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CONCLUSION ON PESTICIDES PEER REVIEW

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Peer review of the pesticide risk assessment of the active substance cyprodinil

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The declarations of interest of all scientific experts active in EFSA's work are available at https://open.efsa.europa.eu/experts

Abstract

The conclusions of the European Food Safety Authority (EFSA) following the peer review of the initial risk assessments carried out by the competent authorities of the rapporteur Member State France and co-rapporteur Member State Bulgaria for the pesticide active substance cyprodinil are reported. The context of the peer review was that required by Commission Implementing Regulation (EU) No 844/2012, as amended by Commission Implementing Regulation (EU) No 2018/1659. The conclusions were reached on the basis of the evaluation of the representative uses of cyprodinil as a fungicide on apples and barley. The reliable end points, appropriate for use in regulatory risk assessment are presented. Missing information identified as being required by the regulatory framework is listed. Concerns are reported where identified.

KEYWORDS

cyprodinil, fungicide, peer review, pesticide, risk assessment

CONTENTS

SUMMARY

Commission Implementing Regulation (EU) No 844/2012, as amended by Commission Implementing Regulation (EU) No 2018/1659, lays down the procedure for the renewal of the approval of active substances submitted under Article 14 of Regulation (EC) No 1107/2009. The list of those substances is established in Commission Implementing Regulation (EU) No 686/2012. Cyprodinil is one of the active substances listed in Regulation (EU) No 686/2012.

In accordance with Article 1 of the Regulation, the rapporteur Member State (RMS) France and co-rapporteur Member State (co-RMS) Bulgaria, received an application from Syngenta Crop Protection AG for the renewal of approval of the active substance cyprodinil.

An initial evaluation of the dossier on cyprodinil was provided by the RMS in the renewal assessment report (RAR), and subsequently, a peer review of the pesticide risk assessment on the RMS evaluation was conducted by EFSA in accordance with Article 13 of Commission Implementing Regulation (EU) No 844/2012, as amended by Commission Implementing Regulation (EU) No 2018/1659. The following conclusions are derived.

The uses of cyprodinil according to the representative use of cyprodinil as a **fungicide** on apples and barley, as proposed at EU level, result in a sufficient fungicidal efficacy against the target organisms.

The assessment of the data package revealed no issues that need to be included as critical areas of concern with respect to the **identity, physical, chemical and technical properties** of cyprodinil or the formulations for representative uses, and **analytical methods**.

In the area of **mammalian toxicology** and non-dietary exposure, a data gap has been identified for the characterisation of toxicity profiles for several metabolites. No critical areas of concern or issues not finalised were identified.

In the area of **residues**, due to the multiple data gaps identified including data gaps for the characterisation of the toxicity profile for major residue metabolites, the consumer dietary risk assessment could not be finalised.

In to the area of **environmental fate and behaviour**, appropriate information was lacking to address the effect of water treatment processes on the nature of residues of the active substance and its possible metabolites, potentially present in surface water, when surface water is abstracted for drinking water.

In the area of **ecotoxicology**, the high risk for wild non-target terrestrial vertebrates and the high risk for aquatic organisms were identified as critical areas of concern. In addition, the risk assessment for sediment dwelling organisms, for honey bee larva and for earthworms could not be finalised.

Regarding the assessment of the **endocrine disruption** (ED) properties, based on the available data and assessments, it can be concluded that cyprodinil meets the ED criteria for humans and non-target-organisms according to points 3.6.5 and 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605.

BACKGROUND

Commission Implementing Regulation (EU) No 844/2012,[1] as amended by Commission Implementing Regulation (EU) No 2018/1659[2] (hereinafter referred to as 'the Regulation'), lays down the provisions for the procedure of the renewal of the approval of active substances, submitted under Article 14 of Regulation (EC) No 1107/2009.[3] This regulates for the European Food Safety Authority (EFSA) the procedure for organising the consultation of Member States, the applicant(s) and the public on the initial evaluation provided by the rapporteur Member State (RMS) and/or co-rapporteur Member State (co-RMS) in the renewal assessment report (RAR), and the organisation of an expert consultation where appropriate.

In accordance with Article 13 of the Regulation, unless formally informed by the European Commission that a conclusion is not necessary, EFSA is required to adopt a conclusion on whether the active substance can be expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009 within 5 months from the end of the period provided for the submission of written comments, subject to an extension of up to 8 months where additional information is required to be submitted by the applicant(s) in accordance with Article 13(3). Furthermore, in accordance with Article 13(3a), where the information available in the dossier is not sufficient to conclude the assessment on whether the approval criteria for endocrine disruption are met, additional information can be requested to be submitted in a period of minimum 3 months, not exceeding 30 months, depending on the type of information requested.

In accordance with Article 1 of the Regulation, the RMS France and co-RMS Bulgaria received an application from Syngenta Crop Protection AG for the renewal of approval of the active substance cyprodinil. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicant, the co-RMS (Bulgaria), the European Commission and EFSA about the admissibility.

The RMS provided its initial evaluation of the dossier on cyprodinil in the RAR, which was received by EFSA on 2 October 2017 (France, 2017).

In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicant, Syngenta Crop Protection AG, for consultation and comments on 14 December 2017. EFSA also provided comments. In addition, EFSA conducted a public consultation on the RAR. EFSA collated and forwarded all comments received to the European Commission on 15 February 2018. At the same time, the collated comments were forwarded to the RMS for compilation and evaluation 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.

The need for expert consultation and the necessity for additional information to be submitted by the applicant in accordance with Article 13(3) of the Regulation were considered in a telephone conference between EFSA and the RMS on 23 March 2018. On the basis of the comments received, the applicant's' response to the comments and the RMS's evaluation thereof, it was concluded that additional information should be requested from the applicant and that EFSA should conduct an expert consultation in the areas of mammalian toxicology, residues and ecotoxicology.

In addition, following a consultation with Member States in the Pesticides Peer Review Experts' meetings PREV 05 in Mammalian toxicology – Ecotoxicology (joint session on ED) (May 2019), it was considered necessary to apply an additional clock stop of 30 months in accordance with Commission Implementing Regulation (EU) No 2018/1659, to be able to conclude whether the approval criteria for endocrine disruption (ED) in line with the scientific criteria for the determination of endocrine disrupting properties, as laid down in Commission Regulation (EU) 2018/605,[4] are met.

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 an expert consultation, were compiled by EFSA in the format of an evaluation table.

The conclusions arising from the consideration by EFSA, and as appropriate by the RMS, of the points identified in the evaluation table, together with the outcome of the expert consultation and the written consultation on the assessment of additional information, 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 November 2018 and following the ED clock stop in October–November 2024.

This conclusion report summarises the outcome of the peer review of the risk assessment of the active substance and the representative formulations, evaluated on the basis of the representative uses of cyprodinil as a fungicide on apples and barley, as proposed by the applicant. In accordance with Article 12(2) of Regulation (EC) No 1107/2009, risk mitigation options identified in the RAR and considered during the peer review are presented in the conclusion. It is noted that, outside of the regulatory clock stop applied for the determination of endocrine disrupting properties, the applicant submitted additional information in June 2022 on negligible exposure of humans and the environment to cyprodinil. However, since

[1]Commission Implementing Regulation (EU) No 844/2012 of 18 September 2012 setting out the provisions necessary for the implementation of the renewal procedure for active substances, as provided for in Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market. OJ L 252, 19.9.2012, pp. 26–32.

[2]Commission Implementing Regulation (EU) No 2018/1659 of 7 November 2018 amending Implementing Regulation (EU) No 844/2012 in view of the scientific criteria for the determination of endocrine disrupting properties introduced by Regulation (EU) 2018/605.

[3]Regulation (EC) No 1107/2009 of 21 October 2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. OJ L 309, 24.11.2009, pp. 1–50.

[4]Commission Regulation (EU) 2018/605 of 19 April 2018 amending Annex II to Regulation (EC) No 1107/2009 by setting out scientific criteria for the determination of endocrine disrupting properties. OJ L 101, 20.4.2018, pp. 33–36.

this information was provided outside of the regulatory clock stop, it was not further considered in the present Conclusion. Nevertheless, the applicant concluded that for this active substance the exposure to human cannot be considered as negligible. Furthermore, no additional documentation was provided to demonstrate negligible exposure to humans (dietary and non-dietary) and non-target organisms. As a result, an assessment of negligible exposure for the representative uses has not been included in this Conclusion. Additionally, in April 2022, the applicant requested a derogation under Article 4(7) of Regulation (EC) 1107/2009, providing documentary evidence on the necessity of cyprodinil as a fungicide to control a serious danger to plant health. The evidence considered the authorised uses of cyprodinil in 7 Member States. However, as this submission also fell outside of the regulatory clock stop, it was not further considered in the present Conclusion.

A list of the relevant end points for the active substance and the formulation is provided in Appendix B. In addition, the considerations as regards the cut-off criteria for cyprodinil according to Annex II of Regulation (EC) No 1107/2009 are summarised in Appendix A.

In addition, a key supporting document to this conclusion is the peer review report (EFSA, 2024), 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 comprises the following documents, in which all views expressed during the course of the peer review, including minority views, where applicable, can be found:

- the comments received on the RAR;
- the reporting table (23 March 2018 and 17 July 2023[5]);
- the evaluation table (11 December 2024);
- the reports of the scientific consultation with Member State experts (where relevant);
- the comments received on the assessment of the additional information (where relevant);
- the comments received on the draft EFSA conclusion.

Given the importance of the RAR, including its revisions (France, 2023), and the peer review report, both documents are considered as background documents to this conclusion and thus are made publicly available.

It is recommended that this conclusion report and its background documents would not be accepted to support any registration outside the EU for which the applicant has not demonstrated that it has regulatory access to the information on which this conclusion report is based.

THE ACTIVE SUBSTANCE AND THE FORMULATION(S) FOR REPRESENTATIVE USES

Cyprodinil is the ISO common name for 4-cyclopropyl-6-methyl-*N*-phenylpyrimidin-2-amine (IUPAC).

The formulations for representative uses for the evaluation were 'A8637C (Chorus 50 WG)', a water-dispersible granule (WG) containing 500 g/kg cyprodinil, and 'A14325E (Kayak)', an emulsifiable concentrate (EC) containing 300 g/L cyprodinil. It should be noted that FAO specifications under the new procedure belonging to Syngenta exist for both type of formulations: 511/WG (May 2009) and 511/EC (May 2009).

