Quantum yield of direct phototransformation	Not studied.
Photochemical oxidative degradation in air ‡	**Cyproconazole** DT_{50} of 1 day derived by the Atkinson model (Aopwin version 1.5). OH (24 h) concentration assumed = 0.5 x 10^6 radicals/cm^3 **1,2,4-triazole** DT_{50} of 160 days derived by the Atkinson model (Aopwin version 1.5). OH (24 h) concentration assumed = 0.5 x 10^6 radicals/cm^3
Volatilisation ‡	from plant surfaces (BBA guideline): ≤ 17 % after 24 hours (Bean plants) from wheat plant surfaces (US EPA guideline): ~10% after 24 hours.
	from soil surfaces (BBA guideline): negligible after 24 hours
Metabolites	1,2,4-triazole is a potential metabolite in the air compartment

PEC (air)

Method of calculation	Not calculated.

$PEC_{(a)}$

Maximum concentration	Not calculated, but predicted to be negligible based on the vapour pressure (2.6 x 10^{-5} Pa) and Henry's law constant (5.0 x 10^{-5} Pa m^3/mol).

Residues requiring further assessment

Environmental occurring metabolite requiring further assessment by other disciplines (toxicology and ecotoxicology).	**Soil:** cyproconazole, 1,2,4-triazole **Surface water:** cyproconazole, 1,2,4-triazole **Ground water:** cyproconazole, 1,2,4-triazole, triazole acetic acid (TAA) **Air:** cyproconazole

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

Soil (indicate location and type of study)	No data provided - none requested
Surface water (indicate location and type of study)	No data provided - none requested.
Ground water (indicate location and type of study)	No data provided - none requested.
Air (indicate location and type of study)	No data available.

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

Not readily biodegradable

Candidate for R53

Ecotoxicology

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

Species	Test substance	Time scale	End point (mg/kg bw/day)	End point (mg/kg feed)
Birds ‡				
Bobwhite quail *Colinus viriginianus*	Cyproconazole (SAN 619F)	Acute	**94***	Not applicable
Bobwhite quail *Colinus viriginianus*	Cyproconazole (SAN 619F)	Acute	183	Not applicable
Mallard duck *Anas platyrhynchos*	Cyproconazole (SAN 619F)	Acute	> 2000	Not applicable
Japanese quails *Coturnix coturnix japonica*	Formulation (A-9898A) Alto100 SL	Acute	1304 (130 mg a.s./kg bw)	Not applicable
Bobwhite quail *Colinus viriginianus*	Cyproconazole (SAN 619F)	Short-term	478	567
Bobwhite quail *Colinus viriginianus*	Cyproconazole (SAN 619F)	Short-term	585	1292
Mallard duck *Anas platyrhynchos*	Cyproconazole (SAN 619F)	Short-term	**151***	851
Mallard duck *Anas platyrhynchos*	Triazole alanine (CGA 13013)	Short-term	> 1342	> 5000
Bobwhite quail *Colinus viriginianus*	Triazole alanine (CGA 13013)	Short-term	> 1404	> 5000
Bobwhite quail *Colinus viriginianus*	Cyproconazole (SAN 619F)	Long-term	6.6	50
Mallard Duck *Anas platyrhynchos*	Cyproconazole (SAN 619F)	Long-term	1.4	10
Mallard Duck # *Anas platyrhynchos*	Cyproconazole (SAN 619F)	Long-term	**2.4***	18
Mammals ‡				
Mouse	Cyproconazole (SAN 619F)	Acute	**200***	Not applicable
Rat	Cyproconazole (SAN 619F)	Long-term	1.4 (males) **1.7* (females)**	20
Additional higher tier studies ‡ Not submitted, not required				

*Value in bold were used in risk assessment

PRAPeR 80 experts were in agreement that this study was more appropriate for use in the risk assessment.

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

Cereals 2 x 100 g a.s./ha.

