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CONCLUSION ON PESTICIDES PEER REVIEW

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

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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 Spain for the pesticide active substance fludioxonil 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 use of fludioxonil as a fungicide on wheat, oats, grapes, pome fruit and strawberry. 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

fludioxonil, 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. Fludioxonil is one of the active substances listed in Regulation (EU) No 686/2012.

In accordance with Article 1 of Regulation (EU) No 844/2012, the rapporteur Member State (RMS), France and co-rapporteur Member State (co-RMS), Spain, received an application from Syngenta Crop Protection AG for the renewal of approval of the active substance fludioxonil. In addition, Syngenta Crop Protection AG submitted an application for the assessment of confirmatory data following the Article 12 MRL review under Regulation (EC) No 396/2005. It is noted that the MRL Art.12 confirmatory data application for fludioxonil, and the related confirmatory data were assessed in a separate Reasoned Opinion.

An initial evaluation of the renewal dossier on fludioxonil 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 fludioxonil according to the representative uses as a **fungicide** by foliar application on wine and table grapes, field and greenhouse strawberries, for the control of storage fungal diseases in pome fruit (apple and pear) and applications by seed treatment in wheat and oat, 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 fludioxonil or the formulations for representative uses, and **analytical methods**.

In the area of **mammalian toxicology** and non-dietary exposure, the batches used in the toxicity studies could not be concluded to be representative of the originally and newly proposed technical specification for the active substance and associated impurities, leading to an issue that could not be finalised. Metabolite CGA227731 is considered to be genotoxic in vitro and in vivo.

In the **residue** section, the consumer dietary risk assessment could not be finalised due to data gaps related to the residue definition for risk assessment for primary and rotational crops and due to lack of data on the magnitude of residues of metabolite CGA227731, considered genotoxic in vitro and in vivo, in cereal forage, grain and straw grown in rotation. The consumer risk assessment is also not finalised as appropriate information is missing to address the effect of water treatment processes on the nature of the residues that might be present in surface water and groundwater, when surface water or groundwater are abstracted for the production of drinking water.

The data available on **environmental fate and behaviour** are sufficient to carry out the required environmental exposure assessments at EU level for the representative uses, with the notable exception that information is missing regarding the identity of components in two chromatographically resolved fractions in soil extracts, assessed as reaching levels triggering assessment, based on the available information. This led to the groundwater exposure assessment for these possible soil metabolites being not finalised. Consequently, their groundwater relevance assessment is an open issue. For representative uses other than cereal seed treatments, the parametric drinking water limit of 0.1 µg/L is predicted to be exceeded for metabolites that may be considered relevant, in 80th percentile annual average soil water concentrations moving below 1m depth, that is used in assessments to represent vulnerable groundwater.

In the area of **ecotoxicology**, no concern other than the one reported below for the ED assessment was identified.

Regarding the assessment of the **endocrine disruption** (ED) properties, based on the available data and assessments, it can be concluded that fludioxonil meets the ED criteria for the oestrogen, androgen and steroidogenesis (EAS)-modalities 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 an additional 3 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 Spain received an application from Syngenta Crop Protection AG for the renewal of approval of the active substance fludioxonil. In addition, Syngenta Crop Protection AG submitted an application for the assessment of confirmatory data following the Article 12 MRL review under Regulation (EC) No 396/2005.[4] Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicant, the co-RMS (Spain), the European Commission and EFSA about the admissibility.

The RMS provided its initial evaluation of the dossier on fludioxonil in the RAR, which was received by EFSA on 21 February 2018 (France, 2018).

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 17 July 2018. 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 19 September 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 12 November 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 1 and 3 (April 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 in line with the scientific criteria for the determination of endocrine disrupting properties, as laid down in Commission Regulation (EU) 2018/605,[5] 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 July – August 2024.

This conclusion report summarises the outcome of the peer review of the risk assessment of the active substance and the formulations for representative uses, evaluated on the basis of the representative use of fludioxonil as a fungicide on wheat, oats, grapes, pome fruit and strawberry, as proposed by the applicant. In accordance with Article 12(2) of Regulation (EC) No

[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]Regulation (EC) No 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC. OJ L 70, 16.3.2005, pp. 1–16.

[5]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.

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, in June 2022, the applicant provided further information aimed at demonstrating that the exposure of humans and the environment to fludioxonil was negligible under realistic conditions of use, for uses as a fungicide in ornamentals in permanent (high technology) greenhouses i.e. in a non-representative use which was not part of the dossier for renewal of approval. Since the legislation does not provide for changes to the representative uses during the renewal process which were not part of the supplementary dossier submitted for the renewal, an assessment of negligible exposure for these uses has not been included in this Conclusion. Nevertheless, some considerations by the RMS on what was provided by the applicant are available in the final RAR (France, 2024). An assessment of any potential for negligible exposure from the representative uses has not been provided by the applicant or RMS. Furthermore, in April 2022 the applicant requested a derogation under Article 4(7) of Regulation (EC) 1107/2009, submitting documentary evidence regarding the necessity of fludioxonil as a fungicide to control a serious danger to plant health which considered the authorised uses of fludioxonil in 19 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.