The information on the active substance and the formulation for representative uses, including the co-formulants in these formulations, was considered in the assessment during the peer review. None of the co-formulants is an unacceptable co-formulant listed in Annex III of Regulation (EC) No 1107/2009,[6] however two co-formulants are currently approved active substances under Regulation (EC) 1107/2009.[7] Details on the composition of the formulation cannot be reported in conclusions because of the provisions in Article 63(2)(d) of Regulation (EC) No 1107/2009, however this information was fully available and evaluated during the peer review. A proposal for classification of the formulation according to Regulation (EC) 1272/2008 was provided by the applicant and assessed by the RMS (please see Volumes 3 CP of the RAR).

The representative uses evaluated were spray applications for the control of *Venturia inaequalis* in apples and for the control of *Pyrenophora teres* in barley, in the EU. Full details of the GAPs can be found in the list of end points in Appendix B.

Data were submitted to conclude that the representative uses of cyprodinil proposed at EU level result in a sufficient fungicidal efficacy against the target organisms, following the guidance document SANCO/2012/11251-rev. 4 (European Commission, 2014b).

[5]Reporting Table following consultation on the revised RAR on the assessment of the endocrine disrupting properties made available after the 30-month clock stop.

[6]Commission Regulation (EU) 2021/383 of 3 March 2021 amending Annex III to Regulation (EC) No 1107/2009 of the European Parliament and Council listing co-formulants which are not accepted for inclusion in plant protection products. OJ L 74, 4.3.2021, pp. 7–26.

[7]Please see Regulation (EC) No 1107/2009 for acceptability criteria for co-formulants and Section 2.13.6 of the Technical report on the outcome of the pesticides peer review meeting on general recurring issues in physical and chemical properties and analytical methods. EFSA supporting publication 2019:EN-1623. 32 pp. https://doi.org/10.2903/sp.efsa.2019.EN-1623.

CONCLUSIONS OF THE EVALUATION

General aspects

With regard to the toxicological information available for the formulations for representative uses 'A8637C' and 'A14325E', studies were performed on acute toxicity endpoints. Considering the information made available in the revised RAR after the experts' meeting with regard to the co-formulants contained in 'A8637C' and 'A14325E', EFSA concluded that sufficient toxicological data were not available for all components, except for two. One co-formulant lacked sufficient information about its specification/composition. For the insufficiently characterised co-formulants, EFSA confirmed the conclusion of the experts that the available toxicological information did not adequately address the genotoxicity and repeated dose toxicity potential of 'A8637C' and 'A14325E' over the short- and long-term and that they might be considered for further assessment. The collected information on the existing uses other than plant protection products, under regulated EU frameworks, did not highlight any concern (see Section 10).[8]

The availability of ecotoxicity data with the formulation for representative uses was discussed at the experts' meeting.[9] It was noted that, based on the available acute data (see Section 5), the formulation for representative uses is not more acutely toxic than expected from the active substance. Therefore, available data for the individual components were retrieved and were discussed at the experts meeting.[10] Data on components were limited and some issues were identified, therefore it was not possible to reach a conclusion on the safety of the formulation for representative uses (see Section 10).

A data gap has been identified in the residues section for an updated literature search using appropriate criteria for selecting studies in accordance with EFSA guidance on the submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (EFSA, 2011) (see Section 10).

1 | IDENTITY, PHYSICAL/CHEMICAL/TECHNICAL PROPERTIES AND METHODS OF ANALYSIS

The following guidance documents were followed in the production of this conclusion: European Commission (2000a, 2000b, 2010a, 2012).

The proposed specification for cyprodinil is based on batch data from industrial scale production. The minimum purity of the active substance as manufactured is 990 g/kg. It is proposed to update the current reference specification as the new proposed reference specification is supported by the batches used in the (eco)toxicological assessment (see Sections 2 and 5) and complies with the requirements of the FAO specification 511/TC (May 2009) published under the FAO New Procedure with minimum cyprodinil content of 990 g/kg. The current reference specification is not supported by the batches used in the (eco)toxicological assessment (EFSA, 2006), and does not comply with the FAO specification for cyprodinil due to the lower specified minimum purity of 980 g/kg.

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

Adequate methods are available for the generation of the data required for the risk assessment. Methods of analysis are available for the determination of the active substance in the technical material and in the formulations for representative uses.

The residue definition for monitoring in fruit and cereal/grass crops was defined as cyprodinil (see Section 3). The QuEChERS multi-residue enforcement method with liquid chromatography with tandem mass spectrometry (LC–MS/MS) can be used for the determination of residues of cyprodinil in high-water content, high-acid content, high-oil content and dry crop matrices with a LOQ of 0.01 mg/kg. A data gap was however identified to address the extraction efficiency of the method (see Section 10). It was proposed however to include NOA422054 (free and conjugated) as a provisional residue definition for both enforcement and risk assessment for rotational crops (see Section 3). As a consequence, a data gap was set for a validated monitoring method and its ILV for monitoring cyprodinil and NOA422054 (free and conjugated) in rotational crops and for n-octanol/water partition coefficient data of NOA422054 (free and conjugated) (see Section 10). The residue definition for food and feed of animal origin was defined as sum of cyprodinil and CGA304075 (free and conjugated), expressed as cyprodinil. A high-pressure liquid chromatography–tandem mass spectrometry (HPLC–MS/MS) method exists for the determination of the residues of cyprodinil and CGA 304075 (free and conjugated) in animal commodities (meat, fat, liver, kidney, milk and eggs) with a LOQ of 0.01 mg/kg for each analyte.

Appropriate LC–MS/MS methods exist for monitoring cyprodinil in the environmental compartments with LOQs of 0.01 mg/kg in soil, 0.05 µg/L in water and 0.5 µg/m^3 in the air, respectively. It should be mentioned that monitoring methods exist also for the determination of the residues of the metabolites CGA249287, CGA275535 and CGA321915 in soil and water with LOQs of 0.01 mg/kg and 0.05 µg/L, respectively, for each compound.

Monitoring of cyprodinil in body fluids is possible with the QuEChERS multi-residue method by LC–MS/MS with a LOQ of 0.01 mg/kg and in body tissues using the methods for the determination of cyprodinil residue in foodstuffs of animal origin. It was proposed however to include additionally to cyprodinil also the major metabolite 1U in the residue definition

[8]Refer to experts' consultation 2.18 in the Report of Pesticides Peer Review TC 119 (November 2023) (EFSA, 2024).

[9]Refer to experts' consultation 5.6 in the Report of Pesticides Peer Review TC 123 (20–24 November 2023) (EFSA, 2024).

[10]Refer to experts' consultation 5.6 in the Report of Pesticides Peer Review TC 123 (20–24 November 2023) (EFSA, 2024).

for monitoring in body fluids and tissues (see Section 2), as a consequence a data gap was identified for a validated monitoring method in body fluids and tissues (see Section 10).

2 | MAMMALIAN TOXICITY

The following guidance documents were followed in the production of this conclusion: European Commission (2003, 2012), EFSA PPR Panel (2012), EFSA (2014) and ECHA (2017).

Cyprodinil was discussed at the Pesticides Peer Review Experts' Meeting 182 in September 2018, at the Pesticides Peer Review Meeting 05 Mammalian toxicology – Ecotoxicology (joint session on ED) (May 2019) and TC 119 (November 2023).

The newly proposed reference specification is supported by the batches used in the toxicological studies, while the current reference specification is not supported. An assessment of the toxicological relevance of the individual impurities present in the technical specification (including detailed quantitative structure–activity relationship (QSAR) analysis) was provided. Toxicologically relevant impurities were not identified. The analytical methods used in the toxicological studies were appropriately validated or considered fit-for-purpose.

With limited absorption after oral administration (76%), cyprodinil is widely distributed (liver, kidney, lung, blood, plasma, thyroid) with no evidence for accumulation. Excretion occurs primarily via urine (35%), faeces (14%) and bile (39%) within 24 h. Cyprodinil is rapidly and extensively metabolised, mainly through sequential oxidation of the phenyl and/or the pyrimidyl rings. No unique human metabolites were formed in an in vitro interspecies comparative metabolism study showing consistent metabolic profile across species. The residue definition for body fluids (blood) should include cyprodinil and the major metabolite 1U for the purpose of human biomonitoring.

Cyprodinil showed low **acute toxicity** via oral and dermal routes and via inhalation (no classification). Cyprodinil demonstrated dermal sensitising potential (harmonised classification as Skin Sens.1).[11] Although not required, a phototoxicity study was provided showing negative results.

In **short-term** dietary studies, the target organs/critical effects included liver in rat and mouse, thyroid, kidney and pituitary in rat, and body weight, food consumption and liver in dog. In the 90-day oral study in rat with a NOAEL of 3.14 mg/kg bw per day, hepatocellular necrosis and hepatocellular hypertrophy, hypertrophy of pituitary cells and of thyroid's follicular epithelium, and tubular lesions of kidney were observed. The relevant short-term NOAEL is concluded to be 3.14 mg/kg bw per day from the 90-day study in rat.

Based on the available **genotoxicity** studies, cyprodinil is considered unlikely to be genotoxic.

In the **long-term toxicity** studies, target organs were liver in rat and pancreas in mouse. The relevant long-term NOAEL is 2.7 mg/kg bw per day from the 2-year study in rat, based on liver weight increase and sinusoidal cystic dilatation. Cyprodinil does not show carcinogenic potential in rat and mouse.

In the two-generation **reproductive toxicity** studies in rat, the NOAEL for parental toxicity is 74 mg/kg bw per day, based on effects in liver and kidney, and decreased body weight gain; the NOAEL for reproductive and offspring toxicity is 23 mg/kg bw per day, based on delayed sexual maturation in males (increased age at balanopreputial separation) and decreased ano-genital distance (index) observed in both sexes of both generations. Criteria for classification according to Regulation (EC) No 1272/2008[12] (ECHA, 2017) may be met for cyprodinil either in category 2 (Repr 2 H361f 'Suspected of damaging fertility') or in category 1B (Repr 1B H360F 'May damage fertility') based on adverse effects on sexual function and fertility.[13] In the **teratogenicity** studies in rat and rabbit, the NOAEL for maternal and developmental toxicity is 200 mg/kg bw per day in rat and 150 mg/kg bw per day in rabbit.

Three acute **neurotoxicity** studies (one range finding and two acute) were conducted with cyprodinil in rat. Acute neurotoxicity NOAEL is 200 mg/kg bw, based on functional observation battery (FOB) and motor activity alteration and hypothermia. In the same study a systemic NOAEL of 200 mg/kg bw per day is set, based on clinical signs. No effects on the nervous system were observed in the 90-day neurotoxicity study in rat, with a neurotoxicity NOAEL of 601 mg/kg bw per day. In the same study a systemic NOAEL of 54.5 mg/kg bw per day is set, based on reduced body weight (gain), effects on liver, kidney and thyroid.