Indicator species/Category	Time scale	ETE	TER	Annex VI Trigger
Tier 1 (Birds) **According to SANCO 4145/2000 (European Commission, 2002)**				
Large herbivorous bird	Acute	6.87	13.7	> 10
Insectivorous bird	Acute	5.41	17.4	> 10
Large herbivorous bird	Short-term	3.82	39.5	> 10
Insectivorous bird	Short-term	3.02	>50	> 10
Large herbivorous bird	Long-term	2.03	**1.2**	> 5
Insectivorous bird	Long-term	3.02	**0.79**	> 5
Earthworm-eating small bird	Long-term	0.115	28.9*	> 5
Fish-eating bird	Long-term	0.34	7.1*	> 5
Higher tier refinement (Birds)				
Insectivore: Skylark – with refined FIR/bw (specific food type) and RUD	Long-term	0.375	6.4	> 5
Insectivore: Yellowhammer – with refined FIR/bw (specific food type) and RUD	Long-term	0.420	5.7	> 5
Insectivore: Yellow wagtail – with refined FIR/bw (specific food type) and RUD	Long-term	0.43	5.6	> 5
Risk assessment (Birds) according to the new EFSA (2009) guidance document and its calculation tool. This approach identifies the most appropriate focal species across all growth stages as indicated by the GAP. The short cut values are based on crop specific mean RUDs inherent in the calculation tool. The focal species for the relevant BBCH stages (31-65 (SEU); 31-69 (NEU)) is the small omnivorous bird 'lark' Combination (invertebrates with interception) 25% crop leaves 25% weed seeds 50% ground arthropods.				
BBCH 30-39-small omnivorous bird 'lark'	Acute	1.32	71.2	>10
BBCH ≥ 40- small omnivorous bird 'lark'	Acute	0.792	118.7	>10
BBCH 30-39- small omnivorous bird 'lark'	Long-term	0.315	7.6	> 5
BBCH ≥ 40- small omnivorous bird 'lark'	Long-term	0.192	12.5	> 5
Tier 1 (Mammals) **According to SANCO 4145/2000 (European Commission, 2002)**				
Small herbivorous mammal	Acute	21.7	**9.2**	> 10
Insectivorous mammal	Acute	0.88	227	> 10
Small herbivorous mammal	Long-term	6.4	**0.27**	> 5
Insectivorous mammal	Long-term	0.32	5.3	> 5
Earthworm-eating mammal	Long-term	0.147	11.6*	> 5
Fish-eating mammal	Long-term	0.21	8.1*	> 5

Indicator species/Category	Time scale	ETE	TER	Annex VI Trigger
Risk assessment (Mammals) according to the new EFSA (2009) guidance document and its calculation tool. This approach identifies the most appropriate focal species across all growth stages as indicated by the GAP. The short cut values are based on crop specific mean RUDs inherent in the calculation tool. The focal species for the relevant BBCH stages (31-65 (SEU), 31-69 (NEU)) are shown in the table below.				
BBCH ≥ 20-small insectivorous mammal 'shrew'	Long-term	1.27	15.3	>5
BBCH 30-39-small omnivorous mammal 'mouse'	Long-term	0.227	7.5	>5
BBCH ≥ 40-small herbivorous mammal 'vole'	Long-term	0.111	**1.3**	>5
Higher tier refinement (Mammals)				
Small herbivorous mammal (will have been only one application in early growth stage cereals, MAF = 1)	Acute	19.7	10.1	> 10

*Exposure estimate based on a highest 21-day TWA soil (earthworm) (see Addendum 3 Section B.8-Environmental Fate and Behaviour) (Ireland, 2010b) or 21 day FOCUS Step 1 water PEC (fish) from 2 applications each of 100 g a.s./ha with 28-day spray interval.

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

Group	Test substance	Time-scale (Test type)	End point	Toxicity (mg/L)
Laboratory tests ‡				
Fish				
Rainbow trout *Salomo gairdneri*	Cyproconazole (SAN 619F)	Acute static	96-h LC_{50}	19 mm
Bluegill sunfish *Lepomis macrochirus*	Cyproconazole (SAN 619F)	Acute static	96-h LC_{50}	21 mm
Carp *Cyprinus carpio*	Cyproconazole (SAN 619F)	Acute static	96-h LC_{50}	20 nom
Sheepshead minnow *Cyprinodon variegatus*	Cyproconazole (SAN 619F)	Acute flow through	96-h LC_{50}	21 mm
Rainbow trout *Oncorhynchus mykiss*	Cyproconazole (SAN 619F)	Chronic flow through (juveniles)	21 day NOEC	0.65 nom
Rainbow trout *Oncorhynchus mykiss*	Cyproconazole (SAN 619F)	Early life stage flow through	89 day LOEC (fry growth)	0.16 mm
Rainbow trout *Oncorhynchus mykiss*	Cyproconazole (SAN 619F)	Early life stage flow through	93 day NOEC	0.305
Fathead minnow *Pimephales promelas*	Cyproconazole (SAN 619F)	Full life cycle flow through	357 day NOEC	0.5 nom (VTG decrease) 0.125 nom (egg production)
Fathead minnow *Pimephales promelas*	Cyproconazole (SAN 619F)	Full life cycle flow through	263 day NOEC	NOEC 0.51 (spawns/female)
Fathead minnow *Pimephales promelas*	Cyproconazole (SAN 619F)	Short-term reproductive assay flow through	21 day NOEC	2.0 mm
Rainbow trout *Oncorhynchus mykiss*	Formulation (A-9898A) Alto100 SL	Acute static	96-h LC_{50}	141 nom (12.6 mg a.s./L)
Carp *Cyprinus carpio*	Formulation (A-9898A) Alto100 SL	Acute static	96-h LC_{50}	64.5 mm (5.7 mg a.s./L)
Rainbow trout *Oncorhynchus mykiss*	Formulation (A-9898A) Alto100 SL	Chronic flow through	21 day NOEC	13.8 (growth) mm <13.8 (behaviour) (0.11 mg a.s./L)
Rainbow trout *Oncorhynchus mykiss*	1,2,4- triazole (CGA 71019)	Acute static	96-h LC_{50}	498 mm