It is noted that the evaluation of **confirmatory data following the Article 12 MRL review** for fludioxonil, originally submitted with the renewal dossier, were assessed in a previous EFSA Reasoned opinion (EFSA, 2019) and are considered as sufficiently addressed.

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

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 tables (14 November 2018 and August 2023[6]);
- the evaluation table (7 August 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, 2024), 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

Fludioxonil is the ISO common name for 4-(2,2-difluoro-1,3-benzodioxol-4-yl)-1*H*-pyrrole-3-carbonitrile (IUPAC).[7]

The formulations for representative uses for the evaluation were 'A8240D', a water dispersible granule (WG) containing 500 g/kg fludioxonil and 'A8207M', a flowable concentrate for seed treatment (FS) containing 25 g/L fludioxonil, respectively.

The information on the active substance and the formulations for representative uses, including the co-formulants in these formulations, was considered in the overall 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,[8] nor considered as an active substance in accordance with Regulation (EC) No 1107/2009. Details on the composition of the formulations 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 formulations 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 foliar applications for the control of *Botrytis cinerea* in wine and table grapes, field and greenhouse strawberries, for the control of storage fungal diseases in pome fruit (apple and pear) and applications by seed treatment to control various fungal diseases in wheat and oat, in the EU. Full details of the representative uses can be found in the list of end points in Appendix B.

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

[7]It should be noted that fludioxonil and most of its metabolites (see Appendix D) are substances that meet the definition of per- and polyfluoroalkyl substances (PFAS) based on their chemical structures, however they all belong to the PFAS subgroups excluded from the ECHA PFAS restriction proposal (https://echa.europa.eu/restrictions-under-consideration/-/substance-rev/72301/term).

[8]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.

Data were submitted to conclude that the representative uses of fludioxonil 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).

CONCLUSIONS OF THE EVALUATION

General aspects

With regard to the toxicological information available for the formulations for representative uses 'A8240D' and 'A8207M', studies were performed on acute toxicity endpoints. Considering information made available in the revised RAR after the experts' meeting with regard to the co-formulants contained in 'A8240D' and 'A8207M', EFSA concluded that sufficient toxicological data were not available for all components, but three. For the insufficiently characterised co-formulants, EFSA confirmed the conclusion of the experts that the available toxicological information did not sufficiently address the genotoxicity and repeated dose toxicity potential of 'A8240D' and 'A8207M' 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).[9]

The availability of ecotoxicity data with the formulations for representative uses was discussed at the experts' meeting[10] (refer to Section 5). It was noted that, based on the available acute data (see Section 5), the formulations for representative uses are not more acutely toxic than expected from the active substance. A data retrieval search for available ecotoxicity data for the individual components was not available and therefore it was not possible to reach a conclusion on the safety of the formulations for representative uses (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, 2010.

The proposed specification for fludioxonil was based on batch data from industrial production. The proposed minimum purity is 950 g/kg. 1-[2-cyano-1-(2,2-difluoro-2*H*-1,3-benzodioxol-4-yl)ethyl]-4-(2,2-difluoro-2*H*-1,3-benzodioxol-4-yl)-1*H*-pyrrole-3-carbonitrile (SYN549129) was considered a relevant impurity with a maximum content of 3 g/kg. It should be noted that the evaluation of the toxicological relevance of some impurities is open (see Section 2) and as a consequence, new data such as spectral data, content of the impurities in the formulations before and after storage, and methods for analysis of the relevant impurities in the formulations might be required. Considering that based on the data submitted for the renewal, at least one new relevant impurity was identified, the reference specification needs to be updated. The batches used in the toxicological assessment could not be concluded to be representative of the original and newly proposed reference specification (see Section 2). The batches used in the ecotoxicological studies were not considered compliant with both the original and the newly proposed reference specifications (see Section 5). There is no FAO specification available for the active substance.

The main data regarding the identity of fludioxonil and their physical and chemical properties are given in Appendix B. **Data gaps** were identified for spectral data of the relevant impurity SYN549129 and for determination of the content of the relevant impurity SYN549129 in the formulations for representative uses before and after storage (see Section 10).

Adequate methods are available for the generation of data required for the risk assessment. Methods of analysis are available for the determination of the active substance in the technical material and the formulations for representative uses. A **data gap** was identified for an analytical method for the determination of the relevant impurity SYN549129 in the formulations for representative uses (see Section 10).

The QuEChERS multi-residue method using high-pressure liquid chromatography with tandem mass spectrometry (HPLC–MS/MS) can be used for the determination of fludioxonil residues in all plant commodity groups with a limit of quantification (LOQ) of 0.01 mg/kg, however a **data gap** was identified for the determination of the extraction efficiency of the method (see Section 10).