No effects indicative of **immunotoxicity** were observed for cyprodinil in a 28-day mouse study.

Toxicity studies were provided on **CGA249287** metabolite; the metabolite is unlikely to be genotoxic, shows similar acute (oral) toxicity potential as the parent and an acceptable daily intake (ADI) of 0.08 mg/kg bw per day is established based on the NOAEL (79.5 mg/kg bw per day) set in the 90-day toxicity study in rat and an uncertainty factor (UF) of 1000 (to account for the limited data package) (see Section 7).

Toxicity studies were provided on **CGA263208** metabolite; the metabolite is unlikely to be genotoxic, shows similar acute (oral) toxicity potential as of the parent and an ADI of 0.02 mg/kg bw per day is established based on the NOAEL (17.8 mg/kg bw per day) set in the 90-day study in rat and an UF of 1000 (to account for the limited data package).

[11]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, pp. 1–1355.

[12]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, pp. 1–1355.

[13]The RMS is invited to consider submitting a CLH dossier to ECHA in order to propose a modification of the existing Annex VI entry of the CLP Regulation for cyprodinil. This dossier could be targeted to one or more hazard classes only based on new data which become available since the harmonised classification was agreed. EFSA recommends the RMS to send an updated CLH dossier to ECHA in order to propose a revision of the current Annex VI entry of the CLP Regulation.

Toxicity studies were provided on **CGA304075** metabolite; the metabolite is unlikely to be genotoxic and shows similar acute (oral) toxicity potential as of the parent. Furthermore, CGA304075 is a major rat metabolite (considering sulfate and glucuronide conjugates amount excreted in urine and bile), therefore the reference values of the parent compound are applicable.

Concerning metabolite **CGA275535**, it is considered unlikely to be genotoxic based on Ames test and QSAR analysis compared to cyprodinil and the structurally similar rat (major) metabolite CGA304075. However, no information on repeated dose toxicity has been provided to conclude on the general toxicity profile of metabolite CGA275535 (see Section 7).

Concerning metabolite **CGA321915**, it is considered unlikely to be genotoxic based on Ames test and in vitro micronucleous assays. Moreover, no further QSAR alerts were captured compared to cyprodinil. However, no information on repeated dose toxicity has been provided to conclude on the general toxicity profile of metabolite CGA321915 (see Sections 3 and 7).

Concerning metabolites NOA422054, CGA232449 and CGA304076, genotoxic potential could not be excluded and no information on repeated dose toxicity has been provided to conclude on their general toxicity profile (**data gap**, see Section 9.1).

The **ADI** of cyprodinil is 0.03 mg/kg bw per day based on the 2-year rat study (NOAEL of 2.7 mg/kg bw per day) applying an UF of 100. The same ADI was established during the previous assessment (European Commission, 2010b). The **acute reference dose (ARfD)** is 2 mg/kg bw based on the acute neurotoxicity study in rat (NOAEL of 200 mg/kg bw per day) applying an UF of 100. An ARfD was not allocated during the previous assessment (European Commission, 2010b).

The **acceptable operator exposure level (AOEL)** is 0.02 mg/kg bw per day based on the rat 90-day study (NOAEL of 3.14 mg/kg bw per day), applying an UF of 100 and considering an oral absorption of 76%. The same study was used to set AOEL of 0.03 mg/kg bw per day in the previous assessment, without correction for oral absorption (European Commission, 2010b). The **acute acceptable operator exposure level (AAOEL)** is 1.52 mg/kg bw, based on the acute neurotoxicity study in rat (NOAEL of 200 mg/kg bw per day), applying an UF of 100 and considering an oral absorption of 76%. An AAOEL was not allocated during the previous assessment (European Commission, 2010b).

Based on human skin in vitro dermal absorption study, dermal absorption values for the formulation for representative uses 'A14325E' are 0.8% for the concentrate (300 g/L cyprodinil), 17% for the spray dilution (1.5 g/L) and 23% for the lowest concentration recommended on the label (1.125 g/L). Based on human skin in vitro dermal absorption study, dermal absorption values for the formulation for representative uses 'A8637C' are 0.3% for the concentrate (250 g/kg cyprodinil), 32% for the intermediate dilution (1.25 g/L) and 40% for the highest dilution (0.25 g/L).

For the formulation for representative uses **Kayak** (A14325E), used on barley, the operator exposure estimates are below the AOEL with the German model when using personal protective equipment (PPE). The worker exposure estimates are above the AOEL with EUROPOEM data (considering 2 applications and the use of work wear). The bystander and resident exposure estimates are below the AOEL with the German approach[14] and EUROPOEM data. It is noted that the EFSA model (EFSA, 2014)[15] predicts an exposure of residential children above the AOEL even with increased buffer strip (10 m) and use of drift reduction technology.

For the formulation for representative uses **Chorus** (A8637C), used on apples, the operator exposure estimates are below the AOEL with the German model when using PPE for the hand-held application, and respiratory protective equipment for the tractor-mounted application.[16] Based on a field study, operator exposure was confirmed to be around 92% of the AOEL with the use of PPE. According to EUROPOEM and dislodgeable foliar residue (DFR) study on apples, the worker exposure estimates are below the AOEL when the re-entry occurs 10 days after the third application. It is noted that the EFSA model predicts a worker exposure below the AOEL for re-entry at 7 days after a single application, with use of PPE. The bystander and resident exposure with the German approach[17] is below the AOEL when considering a buffer zone of 15 and 5 m, respectively. It is noted that the EFSA model predicts an exposure of residents below the AOEL with appropriate mitigation measures (refined DfR, buffer strip 10 m, drift reduction technology).

Cyprodinil meets the criteria for endocrine disruption (ED) (see Section 6). The applicant did not submit an assessment of negligible exposure for the representative uses (see Background section and Section 6).

Overall, the toxicological reference values (ADI, AOEL, ARfD and AAOEL) are not impacted by the newly submitted two-generation reproductive toxicity study. The lowest NOAEL for ED endpoint is 23 mg/kg bw per day (see Section 6). Therefore, the toxicological reference values are considered covering the endocrine effects.

[14]The Martin et al. approach (2008) is no longer scientifically supported, since limited data were included for three-dimensional exposure to spray drift and no estimates are provided for exposure to vapour from low volatility compounds. Accordingly, the predictions are considered underestimated and are given for informative purpose only.

[15]Not yet implemented at the time of dossier submission of cyprodinil.

[16]It is noted that according to the EFSA calculator 2014, for dense scenario and hand-held application, the operator exposure is exceeding the (A)AOEL even when all available risk mitigation measures are included.

[17]The Martin et al. approach (2008) is no longer scientifically supported, since limited data were included for three-dimensional exposure to spray drift and no estimates are provided for exposure to vapour from low volatility compounds. Accordingly, the predictions are considered underestimated and are given for informative purpose only.

3 | RESIDUES

The assessment in the residue section is based on the following guidance documents: OECD (2009, 2011), European Commission (2011) and JMPR (2004, 2007).

Cyprodinil was discussed at the Pesticides Peer Review Experts' Meeting 184 in September 2018.

The metabolism of cyprodinil was investigated upon foliar application, in five different crops representative of three crop groups, i.e. root crops (potato), fruit (apple, peach, tomato) and cereals/grass crops (wheat greenhouse and field studies) using ^{14}C-cyprodinil separately labelled in the phenyl and pyrimidine rings. During the review of the existing MRLs (EFSA, 2013b) a global residue definition for both enforcement and risk assessment was proposed as cyprodinil only. However, during the renewal peer review, a global residue definition could not be concluded since the wheat study is not suitable to support the proposed representative use on barley (data gap, see Section 9.1). Furthermore, no residue definition for root crops could be derived based on the potato study as the characterisation/identification of residues in tubers was limited and due to field trials with root crops that contradict the observations in the metabolism study.

In fruit crops and wheat grain, cyprodinil represents the largest part of the residues (18%–90% total radioactive residue (TRR)). CGA232449 was the most prevalent metabolite in fruit (tomatoes), where it was found in its conjugated and free form at 0.63 mg/kg (12.6% TRR) and 0.12 mg/kg (2.5% TRR), respectively in the fruit.

For **fruit crops** the **residue definition for enforcement** is set as 'cyprodinil' and the **residue definition for risk assessment**, is set provisionally as 'cyprodinil and CGA232449 (free and conjugated)' pending the submission of toxicity data on CGA232449 (see **data gap** in Sections 2 and 9.1). For **cereal/grass crops**, pending a new metabolism study at a higher rate (**data gap**, see Section 9.1), the **residue definition for both enforcement and risk assessment** is set provisionally as 'cyprodinil' only.

For apples, only one NEU and five SEU trials compliant with the cGAP are available. Due to an incomplete data set, a **data gap** was identified for residue trials in apple compliant with the NEU and SEU GAPs (see Section 9.1). In all trials, only cyprodinil was determined, no data were available regarding the residue levels of the metabolite CGA232449 (free and conjugates) in apples. Should the finalisation of the risk assessment residue definition for fruit confirm the inclusion of CGA232449 (free and conjugated), a complete set of eight residue trials for each NEU and SEU is required. In the case of barley, seven NEU and seven SEU trials compliant with the cGAP are available. Due to an incomplete data set, a **data gap** was identified for additional residue trials in barley, compliant with the NEU and SEU GAPs (see Section 9.1). In addition, further validation data on the analytical method for the available trials should be submitted (data gaps, see Section 10). Valid storage stability data covering the maximum storage period of the residues from the residue trials were provided.

The persistence in soil of cyprodinil and the soil metabolites CGA249287 and CGA321915 (see Section 4) triggered the investigation of residues also in rotational crops. Two acceptable rotational crop metabolism studies were available in which cyprodinil was rarely recovered in succeeding crops but the metabolites CGA263208, NOA422054, CGA249287 and CGA321915 were identified as the pertinent residues. In addition, four NEU rotational crop field trials, analysing for cyprodinil, NOA422054 and CGA321915 at all plant back intervals (PBI) were available, however these had shortcomings regarding uncertain freezer storage stability periods of samples and insufficient method validation data (**data gaps**, see Section 10). In addition, the studies were conducted at 0.75N, 0.61N and 0.48 N of the PEC accumulation in 20 cm of soil for cyprodinil, CGA249287 and CGA321915, respectively, underestimating the possible concentrations of cyprodinil and metabolites NOA422054 and CGA321915 in rotational crops (**data gap**, see Section 9.1). Two additional studies (NEU and SEU) with a higher dose are available but analyse only cyprodinil and none of the metabolites. Pending the availability of data to address the data gap for new rotational crop trials, the **residue definition for both enforcement and risk assessment for rotational crops** is set provisionally as NOA422054 (free and conjugated), taking into account the presence of NOA 422054 as the highest and most frequently occurring residue in rotational crops based on the currently available studies. It is noted that the toxicological properties of NOA422054 are not addressed (see data gap in Sections 2 and 9.1). The general toxicity of CGA321915 is also not addressed but may be necessary if sufficiently dosed rotational crop trials have been carried out that suggest significant residues of CGA321915 in crops for human consumption.