Group	Test substance	Time-scale (Test type)	End point	Toxicity (mg/L)
Rainbow trout *Oncorhynchus mykiss*	1,2,4-triazole (CGA 71019)	Chronic static-renewal	28 day NOEC	100 nom
Rainbow trout *Oncorhynchus mykiss*	Triazole acetic acid (CGA 142856)	Acute static	96-h LC_{50}	> 100 nom
Aquatic invertebrates				
Daphnia magna	Cyproconazole (SAN 619F)	Acute static	48-h EC_{50}	> 22 mm
Daphnia magna	Cyproconazole (SAN 619F)	Acute static	48-h EC_{50}	26 mm
Mysidopsis bahia	Cyproconazole (SAN 619F)	Acute flow through	96-h EC_{50}	9.6 mm
Crassostrea virginica	Cyproconazole (SAN 619F)	Acute flow through	96-h EC_{50}	2.6 nom
Daphnia magna	Cyproconazole (SAN 619F)	Chronic flow through	21 day NOEC (reproduction)	0.29 mm
Daphnia magna	Cyproconazole (SAN 619F)	Chronic semi-static	21 day NOEC	0.023 nom
Daphnia magna	Formulation (A-9898A) Alto100 SL	Acute static	48-h EC_{50}	56 nom (5 mg a.s./L**)**
Daphnia magna	Formulation (A-9898A) Alto100 SL	Chronic flow through	21 day NOEC	5.6 nom (0.5 mg a.s./L)
Daphnia magna	1,2,4-triazole (CGA 71019)	Acute static	48-h EC_{50}	100 nom
Daphnia magna	Triazole acetic acid (CGA 142856)	Acute static	48-h EC_{50}	> 100 nom
Sediment-dwelling organisms				
Chironomus riparius	Cyproconazole (SAN 619F)	Static water-sediment	28 day NOEC	5,0 mg/l (development 50 mg/kg (emergence & development) nom
Algae				
Scenedesmus subspicatus	Cyproconazole (SAN 619F)	Acute static	72-h E_bC_{50} 96-h E_bC_{50} 96-h NOEC	0.099 0.077 mm 0.021
Chlorella vulgaris	Cyproconazole (SAN 619F)	Acute static	72-h EC_{50} 72-h NOEC	0.66 mm 0.392

Group	Test substance	Time-scale (Test type)	End point	Toxicity (mg/L)
Selenastrum capricornutum	Formulation (A-9898A) Alto100 SL	Static	72-h E_bC_{50} 96-h NOEC	5.3 nom (0.47 mg a.s./L) <0.91nom
Selenastrum capricornutum Supplementary test	Formulation (A-9898A) Alto100 SL	Static	72-h E_bC_{50} 96-h NOECb 96-h NOECr	6.49 (0.58 mg a.s./L) 0.52 nom 1.35 nom
Selenastrum capricornutum	1,2,4-triazole (CGA 71019)	Static	72-h E_bC_{50} 72-h NOEC	12 mm (cell density) 3.1
Scenedesmus subspicatus	Triazole acetic acid (CGA 142856)	Static	72-h E_bC_{50} 72-h E_rC_{50} 72-h NOEC	12.2 nom 135.1 nom 2.1 nom
Higher plant				
Lemna gibba	Cyproconazole (SAN 619F)	Semi-static	7 day EC_{50} (frond number) 7 day NOEC AUC and increase in d.w.	0.059 nom 12.5 nom
Microcosm or mesocosm tests				
Not submitted, not required				

mm – endpoints is expressed as mean measured concentrations
nom - endpoints is expressed as nominal concentrations

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

FOCUS Step 1

Cereals, 2 x 100 g a.s./ha, 28 day application interval

Test substance	Organism	Toxicity end point (mg/L)	Time scale	PEC_i (mg/L)	PEC_{sed} (mg/kg)	TER*	Annex VI Trigger
Cyproconazole (SAN 619F)	Fish	19	Acute	0.0491	-	387	> 100
		0.160	Chronic	0.0491	-	**3.3**	> 10
	Aquatic invertebrates	2.6	Acute	0.0491	-	**52.9**	> 100
		0.023	Chronic	0.0491	-	**0.5**	> 10
	Algae	0.077	72-h	0.0491	-	**1.6**	> 10
	Aquatic plants	0.059	7-day	0.0491	-	**1.2**	> 10
	Sediment dwelling organisms	5.0	Chronic	0.0491	-	101.8	> 10
		50 mg/kg		0.1459	-	342.7	>10
1,2,4-triazole (CGA 71019)	Fish	498	Acute	0.00245	-	203265.3	> 100
		100	Chronic	0.00245	-	40816.3	> 10