The metabolism of cyprodinil has been investigated in ruminants and laying hens, using both labels of cyprodinil (phenyl and pyrimidine rings). In ruminants, cyprodinil and metabolites CGA304075, CGA304076 (both free and glucuronide and sulfate conjugates) are the major components found in liver, kidney, muscle, fat and milk. In poultry, CGA304075 (glucuronide and sulfate conjugates) was the major compound identified in liver, kidney and eggs. Considering the high administered dose in the feeding studies (284N in laying hens, 16.8N in cow and 29.7N in goat), residues of cyprodinil or metabolites above the LOQ are not expected in animal commodities except in ruminant liver and kidney, however no information is available regarding the stability of incurred CGA304075 in liver and kidney. Pending the necessity of a new feeding study to support a higher dietary burden, in the case of future uses in commodities that can be feed to animals, the issue on storage stability data for metabolite CGA304075 in liver and kidney might have to be reconsidered. The **residue definition in products of animal origin**, for both **enforcement and risk assessment**, is proposed as the 'sum of cyprodinil and CGA304075 (free and glucuronide) expressed as cyprodinil'. As CGA304076, present as glucuronide and sulfate conjugate, was a major residue in milk (12%–20% TRR), a food commodity that is a high contributor to consumer dietary exposure, genotoxicity should be addressed for CGA304076 (**data gap**, see Section 9.1). Information on flow-through studies with fish was presented but a metabolism study is required upon dietary exposure to residues of cyprodinil (**data gap**, see Section 10).

Cyprodinil was shown to be stable under pasteurisation, baking, brewing, boiling and sterilisation conditions. Processing factors have been established for apple pomace (wet and dry), juice (raw and pasteurised), puree, malt, wort, pearl barley and beer. A hydrolysis study is not available with CGA 304075 and the necessity of such a study needs to be re-assessed once the residue definition for plant commodities is finalised.

Sufficient data to address potential residues in pollen and bee products for human consumption related to the representative uses are not available (**data gap**, see Section 10).

For the consumer risk assessment, the tentative MRLs from residue data (apple, barley, animal commodities) were considered for the chronic intake and the highest residue (HR) derived from supervised field trials for the acute intake calculations. All the input values took into consideration residues of cyprodinil only. An assessment could not be performed for the metabolites CGA232449 and NOA422054 due to lack of information on toxicity and lack of reliable exposure data for both metabolites.

In this provisional assessment using EFSA PRIMO rev. 3.1, the chronic intake was below the ADI, the theoretical maximum daily intake (TMDI) was accounted for up to 64% (DE child) with apples being the highest contributor (62%). The acute intake (IESTI) for the representative uses were below the ARfD, the maximum IESTI accounted for 4% apple juice/3% for apples and was below 1% for all barley raw and processed commodities and for animal commodities.

Pending finalisation of the residue definition for risk assessment in fruit, cereal/grass crops and rotational crops, availability of additional residue trials in apple and barley according to the residue definition for risk assessment, availability of the rotational crop residue trials analysing for metabolites NOA422054 and CGA321915 and data addressing the toxicity of pertinent metabolites, the consumer risk assessment is considered provisional (see Section 9.1).

The consumer risk assessment is also not finalised as the appropriate information to address the effect of water treatment processes on the nature of the residues that might be present in surface water, when surface water is abstracted for drinking water is missing (see **data gap** in Sections 4 and 9.1).

Cyprodinil met the criteria for ED (see Section 6). It was not demonstrated that one or more of the representative uses could satisfy the requirements regarding negligible dietary exposure as set out in point 3.6.5 of Annex II to Regulation (EC) No 1107/2009.

4 | ENVIRONMENTAL FATE AND BEHAVIOUR

The degradation of cyprodinil in soil was investigated in 12 different soils in the laboratory in the dark under aerobic conditions (results of 10 of these experiments were considered for deriving normalised degradation endpoints). Degradation was shown to involve hydroxylation of the phenyl or the pyrimidyl ring of cyprodinil to give the major (> 10% applied radioactivity (AR)) metabolite CGA275535 (max. 10.4% AR after 14 day) and other minor metabolites. Cleavage of the anilino-pyrimidyl bridge of cyprodinil and its hydroxy-phenyl derivatives gave the major metabolite CGA249287 (max. 14.3% AR after 180 day) and then the minor non transient metabolite CGA321915 (max 6% AR after 120 day). In these studies, cyprodinil exhibited moderate to high persistence with clear pH dependence, being more persistent in acidic soils. In previous assessment (EFSA, 2006) the possibility of pH dependent degradation was only suggested due to the limited data, while this pH dependence is now confirmed with additional laboratory and field data. Metabolite CGA249287 exhibited moderate to medium persistence and metabolite CGA321915 moderate to high persistence in these experiments, no pH dependence is observed in the degradation of metabolites. Metabolite CGA275535 exhibited very low persistence in three reliable experiments available where it is applied as parent compound, with no apparent pH dependence in its degradation. The phenyl ring and the pyrimidyl ring were poorly mineralised: 2.6%–24.7% AR after 110–363 days and 1%–24.4% AR after 120–366 days, respectively. The maxima for not extracted residues for the phenyl ring and the pyrimidyl ring were 72.7% AR and 71.0% AR respectively.

Field studies are available in 12 different sites, 9 of which were considered for deriving normalised degradation end points. Behaviour of the parent compound in field is in line with what is observed in laboratory studies for soils with $pH_{H_2O} \geq 6.7$ and combined degradation normalised end points have been used for the exposure assessment. For soils with $pH_{H_2O} < 6.7$ field and laboratory data are significantly different and geomean field DT_{50} endpoint are to be used for the exposure assessment in situations of lower pH.

Three (3) reliable degradation studies in soil under anaerobic conditions are available. Cyprodinil is stable under these conditions and degradation end points were not determined.

In laboratory soil photolysis experiment the degradation of cyprodinil was faster in light exposed samples than in dark moist soil control samples. Novel extractable breakdown products were not identified.

Batch adsorption/desorption studies are available for cyprodinil, CGA249287, CGA321915 and CGA 275535. These studies indicated that cyprodinil exhibited slight to low mobility in soil, CGA249287 exhibited low to medium mobility, CGA321915 medium to very high mobility and CGA275535 was immobile to low mobile. The available data did not indicate any pH dependence with respect to adsorption to soil for any of the compounds. Column leaching studies showed low mobility of cyprodinil. Aged residue column leaching studies confirmed the low mobility of cyprodinil whereas limited movement was observed for the metabolites.

Cyprodinil, CGA249287 and CGA275535 were stable to aqueous hydrolysis in sterile buffers at pH 4 to 9.

Aqueous photodegradation of cyprodinil was quite variable and a lag phase was observed in some of the experiments. Photodegradation of the metabolite CGA249287 was observed in buffers at pH 5–9 (0.5% acetonitrile) and single first-order

DT_{50} were estimated to be 15.5–31.9 days summer sunlight at latitude 30–50° N. Several metabolites were observed in these photolysis studies, but only CGA249287, CGA263208, CGA048109 (guanidine) and R008591 (succinic acid) were considered to trigger a risk assessment for the aquatic compartment.

Based on the results of an OECD guideline ready biodegradability test cyprodinil is regarded as 'not readily biodegradable'.

Aerobic mineralisation of cyprodinil in surface water was investigated in two fresh water pelagic tests showing high persistence of cyprodinil under these conditions (DT_{50} = 146–298 days).

The fate and behaviour of cyprodinil was investigated in two natural water sediment systems in dark 20°C laboratory experiments, where cyprodinil was rapidly adsorbed to sediment (max. 87.3% AR after 21 day) where it slowly declined. Cyprodinil was poorly mineralised (4.8%–11.1% AR after 260 day). Significant amounts of residues were not extracted from sediment (about 48% AR for both labels after 260 day), so the formation of unextracted sediment residue was the most significant sink. CGA249287 was the only significant metabolite detected in water (max. 6.9% AR after 112 day) and in sediment (max. 14.2% AR after 112 day). Rapid dissipation of cyprodinil was observed in water; however, degradation in the whole systems was slow (single first order DT_{50} 129–188 day). For CGA249287, it was not possible, with the data in the study, to derive reliable degradation parameters; therefore, a default half-life of 1000 day has been assumed for this metabolite in the aquatic system.

For the representative uses in apple and barley $PEC_{SW/sed}$ were calculated for the parent and metabolites CGA275535, CGA249287, CGA321915, CGA048109, CGA263208 and R008591 with FOCUS SW models up to Step 2 (FOCUS, 2001). For the active substance cyprodinil $PEC_{SW/sed}$ were calculated for the uses in barley and apple assuming mitigation measures of up to 20 m non-spray buffer zone (and/or up to 90% reduction nozzles) in combination to up to 45 m vegetative run off vegetative strip, using the SWAN tool (v.4.01) (FOCUS, 2007). However, results presented in the LoEP are only those for which the drift mitigation was < 95% or runoff mitigation was < 90% as higher mitigation is not considered acceptable according to the Landscape and Mitigation guidance document (FOCUS, 2007). The higher mitigation options proposed clearly exceeded the maximum mitigation attainable according with FOCUS landscape guidance. Therefore, only those values respecting the limits established by FOCUS landscape guidance have been used for the EU risk assessment (FOCUS, 2007). PEC sediment for cyprodinil and metabolite CGA249287 include calculation of potential accumulation in sediment from use in consecutive years.

The necessary groundwater exposure assessments were carried out using FOCUS (European Commission, 2014a) scenarios and the models PEARL 4.4.4, PELMO 5.5.3 and MACRO 5.5.4.[18] The potential for groundwater exposure from the representative uses by cyprodinil and metabolites CGA275535, CGA249287, CGA321915 above the parametric drinking water limit of 0.1 µg/L was concluded to be low in geoclimatic situations that are represented by all relevant FOCUS groundwater scenarios.