Test substance	Organism	Toxicity end point (mg/L)	Time scale	PEC_i (mg/L)	PEC_{sed} (mg/kg)	TER*	Annex VI Trigger
	Aquatic invertebrates	> 100	Acute	0.00245	-	40816.3	>100
	Algae	12	72-h	0.00245	-	4897.9	> 10
	Sediment dwelling organisms	5	Chronic		0.002182	2291	>10
Triazole acetic acid (CGA 142856)	Fish	> 100	Acute	0.002	-	50000	> 100
	Aquatic invertebrates	> 100	Acute	0.002	-	50000	> 100
	Algae	12.2	72-h	0.002	-	6100	> 10
Alto100 SL (A-9898A)	Fish	5.7	Acute	0.0491	-	116.1	> 100
		12.6	Acute	0.0491	-	256.6	> 100
		0.11	Chronic	0.0491	-	**2.2**	> 10
	Aquatic invertebrates	5.0	Acute	0.0491	-	101.8	> 100
		0.5	Chronic	0.0491	-	10.2	> 10
	Algae	0.47	72-h	0.0491	-	**9.6**	> 10

* TER at field border

FOCUS Step 2

Cereals, 2 x 100 g a.s./ha, 28 day application interval

Test substance	Organism	Toxicity end point (mg/L)	Time scale	PEC_{INI} [mg a.s./L]		TER* Step 2		Annex VI Trigger
				NEU	SEU	NEU	SEU	
Cyproconazole (SAN 619F)	Fish	0.160	Chronic	0.00386	0.00646	41.5	24.8	> 10
	Green algae	0.077	72-h	0.00386	0.00646	19.9	11.9	> 10
	Aquatic plants	0.059	7 day	0.00386	0.00646	15.3	**9.1**	> 10
	Aquatic invertebrates	2.6	Acute	0.00386	0.00646	673.6	402.5	> 100
		0.023	Chronic	0.00386	0.00646	**6.0**	**3.6**	> 10
Alto100 SL (A-9898A)	Fish	0.11	Chronic	0.00386	0.00646	28.5	17.0	> 10
	Green algae	0.47	72-h	0.00386	0.00646	121.8	72.7	> 10

* TER at field border

FOCUS Step 3

Cereals, worst case maximum PEC between winter and spring cereals and between 1 x 100 g a.s./ha and 2 x 100 g a.s./ha 28 day application interval

FOCUS Scenario	2 x 100 g/ha	Species			
Class type of study	Maximum PECsw [µg/L]	Invertebrates Chronic *Daphnia magna*		Aquatic plants *Lemna gibba*	
Endpoint		21-day NOEC [mg a.s./L]	TER	7 day EC_{50} [mg a.s./L]	TER
D1 - ditch	2.531	0.023	**9.1***	0.059	23.3
D1 - stream	1.579	0.023	14.6	0.059	37.4
D2 – ditch	3.17	0.023	**7.3***	0.059	18.6
D2 – stream	1.973	0.023	11.7	0.059	29.9
D3 – ditch	0.633	0.023	36.3	0.059	93.2
D4 – stream	0.54	0.023	42.6	0.059	109.3
D4 – pond	0.458	0.023	50.2	0.059	128.8
D5 – stream	0.545	0.023	42.2	0.059	108.3
D5 – pond	0.245	0.023	93.9	0.059	240.8
D6 – ditch	0.641	0.023	35.9	0.059	92.0
R1 - stream	0.803	0.023	28.6	0.059	73.5
R1 – pond	0.118	0.023	194.9	0.059	500.0
R3 - stream	0.911	0.023	36.2	0.059	64.8
R4 - stream	0.632	0.023	36.4	0.059	93.4

*In the FOCUS Step 3 calculations, the D1 scenario for spring cereals marginally fails to exceed the Annex VI Trigger of 10. The FOCUS Step 3 D2 scenario for winter cereals fails to exceed the Annex VI trigger of 10. Member States may consider the relevance of these scenarios in relation to the direct significance of these results. Additionally, Member States may consider the validity of applying the geomean of the 2 studies, which yielded NOEC values which differed by a factor of 10 (flow-through NOEC=0.29 mg/L; semi-static NOEC=0.023 mg/L). PRAPeR 80 experts were not supportive of the opinion to apply this geomean value due to the large difference in NOEC values, but agreed that if the differences are resolved, Member States may apply the geomean for the risk assessment, which would result in overall exceedence of the Annex VI trigger of 10.

FOCUS Step 4

Not performed.

Bioconcentration				
	Cyproconazole (SAN 619F)	Metabolite 1	Metabolite 2	Metabolite 3
$logP_{O/W}$	3.1	-	-	-
Bioconcentration factor (BCF)[1] ‡	28 59 (non-edible tissues) 34 (whole fish) 8.1 (edible tissues)	-	-	-
Annex VI Trigger for the bioconcentration factor	100	-	-	-
Clearance time (days) (CT_{50}) (CT_{90})	0.87 -	-	-	-

Bioconcentration				
Level and nature of residues (%) in organisms after 14 day depuration phase	0.61 mg a.s./kg (6%) in non-edible tissues (viscera) 0.41 mg a.s./kg (7%) in whole fish tissues < 0.3 mg a.s./kg (< 17%) in edible tissue	-	-	-

[1] only required if log $P_{O/W}$>3

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

Test substance	Acute oral toxicity (LD_{50} µg/bee)	Acute contact toxicity (LD_{50} µg/bee)
Cyproconazole (SAN 619F) ‡	> 100 (24-96 h)	> 100 (24 –96 h)
Formulation (A-9898 A) 'Alto100 SL' [1)]	> 1000 (24 h)	13 (24 h)
Field or semi-field tests		
Not submitted, not required		

[1] formulation endpoints expressed as µg product/bee

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

Cereals, 100 g a.s./ha

Test substance	Route	Hazard quotient	Annex VI Trigger
Cyproconazole (SAN 619F)	oral	<1.0	< 50
	contact	<1.0	
Formulation (A-9898 A) 'Alto100 SL'	oral	7.7	< 50
	contact	<0.1	

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

Laboratory tests with standard sensitive species

Species	Test Substance	End point	Effect (LR_{50} g a.s/ha)
Typhlodromus pyri ‡	Formulation (A-9898 A) 'Alto 100 SL'	Mortality	29.4
Aphidius rhopalosiphi ‡		Mortality	Not available (80 g a.s./ha = 100 % mortality)

Cereals, 2 x 100 g a.s./ha, 28 day application intervals

Test substance	Species	Effect (LR_{50} g a.i/ha)	HQ in-field	HQ off-field [1)]	Trigger
TIER 1 (correction factor = 10)					
Formulation (A-961 B) Alto 240 EC	*Typhlodromus pyri*	29.4	4.12	0.089	< 2
Formulation (A-9898 A) Alto 100 SL	*Aphidius rhopalosiphi*	<80	>1.38	>0.033	< 2
TIER 2 (correction factor = 5)					
Formulation (A-961 B) Alto 240 EC	*Typhlodromus pyri*	51	2.16	0.026	< 2
Formulation (A-9898 A) Alto 100 SL	*Aphidius rhopalosiphi*	>200	<0.55	<0.065	< 2

[1)] the basic drift value for one application is of 2.38% for field crops and 1 m distance from the field edge and MAF 1,1

Cereals, 1 x 100 g a.s./ha

Test substance	Species	Effect (LR_{50} g a.s./ha)	HQ in-field	HQ off-field [1)]	Trigger
TIER 1 (correction factor = 10)					
Formulation (A-961 B) Alto 240 EC	*Typhlodromus pyri*	29.4	3.4	0.094	< 2
Formulation (A-9898 A) Alto 100 SL	*Aphidius rhopalosiphi*	<80	>1.25	>0.034	< 2
TIER 2 (correction factor = 5)					
Formulation (A-9898 A) Alto 100 SL	*Typhlodromus pyri*	251	1.96	0.027	< 2
	Aphidius rhopalosiphi	>200	<0.50	<0.069	< 2

[1)] the basic drift value for one application is of 2.77% for field crops and 1 m distance from the field edge and MAF 1,0

Further laboratory and extended laboratory studies ‡

Species	Formulation	Test substance, substrate and duration	Endpoint (g a.s./ha)	% effects	Trigger value
Typhlodromus pyri	A-9961 B Alto 240 EC	28, 400, 520 ml/ha (21 days)	Fresh residues **LR_{50} 51** Corrected mortalities 12.5, 57.1, 76.8, 100% Aged residues (7d) **LR_{50} 94.3** Corrected mortalities 9.3, 44.4, 61.1%	No significant effects on fecundity with fresh and aged residues at all treatment rates	50%
Aphidius rhopalosiphi Adult female (<2 day old)	(A-9898 A) Alto 100 SL	100, 200 g a.s./ha (21 day)	LR_{50} > 200	No significant or > 50% effects on fecundity at any rate	50 %
Chrysoperla carnea (1st instar)	(A-9898 A) Alto 100 SL	5,54, 10, 100, 200 g a.s./ha (33 days)	LR_{50} > 200 Correction mortality up to 20%	No significant or > 50% effects on fecundity at any rate	50 %
Poecilus cupreus Adult	(A-9898 A) Alto 100 SL	80, 160 g a.s./ha (14 days)	LR_{50} > 200	No significant or > 50% effects upon feeding behaviour	50%
Orius laevigatus (2nd instar)	(A-9898 A) Alto 100 SL	5,54, 10, 100, 200 g a.s./ha (max. 16 days)	LR_{50} > 200	No significant or > 50% effects on fecundity at any rate	50%