The applicant did not provide appropriate information to address the effect of water treatment processes on the nature of the residues of the active substance and its possible metabolites that might be present in surface water when surface water is abstracted for drinking water. This has led to the identification of a **data gap** and results in the consumer risk assessment not being finalised (see Sections 3 and 9.1).

The PEC in soil, surface water, sediment and groundwater covering the representative uses assessed can be found in Appendix B of this conclusion. A key to the wording used to describe the persistence and mobility of the compounds assessed can be found in Appendix C of this conclusion.

5 | ECOTOXICOLOGY

The following documents were considered in the risk assessment: European Commission (2002a, 2022b), SETAC (2001), EFSA (2009), EFSA PPR Panel (2013) and EFSA (2013a).

Some aspects of the risk assessments for mammals and aquatic organisms were discussed in the Pesticides Peer Review Experts' Teleconference (TC) 194 in September 2018. In addition, the long-term endpoint to be used in the risk assessment for mammals was reconsidered in the Pesticides Peer Review Experts' TC 123 in November 2023, since relevant data were submitted for the assessment of endocrine disruption properties of cyprodinil (see Section 6).

The batches used in the ecotoxicological studies are not supported by the current reference specification, while they are supported by the newly proposed reference specification.

On the basis of the available data and assessments, a low acute risk to **birds and mammals** and a low long-term risk to birds was concluded for both representative uses. However, a high long-term risk was concluded for some scenarios for mammals for both representative uses. Due to lack of higher tier data, these scenarios were not further refined (**data gap** and **critical area of concern**, see Section 9.2). The risk from secondary poisoning and via consumption of contaminated water was assessed as low.

[18]Simulations utilised the agreed Q10 of 2.58 (following EFSA, 2008) and Walker equation coefficient of 0.7.

Toxicity data were available on all relevant **aquatic taxa** and the active substance with the exception for sediment dwelling organisms (**data gap**, see Section 9.1[19]; it is noted that the RMS disagrees with this data gap[20]). The formulations for the representative uses were sufficiently tested. The lowest RAC was the acute RAC for aquatic invertebrates.

As regards the representative use on barley, a low risk to algae and a low acute risk to fish were concluded based on the available Tier 1 data of cyprodinil. However, the Tier 1 data did not demonstrate a low risk for the other scenarios (chronic fish and acute and chronic aquatic invertebrates). No appropriate higher tier assessments were available to refine the risk assessment for chronic exposure to fish. For aquatic invertebrates, a low acute risk was concluded (Tier 2 assessments considering species sensitivity distribution (SSD) approach) except for D1 (winter and spring barley) and D2 (winter barley) FOCUS scenarios. FOCUS step 4 calculations considering a 5 m wide non-sprayed buffer zone were available. Considering this mitigation measure, a low risk was concluded for the D1 scenario, only. A Tier 3 microcosm study was available for aquatic invertebrates. However, it was considered that the available information was insufficient to conclude whether this study would cover the predicted exposure of aquatic organisms for this representative use.[21] Therefore, this study could not be used for refinement of the risk assessment for barley.

As regards the representative use on apple, a low risk to algae was concluded based on the available Tier 1 data of cyprodinil. Low risk was not demonstrated with the Tier 1 data for the other aquatic organisms. No appropriate higher tier assessments were available for fish. Tier 2 assessments considering SSD approach was available to refine the acute risk to invertebrates. This, in combination with mitigation measures (certain widths of non-spray buffer zones combined with different types of drift reducing nozzles, see Appendix B) resulted in a low risk for all FOCUS surface water scenarios, except R4. A Tier 3 microcosm study with agreed ETO and ERO RAC was available for aquatic invertebrates. However, it was considered that the available information was insufficient to conclude whether this study would cover the predicted exposure of aquatic organisms for this representative use.[22] Therefore, this study could not be used for refinement of the risk assessment for apple (**data gap** and **critical area of concern**, see Section 9.2). Since, low risk to aquatic organisms were not demonstrated for any of the representative uses, a **critical area of concern** was identified (see Section 9.2).

Sufficient toxicity data were available for all aquatic metabolites for aquatic invertebrates (the most sensitive group of aquatic organisms for cyprodinil) with the exception for CGA048109 (guanidine) and R008591 (succinic acid). In addition, data were available for fish and algae for several metabolites and data were also available for CGA249287 on sediment dwelling organisms. Considering these data and the available FOCUS tier 2 PECs, a low risk was concluded for these metabolites (i.e. where quantitative risk assessments could be performed). As regards the metabolite CGA048109, the RMS concluded a low risk based on a weight-of-evidence approach which was agreed at the Pesticides Peer Review Experts' TC 194. As regards R008591 (succinic acid), a **data gap** was agreed at TC 194[23] (see Section 10).

Appropriate acute and chronic adult toxicity data were available for **honey bees**. Considering these data, a low risk was concluded for the representative uses according to both the SANCO Guidance on terrestrial ecotoxicology (European Commission, 2002a) and EFSA (2013a). The endpoints from the available in vitro larval tests for honey bees were not considered to be suitable for a quantitative risk assessment (**data gap leading to an issue not finalised**, see Section 9.1).[24]

No data were available on bumble bees, solitary bees or on accumulative effects. No information on sub-lethal effects or on metabolites potentially occurring in pollen and nectar was available (**data gap**, see Section 10).

Based on Tier 1 risk assessment, a high in-field risk to **non-target arthropods** was concluded for the representative use on cereals. However, a number of additional studies were available and the Tier 2 risk assessment considering these data demonstrated a low risk. Regarding the representative use on apples, a low risk to non-target arthropods was concluded based on Tier 1 risk assessment. However, the available additional studies identified some more sensitive species than the standard tier 1 species. Semi-field tests and extended laboratory studies aiming at assessing the potential for recovery after exposure to aged residues of cyprodinil were available on different species. Those demonstrated a potential for recovery of some tested species. However, for some other species the potential for recovery could not be demonstrated with the available data (low application rate or too few applications of those tests). Therefore, a low in-field risk could not be concluded (**data gap**, see Section 10). The off-field risk was concluded to be low for both representative uses.

No sufficient toxicity data were available for cyprodinil or for the representative formulations for earthworms (**data gap leading to an issue not finalised**, see Section 9.1).[25] However, appropriate data were available for other **soil macroorganisms** than earthworms and for **soil microorganisms**. Moreover, sufficient data were available for all soil organisms (earthworms, other soil macroorganisms, soil microorganisms) for the metabolites CGA249287, CGA275535 and CGA321915. The risk assessments using these data indicated a low risk.

Based on the available data, a low risk was concluded to **non-target terrestrial plants** and to organisms involved in **sewage treatment** processes.

[19]Refer to Open point 5.10 in the Evaluation table of cyprodinil (EFSA, 2024).

[20]See further explanations in the RMS comments on the draft EFSA Conclusion on cyprodinil, ecotoxicology comments (EFSA, 2024).

[21]Refer to experts' consultation 5.2 in the Report of Pesticides Peer Review Experts' Teleconference 194 (EFSA, 2024).

[22]Refer to Open point 5.10 in the Evaluation table of cyprodinil (EFSA, 2024).

[23]Refer to Open point 5.10 in the Evaluation table of cyprodinil (EFSA, 2024).

[24]Refer to Data requirement 5.8 in the Evaluation table of cyprodinil (EFSA, 2024).

[25]Refer to Data requirement 5.9 in the Evaluation table of cyprodinil (EFSA, 2024).

6 | ENDOCRINE DISRUPTION PROPERTIES

The endocrine disruption properties of cyprodinil were discussed at the Pesticides Peer Review Experts' Teleconference (TC) 118 (November 2023).

With regard to the assessment of the endocrine disruption potential of cyprodinil **for humans** according to the ECHA/EFSA guidance (2018), in determining whether cyprodinil interacts with the oestrogen, androgen and steroidogenesis (EAS)- and thyroid (T)-mediated pathways, the number and type of effects induced, and the magnitude and pattern of responses observed across studies were considered. Additionally, the conditions under which effects occur were considered, in particular, whether or not endocrine-related responses occurred at dose(s) that also resulted in overt toxicity. The assessment is therefore providing a weight-of-evidence analysis of the potential interaction of cyprodinil with the EAS and T signalling pathways using the available evidence in the data set.

The **T-modality** has been considered sufficiently investigated with evidence of a pattern of T-mediated adversity. Thyroid histological changes (minimal to moderate thyroid follicular cell hypertrophy) were observed in one species (rat) and with a higher prevalence in severity and incidence, mainly confined at doses overcoming the maximum tolerated dose (MTD). A mode of action (MoA), dealing with the peripheral metabolism of thyroid hormones, was initially postulated (CAR/PXR nuclear receptor activation, induction of Phase I and Phase II liver enzymes, increase of thyroid hormones clearance and decrease of the circulating level of thyroid hormones). However, additional molecular initiating events (MIEs) could not be excluded based on the available evidence (i.e. sodium-iodide symporter inhibition, iodotyrosine deiodinase inhibition and type 3 deiodinase inhibition) subsequently retrieved from ToxCast database and from public literature studies. It should be noted that the MIE, CAR/PXR nuclear receptor activation, was not measured, as well as intermediate key events (e.g. hormonal measurements) and/or other adverse outcomes (DNT related endpoints) were not investigated in the dataset. Indeed, the impact of lack of information on the assessment of the hypothalamus–pituitary–thyroid (HPT) axis perturbation on the most sensitive population (pregnant dams, fetuses and newborns) is missing. Therefore, because of lack of data in the sensitive population of concern, the ED assessment for the T-modality for humans according to point 3.6.5 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605, cannot be concluded.

To complete the data package, a study in line with the US EPA Comparative Thyroid Assessment Guidance for Thyroid Assays in Pregnant Animals, Foetuses and Postnatal Animals (US EPA, Office of Pesticide Programs, Health Effects Division, Washington (DC)) would need to be conducted.

A pattern of **EAS-mediated** adversities i.e. delayed sexual maturation (increased age at balanopreputial separation) in F1 generation and decreased ano-genital distance index (AGDI) in F1a in males and F2 animals in both males and female, was observed for cyprodinil in a sufficiently investigated data set. Effects on parameters considered 'sensitive to, but not diagnostic of' i.e. decreased number of ovarian small follicles and decreased number of implantation scars, also contributed to the assessment. Evidence of endocrine activity was observed in the OECD TG 456 steroidogenesis assay (i.e. marginal decrease in testosterone synthesis and positive for increase in estradiol synthesis), aromatase assay (i.e. equivocal evidence of aromatase inhibition) and in the OECD TG 441 Hershberger assay (i.e. equivocal anti-androgenic effect). The observed pattern of EAS-mediated adversities suggested an anti-androgenic MoA. However, other MoAs, affecting steroidogenesis and/or oestrogenic pathways, are also plausible based on the available evidence. In addition, literature studies were also supporting the evidence of a weak anti-androgenic activity (e.g. Yeast androgen screen (YAS) Assay, MDA-kb2 Assay) and of a weak oestrogenic activity (e.g. Yeast Estrogen Screen (YES) assay, in vitro Ishikawa and BG-1 cells, ex vivo ovariectomised xenograft model).