1) a negative value indicates an increase, relative to control

Field or semi-field tests
Not submitted, not required

Effects on earthworms, other soil macro-organisms and soil micro-organisms (Annex IIA points 8.4 and 8.5. Annex IIIA, points, 10.6 and 10.7)

Test organism	Test substance	Time scale	End point
Earthworms			
Acute 14 days	Cyproconazole (SAN 619F)	Acute 14 days	$LC_{50\ corr}$ = 167.5 mg a.s../kg d.w.soil
	Formulation (A-9898 A) Alto100 SL	Acute 14 days	$LC_{50\ corr}$ = 37.5 mg a.s./kg d.w.soil
	Formulation (A-9898 A) Alto 100 SL	Chronic (56 days)	$NOEC_{corr}$ = 0.75 mg a.s../kg d.w.soil

Test organism	Test substance	Time scale	End point
	1,2,4 triazole	Acute 14 days	LC_{50} > 1000 mg /kg d.w.soil
	1,2,4 triazole	Chronic (56 days)	NOEC = 1.0 mg /kg d.w.soil
	Triazole acetic acid	Acute 14 days	LC_{50} > 1000 mg /kg d.w.soil
Other soil macro-organisms			
Collembola			
Falsomia candida	Formulation (A-9898 A) Alto 100 SL	Chronic 28 days	NOEC = 55.8 mg a.s./kg d.w. soil
	1,2,4 triazole	Chronic 28 days	NOEC = 1.8 mg a.s./kg d.w.soil
	Triazole acetic acid	Chronic 28 days	NOEC = 15.6 mg a.s./kg d.w.soil
Soil micro-organisms			
Nitrogen mineralisation	Cyproconazole (SAN 619F)	7 days	< 25% at 2.5 mg a.s./kg d.w. soil
	1,2,4 triazole	28 days	< 25% at 0.353 mg a.s../kg d.w. soil
	Triazole acetic acid	28 days	< 25% effect at 0.08043 mg/kg dry soil
Carbon mineralisation	Cyproconazole (SAN 619F)	28 days	< 25% at 2.5 mg a.s../kg d.w. soil
	1,2,4 triazole	28 days	< 25% at 0.353 mg a.s../kg d.w. soil
	Triazole acetic acid	28 days	< 25% effect at 0.08043 mg/kg dry soil
Field studies			
No effects seen on degradability of soil organic matter in a 245-day litter bag study under exposure conditions, simulating 10 years continual use at an annual rate of 100 g a.s./ha.			

Toxicity/exposure ratios for soil organisms

Cereals, 2 x 100 a.s./ha with 28-day application intervals

Test organism	Test substance	Time scale	PEC plateau plus $PEC_{initial}$	TER	Trigger
Earthworms					
Eisenia foetida	Cyproconazole	Acute	0.0762	2198.2	> 10
	Formulation A-9898 A	Acute	0.0762	492.1	> 10
	Formulation A-9898 A	Chronic	0.0762	9.8	> 5
	1,2,4 triazole	Acute	0.0024	416666.7	> 10
	1,2,4 triazole	Chronic	0.0024	416.7	> 5
	Triazole acetic acid	Acute	0.0017	166666.7	> 10
Other soil macro-organisms					
Folsomia candida	Cyproconazole	Chronic	0.0762	732.3	> 5
	1,2,4 triazole	Chronic	0.0024	750	> 5
	Triazole acetic acid	Chronic	0.0017	9176.5	> 5

Effects on non target plants (Annex IIA, point 8.6, Annex IIIA, point 10.8)

Preliminary screening data

Not submitted, not required

Laboratory dose response tests

Most sensitive species	Test substance	ER_{50} (g a.s./ha) vegetative vigour	ER_{50} (g a.s./ha) emergence	Exposure (g a.s./ha)	TER	Trigger
Beta vulgaris	Formulation (A-9898 A) Alto 100 SL	> 400 (effect <12.5%)	> 400 (effect <12.5%)	100	>4	> 5
Zea mays		> 400 (effect <25%)	> 400 (effect <37.5%)	100	>4	> 5

Additional studies (e.g. semi-field or field studies)

Not submitted, not required

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

Test type/organism	*Pseudomonas sp*
Activated sludge	-
Endpoint – 3 hour EC_{50}	> 100 mg a.s./L