Based on the available and sufficient data set and on the MoA analysis, it was concluded that the ED criteria for the EAS-modalities are met for cyprodinil (Scenario 1b of the ECHA/EFSA ED Guidance, 2018).

In the studies conducted with cyprodinil, the lowest adverse effect level (LOAEL), where EAS-mediated adversities (i.e. delayed sexual maturation and decreased AGDI) were observed, is 77 mg/kg bw per day from a two-generation reproductive toxicity study in the rats. A no observed adverse effect level (NOAEL) of 23 mg/kg bw per day is derived based on these effects.

The conclusion reported above for humans also applies to **wild mammals as non-target organisms** for the EATS-modalities,[26] i.e. inconclusive for the T-modality, while it showed to interfere with the hypothalamus–pituitary–gonad (HPG) axis. The EAS-adversity identified was considered relevant at the level of population and thus relevant for wild mammals for the following reasons:

- Effects in parameters related to sexual maturation were observed;
- Those effects had adverse consequence on the reproductive performance.

For non-target organisms other than mammals, an amphibian metamorphosis assay (AMA, OECD TG 231) and a fish short-term reproduction assay (FSTRA, OECD TG 229) were available.

The AMA was positive for adversity and endocrine activity, showing a clear pattern of effects i.e. change in thyroid histology leading to delay in development in absence of signs of systemic toxicity.[27] A MoA was postulated, i.e. interaction with nuclear receptor leading to upregulation of hepatic enzymes, increased clearance of thyroid hormones and delay in development. However, the MoA was not empirically supported by the available data (AMA). Overall, the available

[26]Refer to Experts' consultation 5.4 in the Pesticides Peer Review meeting Report TC 118 – TC 123, (EFSA, 2024).

[27]Refer to Experts' consultation 5.3 in the Pesticides Peer Review meeting Report TC 118 – TC 123 (EFSA, 2024).

information was considered insufficient to dismiss the findings in the AMA and the relevance at the level of population of the observed delay in metamorphosis.

Regarding the EAS-modalities, it was agreed that the FSTRA showed a pattern of effects, i.e. increase in male vitellogenin, change in female gonad histology and decreased fecundity and fertilisation success.[28] Taking into consideration both the mammalian and non-mammalian dataset, it was concluded that a pattern of adversity and endocrine activity is observed in non-target organisms suggesting an anti-androgenic MoA.

Therefore, overall, the ED criteria are considered met for non-target organisms other than mammals for the EATS-modalities for cyprodinil.

Based on the available information on humans and non-target organisms, it can be concluded that cyprodinil is an endocrine disruptor according to points 3.6.5 and 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605, leading to a critical area of concern (see Section 9.2).

The applicant concluded with a document provided outside of the regulatory clock stop that for this active substance the exposure to human cannot be defined as negligible. Additional documents were not provided to demonstrate that the exposure to human (dietary and non-dietary) and to non-target organism was negligible for cyprodinil. Furthermore, the applicant requested a derogation under Article 4(7) of Regulation (EC) 1107/2009, submitting documentary evidence regarding the necessity of cyprodinil as a fungicide to control a serious danger to plant health which considered the authorised uses of cyprodinil in seven Member States. Since the data were provided outside of the regulatory clock stop, the data could not be further considered in the context of the present Conclusion.

7 | OVERVIEW OF THE RISK ASSESSMENT OF COMPOUNDS LISTED IN RESIDUE DEFINITIONS TRIGGERING ASSESSMENT OF EFFECTS DATA FOR THE ENVIRONMENTAL COMPARTMENTS (TABLES 1–4)

TABLE 1 Soil.

Compound (name and/or code)	Ecotoxicology
Cyprodinil	Data gap
CGA275535	Low risk to soil organisms
CGA 249287	Low risk to soil organisms
CGA321915	Low risk to soil organisms

TABLE 2 Groundwater.[a]

Compound (name and/or code)	>0.1 μg/L at 1 m depth for the representative uses[b] Step 2	Biological (pesticidal) activity/relevance Step 3a	Hazard identified Steps 3b and 3c	Consumer RA triggered Steps 4 and 5	Human health relevance
Cyprodinil	FOCUS modelling: No	Yes	–	–	Yes
CGA275535	FOCUS modelling: No	No data	Not triggered	No	Not triggered
CGA249287	FOCUS modelling: No	No	Not triggered ADI 1.2 mg/kg bw per day	No	Not triggered
CGA321915	FOCUS modelling: No	No	Not triggered	No	Not triggered

[a]Assessment according to European Commission guidance of the relevance of groundwater metabolites (2003).

[b]FOCUS scenarios or relevant lysimeter. Ranges indicated for FOCUS scenarios include the result from the model giving the highest concentration at each scenario, as needed to comply with European Commission (2014a) guidance.

TABLE 3 Surface water and sediment.

Compound (name and/or code)	Ecotoxicology
Cyprodinil	High risk to aquatic organisms
CGA 275535	Low risk to aquatic organisms
CGA 249287	Low risk to aquatic organisms
CGA321915	Low risk to aquatic organisms
CGA048109	Low risk to aquatic organisms
CGA263208	Low risk to aquatic organisms
R008591	Data gap

[28]Refer to Open point 5.10 in the Evaluation table of cyprodinil (EFSA, 2024).

TABLE 4 Air.

Compound (name and/or code)	Toxicology
Cyprodinil	LC_{50} > 1200 mg/m^3/4 h (*nose only*) (maximum attainable concentration)

8 | PARTICULAR CONDITIONS PROPOSED TO BE TAKEN INTO ACCOUNT BY RISK MANAGERS

Risk mitigation measures (RMMs) identified following consideration of Member State (MS) and/or applicant's proposal(s) during the peer review, if any, are presented in this section (Table 5). These measures applicable for human health and/or the environment leading to a reduction of exposure levels of operators, workers, bystanders/residents, environmental compartments and/or non-target organisms for the representative uses are listed below. The list may also cover any RMMs as appropriate, leading to an acceptable level of risks for the respective non-target organisms.

It is noted that final decisions on the need of RMMs to ensure the safe use of the plant protection product containing the concerned active substance will be taken by risk managers during the decision-making phase. Consideration of the validity and appropriateness of the RMMs remains the responsibility of MSs at product authorisation, taking into account their specific agricultural, plant health and environmental conditions at national level.

TABLE 5 Risk mitigation measures proposed for the representative uses assessed.

	CHORUS use on apple	KAYAK use on barley				
Representative use	**3×0.375 g a.s./ha**	**2×0.375 g a.s./ha**	**3×0.225 g a.s./ha**	**2×0.225 g a.s./ha**	**2×0.450 g a.s./ha**	**1×0.450 g a.s./ha**
Operator risk	Use of PPE is required[b]	Use of PPE is required[b]	Use of PPE is required[b]	Use of PPE is required[a]	Use of PPE is required[a]	
Worker exposure	Use of gloves +7 or 10 day before re-entry	Use of gloves +7 day before re-entry		(no safe use)	(no RMM needed)	
Bystander/ resident exposure	EUROPOEM II: no safe use German approach: buffer strip 15 m EFSA 2015*: buffer strip 10 m, drift reduction, DFR 1.8 and DT50 3 day	EUROPOEM II: no safe use German approach: buffer strip 15 m EFSA 2015*: buffer strip 10 m, drift reduction, DFR 1.8 and DT50 3 day	EUROPOEM II: no safe use German approach: buffer strip 15 m EFSA 2015*: buffer strip 10 m, drift reduction, DFR 1.8 and DT50 3 day	EUROPOEM II: buffer strip 5 m German approach: buffer strip 1 m EFSA 2015*: no safe use	EUROPOEM II: buffer strip 5 m German approach: buffer strip 1 m EFSA 2015*: buffer strip 10 m, drift reduction	

[a]For tractor-mounted applications: gloves during mixing/loading and application (M/L & A) + coverall and study footwear during application (A) (German model); gloves during M/L (EFSA, 2014).

[b]For tractor-mounted applications: gloves during M/L & A, coverall during A (German model); gloves during M/L & A and closed cab (EFSA, 2014) – for hand-held applications: gloves (M/L & A) and coverall (A) (German model); gloves (M/L & A) (EFSA, 2014).

*Last version of calculator from EFSA (2014).

9 | CONCERNS AND RELATED DATA GAPS

9.1 | Issues that could not be finalised

An issue is listed as 'could not be finalised' if there is not enough information available to perform an assessment, even at the lowest tier level, for one or more of the representative uses in line with the uniform principles in accordance with Article 29(6) of Regulation (EC) No 1107/2009 and as set out in Commission Regulation (EU) No 546/2011[29] and if the issue is of such importance that it could, when finalised, become a concern (which would also be listed as a critical area of concern if it is of relevance to all representative uses).

An issue is also listed as 'could not be finalised' if the available information is considered insufficient to conclude on whether the active substance can be expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009.

The following issues or assessments that could not be finalised have been identified, together with the reasons including the associated data gaps where relevant, which are reported directly under the specific issue to which they are related:

[29]Commission Regulation (EU) No 546/2011 of 10 June 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards uniform principles for evaluation and authorisation of plant protection products. OJ L 155, 11.6.2011, pp. 127–175.

1. The consumer risk assessment is not finalised in view of the identified data gaps to fully address the nature and magnitude of residues, namely, a new metabolism study on cereals and for sufficient residue trials compliant with the representative uses on apples and barley, for both NEU and SEU, and for adequate rotational crop field trials (see Section 3). The consumer risk assessment is also not finalised because of missing data to sufficiently address the toxicity of metabolites with a relevant consumer dietary exposure potential.

    a. Information on genotoxicity on metabolite CGA304076 should be provided, and information on genotoxicity and repeated dose toxicity should be provided to enable conclusion on the general toxicity profile of metabolites CGA232449, and NOA422054 (relevant for all representative uses evaluated; see Section 2).
    b. Seven additional NEU and three additional SEU GAP compliant residue trials on apples (relevant for representative use in apples; see Section 3).
    c. One additional residue trial on barley compliant respectively with the NEU and SEU GAP (relevant for representative use in barley; see Section 3).
    d. Field rotational crop trials measuring levels of NOA422054 and CGA321915, including conjugated residues, and covering the PEC accumulation in 20 cm of soil for cyprodinil, CGA249287 and CGA321915, corresponding to the intended GAP on barley (relevant for representative use in barley; see Section 3).
    e. A new metabolism study on cereals conducted at a higher rate as to enable further metabolites identification in compliance with the current test guidelines and identification/characterisation in the unextracted fractions (relevant for representative use in barley; see Section 3).

2. The consumer risk assessment from the consumption of drinking water is not finalised considering the lack of appropriate information to address the effect of water treatment processes on the nature of residues of the active substance and its possible metabolites, potentially present in surface water, when surface water is abstracted for drinking water (see Section 4).

    a. Information to address the effect of water treatment processes on the nature of residues present in surface water, when surface water or groundwater are abstracted for drinking water was not available. In a first instance, consideration of the processes of ozonation and chlorination would appear appropriate. If an argumentation was made that concentrations at the point of abstraction for drinking water purposes will be low, this argumentation should cover metabolites predicted to be surface water, as well as the active substance. Should this consideration indicate that novel compounds might be expected to be formed from water treatment, the risk to human or animal health through the consumption of drinking water containing them should be addressed (relevant for all representative uses evaluated; see Sections 3 and 4).

3. The risk assessments for sediment dwelling organisms could not be finalised.

    a. Appropriate data for sediment dwelling organisms and cyprodinil were not available (relevant for all representative uses evaluated; see Section 5).

4. The risk assessments for honey bee larvae could not be finalised.

    a. Appropriate data to address the risk to honey bee brood development were not available (relevant for all representative uses evaluated; see Section 5).

5. The risk assessments for earthworms could not be finalised.

    a. Appropriate data for earthworms and cyprodinil were not available (relevant for all representative uses evaluated; see Section 5).

9.2 | Critical areas of concern

An issue is listed as a critical area of concern if there is enough information available to perform an assessment for the representative uses in line with the uniform principles in accordance with Article 29(6) of Regulation (EC) No 1107/2009 and as set out in Commission Regulation (EU) No 546/2011, and if this assessment does not permit the conclusion that, for at least one of the representative uses, it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater, or any unacceptable influence on the environment.

An issue is also listed as a critical area of concern if the assessment at a higher tier level could not be finalised due to lack of information, and if the assessment performed at the lower tier level does not permit the conclusion that, for at least one of the representative uses, it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater, or any unacceptable influence on the environment.

An issue is also listed as a critical area of concern if, in the light of current scientific and technical knowledge using guidance documents available at the time of application, the active substance is not expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009.

The following critical areas of concern are identified, together with any associated data gaps, where relevant, which are reported directly under the specific critical area of concern to which they are related:

6. High long-term risk to mammals was identified for all representative uses based on tier 1 risk assessments (see Section 5). It may be noted that the available risk assessments for the representative use for apple is based on the maximum application rate. No risk assessment was presented for the minimum application rate (however it is unlikely that a low risk would be demonstrated for all scenarios considering the minimum application rate).
7. High risk to aquatic organisms was identified for all representative uses (see Section 5). It may be noted that the available risk assessments for the representative use for apple is based on the maximum application rate. No risk assessment was presented for the minimum application rate (however it is unlikely that a low risk would be demonstrated for all scenarios considering the minimum application rate).
8. Cyprodinil meets the ED criteria for the EAS-modalities for humans and for the EATS-modalities for non-target organisms as laid down in points 3.6.5 and 3.8.2. of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605 (relevant to comply with the conditions of approval, not dependent of any specific use, see Section 6).

9.3 | Overview of the concerns identified for each representative use considered (Table 6)

(If a particular condition proposed to be taken into account to manage an identified risk, as listed in Section 8, has been evaluated as being effective, then 'risk identified' is not indicated in Table 6.)

TABLE 6 Overview of concerns reflecting the issues not finalised, critical areas of concerns and the risks identified that may be applicable for some but not for all uses or risk assessment scenarios.
In addition to the issues indicated in Table 6 below, the substance was considered to meet the criteria for endocrine disruption for humans and non-target organisms as laid down in points 3.6.5 and 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605.

Representative use		Barley	Apple
Operator risk	Risk identified		
	Assessment not finalised		
Worker risk	Risk identified	X[c]	
	Assessment not finalised		
Resident/bystander risk	Risk identified	X[d]	
	Assessment not finalised		
Consumer risk	Risk identified		
	Assessment not finalised	X[1,2]	X[1,2]
Risk to wild non-target terrestrial vertebrates	Risk identified	X[6]	X[6]
	Assessment not finalised		
Risk to wild non-target terrestrial organisms other than vertebrates	Risk identified		X[e]
	Assessment not finalised	X[4,5]	X[4,5]
Risk to aquatic organisms	Risk identified	X[7]	X[7]
	Assessment not finalised	X[3]	X[3]
Groundwater exposure to active substance	Legal parametric value breached		
	Assessment not finalised		
Groundwater exposure to metabolites	Legal parametric value breached[a]		
	Parametric value of 10 µg/L[b] breached		
	Assessment not finalised		

Note: The superscript numbers relate to the numbered points indicated in Sections 9.1 and 9.2. Where there is no superscript number, see Sections 2 to 7 for further information.

[a]When the consideration for classification made in the context of this evaluation under Regulation (EC) No 1107/2009 is confirmed under Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008.

[b]Value for non-relevant metabolites prescribed in SANCO/221/2000-rev. 10 final, European Commission (2003).

[c]In case of two applications, workers exposure estimates are above the AOEL.

[d]It should be noted that the exposure estimates with the EFSA model (2014), not applicable at the time of dossier submission, are above the AOEL, while the use of previous models (e.g. German model) does not raise any concern.

[e]Low in-field risk was concluded with standard tier 1 data. However, additional tier 2 data were available and the risk assessment using these data could not demonstrate a low risk.

10 | LIST OF OTHER OUTSTANDING ISSUES

Remaining data gaps not leading to critical areas of concern or issues not finalised but considered necessary to comply with the data requirements, and which are relevant for some or all of the representative uses assessed at EU level. Although not critical, these data gaps may lead to uncertainties in the assessment and are considered relevant.

These data gaps refer only to the representative uses assessed and are listed in the order of the sections:

- With the exclusion of two components, information on specification/composition for one co-formulant and genotoxicity and repeated dose toxicity over the short- and long-term for all the other co-formulants was not available for the components of the formulations for representative uses 'A8637C' and 'A14325E'. Therefore, in order to allow a final conclusion on the safety assessment of 'A8637C' and 'A14325E', genotoxicity, repeated dose toxicity data for these components (short- and long-term) and ecotoxicological information might be considered for further assessment (to be confirmed by Member States when assessing applications for PPP authorisation; relevant for all representative uses evaluated; see Section 'General aspects').
- Insufficient information was available to conclude on the ecotoxicological safety of the formulation for representative uses.
- Information to address the extraction efficiency of the monitoring method for the determination of cyprodinil in plants (relevant for all representative uses evaluated; see Section 1).
- A validated monitoring method and its ILV for monitoring NOA422054 (free and conjugated) in rotational crops (relevant for representative use on barley; see Section 1).
- n-octanol/water partition coefficient data of NOA422054 (free and conjugated) (relevant for all representative uses evaluated; see Section 1).
- Validated analytical method for monitoring of metabolite 1U in body fluids and tissues should be provided (relevant for all representative uses evaluated; see Section 1).
- Additional validation data on the analytical method used in study TK0055835 (relevant for representative use in apples; see Section 3).
- Additional validation data on the analytical method used in study R B5092 (relevant for representative use in barley; see Section 3).
- A documentation of the maximum storage duration and storage conditions of the residue samples of the rotational crop field trials (studies 2 to 5) and to what extent these are covered by proven storage stability data for all analyte/matrix combinations investigated in the rotational crop field trials (relevant for representative use in barley; see Section 3).
- Additional validation data on the analytical method REM 141.01 modified for LC/MS/MS used in studies 2 to 5 (relevant for representative use in barley; see Section 3).
- A fish metabolism study upon dietary exposure (relevant for all representative uses evaluated; Section 3).
- Determination of the residues in pollen and bee products for human consumption resulting from residues taken up by honey bees from crops at blossom (relevant for all representative uses evaluated; see Section 3)
- An updated literature search using appropriate criteria for selecting studies to be added to the dossier is needed (relevant for all representative uses evaluated; see Section 3).
- To further assess the risk of R008591 to aquatic organisms (relevant for all representative uses evaluated; see Section 5).
- Potential sub-lethal effects on bees were not addressed (relevant for all representative uses evaluated; unknown; see Section 5).
- Risk assessment for metabolites potentially occurring in pollen and nectar was not available (relevant for all representative uses evaluated; see Section 5).
- To further assess the in-field risk of non-target arthropods (relevant for the use in apple; submission date proposed by the applicant: unknown; see Section 5).
- Further data are needed with the formulation or with the single components in order to characterise the ecotoxicological profile of the formulations for the representative uses (relevant for all representative uses evaluated; see Section 5).