Ecotoxicologically relevant compounds (consider parent and all relevant metabolites requiring further assessment from the fate section)

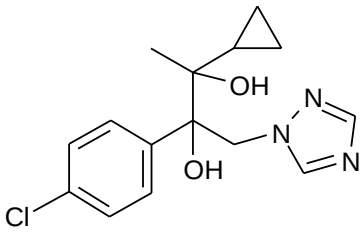
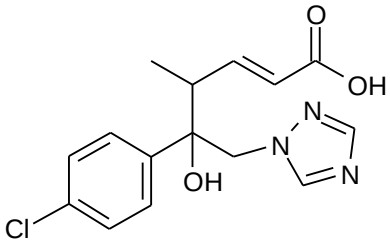
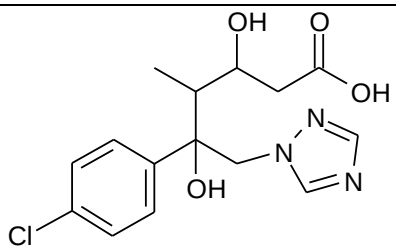
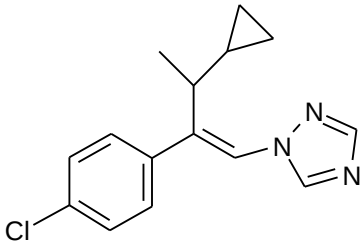
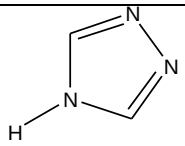
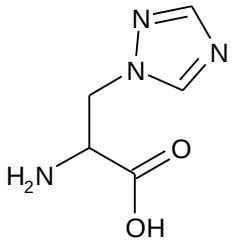
Compartment	
soil	Cyproconazole, 1,2,4 triazole
water	Cyproconazole, 1,2,4 triazole
sediment	Cyproconazole, 1,2,4-triazole
groundwater	Cyproconazole, 1,2,4-triazole, Triazole acetic acid (TAA)

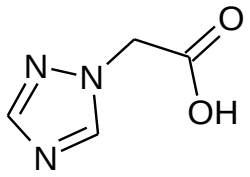
Classification and proposed labelling with regard to ecotoxicological data (Annex IIA, point 10 and Annex IIIA, point 12.3)

	RMS/peer review proposal
Active substance (cyproconazole)	N, R50/53
	S61

	RMS/peer review proposal
Preparation	N, R51/53
	S61

APPENDIX B – USED COMPOUND CODE(S)

Code/Trivial name*	Chemical name	Structural formula
M9/M14 (pair of diastereoisomers) NOA 421153	2-(4-chlorophenyl)-3-cyclopropyl-1-(1H-1,2,4-triazol-1-yl)-2,3-butanediol	
M21/21a NOA 405870	5-(4-chlorophenyl)-5-hydroxy-4-methyl-6-(1H-1,2,4-triazol-1-yl)-2-hexanoic acid	
M36(Z2) NOA 405872	5-(4-chloro-phenyl)-3,5-dihydroxy-4-methyl-6-[1,2,4]triazol-1-yl-hexanoic acid	
M38(Z1) NOA 421155	1-[(E)-2-(4-chloro-phenyl)-3-cyclopropyl-but-1-enyl]-1H-[1,2,4]triazole	
1,2,4-triazole CGA 71019	1,2,4-triazole	
Triazole alanine (TA) CGA 131013 (M39)	2-amino-3- [1,2,4] triazol-1-yl-propionic acid	

Code/Trivial name*	Chemical name	Structural formula
Triazole acetic acid (TAA) CGA 142856	1*H*-1,2,4-triazol-1-ylacetic acid	

* The metabolite name in bold is the name used in the conclusion.

ABBREVIATIONS

1/n	slope of Freundlich isotherm
ε	decadic molar extinction coefficient
°C	degree Celsius (centigrade)
µg	microgram
µm	micrometer (micron)
a.s.	active substance
AChE	acetylcholinesterase
ADE	actual dermal exposure
ADI	acceptable daily intake
AF	assessment factor
AOEL	acceptable operator exposure level
AP	alkaline phosphatase
AR	applied radioactivity
ARfD	acute reference dose
AST	aspartate aminotransferase (SGOT)
AV	avoidance factor
BCF	bioconcentration factor
BUN	blood urea nitrogen
bw	body weight
CAS	Chemical Abstract Service
CFU	colony forming units
ChE	cholinesterase
CI	confidence interval
CIPAC	Collaborative International Pesticide Analytical Council Limited
CL	confidence limits
CYP1A	Cytochrome P450 1A
d	day
DAA	days after application
DAR	draft assessment report
DAT	days after treatment
DFOP	double first order in parallel kinetics
DM	dry matter
DT_{50}	period required for 50 percent disappearance (define method of estimation)
DT_{90}	period required for 90 percent disappearance (define method of estimation)
dw	dry weight
EbC_{50}	effective concentration (biomass)
EC_{50}	effective concentration
ECHA	European Chemical Agency
EEC	European Economic Community
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
ELS	early life stage
EMDI	estimated maximum daily intake
ER_{50}	emergence rate/effective rate, median
ErC_{50}	effective concentration (growth rate)
EU	European Union
EUROPOEM	European Predictive Operator Exposure Model
f(twa)	time weighted average factor
FAO	Food and Agriculture Organisation of the United Nations
FIR	Food intake rate
FOB	functional observation battery
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
g	gram