ABBREVIATIONS

a.s.	active substance
AAOEL	acute acceptable operator exposure level
ADI	acceptable daily intake
AMA	Amphibian Metamorphosis Assay
AOEL	acceptable operator exposure level
ARfD	acute reference dose
bw	body weight
CI	confidence interval
CL	confidence limits
DM	dry matter
DT_{50}	period required for 50% dissipation (define method of estimation)
DT_{90}	period required for 90% dissipation (define method of estimation)
EAS	oestrogen, androgen and steroidogenesis modalities
EC_{50}	effective concentration
ECHA	European Chemicals Agency

EEC	European Economic Community
ETO	ecological threshold option
FAO	Food and Agriculture Organization of the United Nations
FOB	functional observation battery
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
FSTRA	Fish Short-Term Reproduction Assay
GAP	Good Agricultural Practice
HPG	hypopharygeal glands
HPLC–MS	high-pressure liquid chromatography–mass spectrometry
HQ	hazard quotient
HR	hazard rate
IESTI	international estimated short-term intake
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
iv	intravenous
JMPR	Joint Meeting of 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
K_{Foc}	Freundlich organic carbon adsorption coefficient
LC_{50}	lethal concentration, median
LC–MS-MS	liquid chromatography with tandem mass spectrometry
LD_{50}	lethal dose, median; dosis letalis media
LOAEL	lowest observable adverse effect level
LOQ	limit of quantification
MOA	mode of action
MRL	maximum residue level
MS	mass spectrometry
MTD	maximum tolerated dose
NOAEL	no observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
PEC	predicted environmental concentration
pF2	pF value of 2 (suction pressure that defines field capacity soil moisture)
PHI	pre-harvest interval
pK_a	negative logarithm (to the base 10) of the dissociation constant
PPE	personal protective equipment
QSAR	quantitative structure–activity relationship
RAC	regulatory acceptable concentration
RAR	Renewal Assessment Report
SC	suspension concentrate
SD	standard deviation
SFO	single first-order
SMILES	simplified molecular-input line-entry system
SPG	specific protection goal
SSD	species sensitivity distribution
TMDI	theoretical maximum daily intake
ToxCAST	(US EPA) Toxicity Forecaster
TRR	total radioactive residue
UF	uncertainty factor
WG	water-dispersible granule
WHO	World Health Organization

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European Commission

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APPENDIX A

Consideration of cut-off criteria for cyprodinil according to Annex II of Regulation (EC) No 1107/2009 of the European Parliament and of the Council

Properties		Conclusion[a]
CMR	Carcinogenicity (C)	Cyprodinil is not considered to be a carcinogen (category 1A or 1B) according to point 3.6.3 of Annex II of Regulation (EC) No 1107/2009
	Mutagenicity (M)	Cyprodinil is not considered to be a mutagen (category 1A or 1B) according to point 3.6.2 of Annex II of Regulation (EC) No 1107/2009
	Toxic for Reproduction (R)	Cyprodinil is considered to be toxic for reproduction (category 2 or 1B) according to point 3.6.4 of Annex II of Regulation (EC) No 1107/2009, based on: • Harmonised classification according to Regulation (EC) No 1272/2008 and its Adaptations to Technical Process: not available • Peer review outcome: criteria for classification according to Regulation (EC) No 1272/2008 may be met
Endocrine disrupting properties		According to point 3.6.5 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605, it can be concluded that cyprodinil meets the ED criteria for humans for the EAS-modalities According to point 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605, it can be concluded that cyprodinil meets the ED criteria for non-target organisms for the EATS-modalities
POP	**Persistence** **Bioaccumulation** **Long-range transport**	Cyprodinil is not considered to be a persistent organic pollutant (POP) according to point 3.7.1 of Annex II of Regulation (EC) 1107/2009
PBT	**Persistence** **Bioaccumulation** **Toxicity**	Cyprodinil not considered to be a persistent, bioaccumulative and toxic (PBT) substance according to point 3.7.2 of Annex II of Regulation (EC) 1107/2009
vPvB	**Persistence** **Bioaccumulation**	Cyprodinil not considered to be a very persistent, very bioaccumulative substance according to point 3.7.3 of Annex II of Regulation (EC) 1107/2009

[a]Origin of data to be included where applicable (e.g. EFSA, ECHA RAC, Regulation).

APPENDIX B

List of end points for the active substance and the formulations for representative uses

Appendix B can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2025.9209.

APPENDIX C

Wording EFSA used in Section 4 of this conclusion, in relation to DT and Koc 'classes' exhibited by each compound assessed

Wording	DT_{50} normalised to 20°C for laboratory incubations[a] or not normalised DT_{50} for field studies (SFO equivalent, when biphasic, the DT_{90} was divided by 3.32 to estimate the DT50 when deciding on the wording to use)
Very low persistence	< 1 day
Low persistence	1 to < 10 days
Moderate persistence	10 to < 60 days
Medium persistence	60 to < 100 days
High persistence	100 days to < 1 year
Very high persistence	A year or more

Note: These classes and descriptions are unrelated to any persistence class associated with the active substance cut-off criteria in Annex II of Regulation (EC) No 1107/2009. For consideration made in relation to Annex II, see Appendix A.

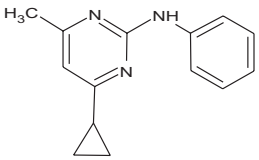
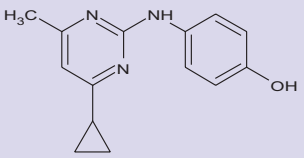
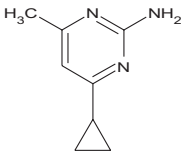
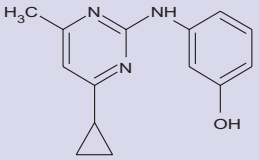
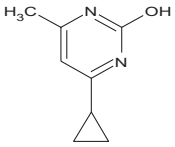
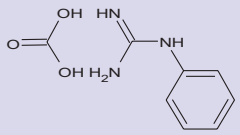
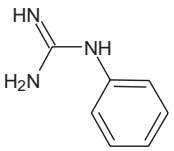
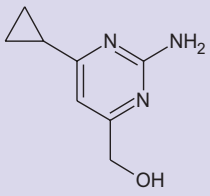
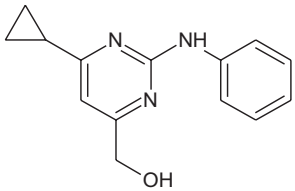
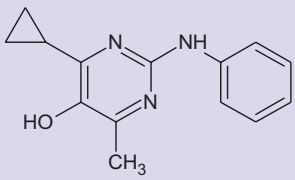
[a]For laboratory soil incubations normalisation was also to field capacity soil moisture (pF2/10 kPa). For laboratory sediment water system incubations, the whole system DT values were used.

Wording	K_{oc} (either K_{Foc} or K_{doc}) mL/g
Very high mobility	0 to 50
High mobility	51 to 150
Medium mobility	151 to 500
Low mobility	501 to 2000
Slight mobility	2001 to 5000
Immobile	> 5000

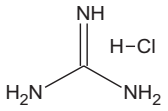
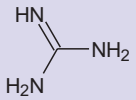
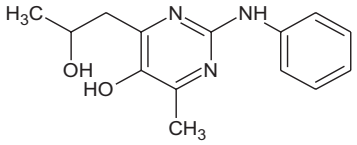
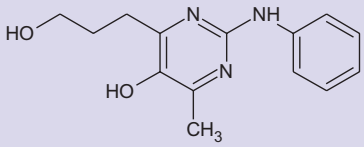
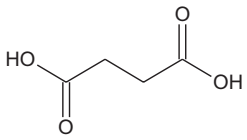
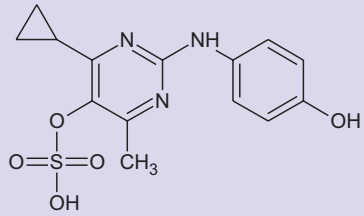
Note: Based on McCall et al. (1980).

APPENDIX D

Used compound codes

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
Cyprodinil **CGA219417**	4-cyclopropyl-6-methyl-*N*-phenylpyrimidin-2-amine Cc1cc(nc(Nc2ccccc2)n1)C1CC1 HAORKNGNJCEJBX-UHFFFAOYSA-N	
CGA304075	4-[(4-cyclopropyl-6-methylpyrimidin-2-yl)amino]phenol Oc1ccc(cc1)Nc1nc(C)cc(n1)C1CC1 LBDZGKRFRHHISM-UHFFFAOYSA-N	
CGA249287	4-cyclopropyl-6-methylpyrimidin-2-amine Cc1cc(nc(N)n1)C1CC1 KPMMRZPKAYBHME-UHFFFAOYSA-N	
CGA275535	3-[(4-cyclopropyl-6-methylpyrimidin-2-yl)amino]phenol Oc1cc(Nc2nc(C)cc(n2)C2CC2)ccc1 IGDCKQUNQPOPEU-UHFFFAOYSA-N	
CGA321915	4-cyclopropyl-6-methylpyrimidin-2-ol Cc1cc(nc(O)n1)C1CC1 QODMYONMGSMOCI-UHFFFAOYSA-N	
CGA263208 **CA1139A**	1-phenylguanidine – carbonic acid (1:1) NC(=N)Nc1ccccc1.O=C(O)O XDSYAIICRRZSJX-UHFFFAOYSA-N	
Phenyl guanidine	1-phenylguanidine NC(=N)Nc1ccccc1 QRJZGVVKGFIGLI-UHFFFAOYSA-N	
NOA422054	(2-amino-6-cyclopropylpyrimidin-4-yl)methanol Nc1nc(cc(CO)n1)C1CC1 SPGFTSNGXQXBSO-UHFFFAOYAM	
CGA232449	(2-anilino-6-cyclopropylpyrimidin-4-yl)methanol OCc1cc(nc(Nc2ccccc2)n1)C1CC1 KWORTNPHVKWENH-UHFFFAOYSA-N	
CGA304076	2-anilino-4-cyclopropyl-6-methylpyrimidin-5-ol Oc1c(nc(Nc2ccccc2)nc1C)C1CC1 XEFZMEARAKSJMJ-UHFFFAOYSA-N	

(Continued)

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
CGA048109	Guanidine hydrochloride (1:1) Cl.N=C(N)N PJJJBBJSCAKJQF-UHFFFAOYSA-N	
Guanidine	Guanidine N=C(N)N ZRALSGWEFCBTJO-UHFFFAOYSA-N	
I13c	2-anilino-4-(2-hydroxypropyl)-6-methylpyrimidin-5-ol CC(O)Cc1nc(Nc2ccccc2)nc©c1O OAXJHFKSINNKRT-UHFFFAOYSA-N	
I13b	2-anilino-4-(3-hydroxypropyl)-6-methylpyrimidin-5-ol OCCCc1nc(Nc2ccccc2)nc(C)c1O DRYHNMJRTIBVFR-UHFFFAOYSA-N	
R008591, succinic acid	Butanedioic acid O=C(O)CCC(=O)O KDYFGRWQOYBRFD-UHFFFAOYSA-N	
1U	4-cyclopropyl-2-(4-hydroxyanilino)-6-methylpyrimidin-5-yl hydrogen sulfate O=S(=O)(O)Oc1c(nc(Nc2ccc(O)cc2)nc1C)C1CC1 KFIJYTIQTGZCLA-UHFFFAOYSA-N	

[a]The metabolite name in bold is the name used in the conclusion.

[b]ACD/Name 2021.1.3 S:\Journals\WILEY_JNLS\PAGINGFILES\EFS2\VOL000\EFS2_9151/Labs 2021.1.3 (File Version N15E41, Build 123232, 07 Jul 2021).

[c]ACD/ChemSketch 2021.1.3 ACD/Labs 2021.1.3 (File Version C25H41, Build 123835, 28 Aug 2021).