GAP	good agricultural practice
GC	gas chromatography
GC-FID	gas chromatography with flame ionisation detector
GCPF	Global Crop Protection Federation (formerly known as GIFAP)
GC-MSD	gas chromatography with mass spectrometric detection
GGT	gamma glutamyl transferase
GLC-MSD	gas liquid chromatography with mass spectrometric detection
GM	geometric mean
GPC	gel-permeation chromatography
GS	growth stage
GSH	glutathion
GST	gluthatione S-transferase
h	hour(s)
ha	hectare
Hb	haemoglobin
Hct	haematocrit
hL	hectolitre
HPLC	high pressure liquid chromatography or high performance liquid chromatography
HPLC-MS	high pressure liquid chromatography – mass spectrometry
HPLC-UV	high pressure liquid chromatography with ultraviolet detector
HQ	hazard quotient
IEDI	international estimated daily intake
IESTI	international estimated short-term intake
ILV	inter laboratory validation
ISO	International Organisation for Standardisation
IUPAC	International Union of Pure and Applied Chemistry
JMPR	Joint Meeting on the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
K_{doc}	organic carbon linear adsorption coefficient
kg	kilogram
K_{Foc}	Freundlich organic carbon adsorption coefficient
L	litre
LC	liquid chromatography
LC_{50}	lethal concentration, median
LC-MS	liquid chromatography-mass spectrometry
LC-MS-MS	liquid chromatography with tandem mass spectrometry
LD_{50}	lethal dose, median; dosis letalis media
LDH	lactate dehydrogenase
LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOEL	lowest observable effect level
LOQ	limit of quantification (determination)
m	metre
M/L	mixing and loading
MAF	multiple application factor
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
mg	milligram
mL	millilitre
mm	millimetre
MRL	maximum residue limit or level
MS	mass spectrometry

MSDS	material safety data sheet
MTD	maximum tolerated dose
MWHC	maximum water holding capacity
NADPH	nicotinamide adenine dinucleotide phosphate
NCPR	NADPH-cytochrome P-450 reductase
ND	not determined
NESTI	national estimated short-term intake
NEU	northern Europe
ng	nanogram
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
OM	organic matter content
Pa	Pascal
PD	proportion of different food types
PEC	predicted environmental concentration
PEC_{air}	predicted environmental concentration in air
PEC_{gw}	predicted environmental concentration in ground water
PEC_{sed}	predicted environmental concentration in sediment
PEC_{soil}	predicted environmental concentration in soil
PEC_{sw}	predicted environmental concentration in surface water
pH	pH-value
PHED	pesticide handler's exposure data
PHI	pre-harvest interval
PIE	potential inhalation exposure
pK_a	negative logarithm (to the base 10) of the dissociation constant
POEM	predictive operator exposure model
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
PTT	partial thromboplastin time
QSAR	quantitative structure-activity relationship
r^2	coefficient of determination
RPE	respiratory protective equipment
RUD	residue per unit dose
SD	standard deviation
SEU	southern Europe
SF	safety factor
SFO	single first-order
SIM	selected ion mode
SL	soluble concentrate
SPE	solid phase extraction
SSD	species sensitivity distribution
STMR	supervised trials median residue
$t_{1/2}$	half-life (define method of estimation)
TDM	Triazole Derivative Metabolite
TER	toxicity exposure ratio
TER_A	toxicity exposure ratio for acute exposure
TER_{LT}	toxicity exposure ratio following chronic exposure
TER_{ST}	toxicity exposure ratio following repeated exposure
TK	technical concentrate
TLV	threshold limit value

TMDI	theoretical maximum daily intake
TRR	total radioactive residue
TSH	thyroid stimulating hormone (thyrotropin)
TWA	time weighted average
UDP	Uridine diphosphate
UDPGT	UDP-glucuronyl transferase
UDS	unscheduled DNA synthesis
UV	ultraviolet
VTG	vitellogenin
W/S	water/sediment
w/v	weight per volume
w/w	weight per weight
WBC	white blood cell
WG	water dispersible granule
WHO	World Health Organisation
wk	week
yr	year