The residue definition in food and feed of animal origin was defined as sum of fludioxonil and its metabolites, which can be oxidised to metabolite CGA192155 (2,2-difluoro-*2H*-1,3-benzodioxole-4-carboxylic acid), expressed as fludioxonil. The compounds of the residue definition for monitoring in the animal matrices (milk, muscle, liver, fat, kidney, eggs and blood) can be determined by HPLC-MS/MS as CGA192155 with a LOQ of 0.01 mg/kg, expressed as fludioxonil.

The residue definition in the environmental matrices was defined as fludioxonil. Appropriate HPLC–MS/MS methods exist for monitoring fludioxonil in soil and water with LOQs of 0.01 mg/kg and 0.05 µg/L, respectively. Fludioxonil can be determined in air by HPLC-UV with a LOQ of 2 µg/m^3.

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

[10]See experts' consultation point 5.11 in the Report of the Pesticides Peer Review Experts' TC 123 (November 2023) (EFSA, 2024).

The residue definition in body fluids and tissues was defined as sum of fludioxonil and its metabolites, which can be oxidised to metabolite CGA192155, expressed as fludioxonil. Determination of the compounds of the residue definition in body fluids and tissues can be performed by HPLC–MS/MS with a LOQ of 0.01 mg/kg, expressed as fludioxonil.

2 | MAMMALIAN TOXICITY

The toxicological profile of the active substance fludioxonil was discussed at the Pesticides Peer Review Experts' Meeting PREV 01 – Session 2 (April 2019) and at the Pesticides Peer Review Experts' Teleconference (TC) 119 (November 2023), and assessed based on the following guidance documents: European Commission (2003, 2012), EFSA PPR (2012), EFSA (2014c) and ECHA (2017a).

The batches used in toxicity studies could not be concluded to be representative of the original and newly proposed **reference specification** for the active substance and associated impurities, leading to a data gap and an **issue that could not be finalised** (see Sections 1 and 9.1). For some impurities, the applicant did not provide enough information to exclude their relevance from the toxicological point of view (**data gap**, see Section 9.1). Impurity SYN549129 is considered relevant (teratogenicity concern based on QSAR prediction, maximum content of 3 g/kg). The analytical methods used in the toxicity studies were overall considered fit-for-purpose.

In the **toxicokinetics** studies in rats, systemic bioavailability was estimated to be 56% in males and 76% in females. There was no evidence for accumulation. Excretion of fludioxonil was predominantly through the faecal route. The main metabolic pathway identified was oxidation and glucuronidation. No unique human metabolite is expected (in vitro metabolism study). The residue definition for body fluids and tissues is the sum of fludioxonil and mammalian metabolites which can be oxidised to metabolite CGA192155. In the **acute toxicity** studies, fludioxonil has low acute toxicity when administered orally, dermally or by inhalation to rats. It is not a skin or eye irritant or a skin sensitiser. Fludioxonil is not phototoxic. In **short- and long-term** oral toxicity studies, the target organs of toxicity were the liver (rat, mice and dog) and kidney (rat, mice). Dog was the most sensitive species after short-term exposure and rat after long-term exposure. The relevant short-term oral NOAEL is 33 mg/kg bw per day (1-year dog). The relevant long-term oral NOAEL is 37 mg/kg bw per day (2-year rat). Fludioxonil showed no carcinogenic potential both in rats and mice. Based on the available **genotoxicity** studies fludioxonil is unlikely to be genotoxic in vivo. Considering both the existing and the newly submitted two-generation **reproductive toxicity** studies, the relevant (lowest) NOAEL was 18.9 mg/kg bw per day for parental toxicity, 58 mg/kg bw per day for reproductive toxicity and 18.9 mg/kg bw per day for offspring toxicity. Maternal toxicity included reduced body weight gain and food consumption in rats and rabbits. **Developmental toxicity** (increased foetal and litter incidences of ureteral and/or pelvic dilatations) was only observed in rats (developmental NOAEL of 10 mg/kg bw per day). Fludioxonil did not show **neurotoxicity** or **immunotoxicity** in standard toxicity studies, neither in the acute neurotoxicity study in rats, nor in the 28-day immunotoxicity study in mice.

The **agreed acceptable daily intake** (ADI) is 0.37 mg/kg bw per day, on the basis of the relevant long-term NOAEL of 37 mg/kg bw in the 2-year study in rats based on kidney toxicity (renal tubular casts) and liver (increased weight, hepatocyte hypertrophy, bile duct proliferation) observed at 137 mg/kg bw per day. An uncertainty factor of 100 was applied. The ADI is also supported by the 1-year dog study. It is noted that during the previous peer review the same ADI was set (EFSA, 2007).

The **agreed acute reference dose** (ARfD) is 1 mg/kg bw based on the maternal NOAEL of 100 mg/kg bw per day for reduced body weight gain observed at the beginning of treatment at 1000 mg/kg bw per day in the developmental toxicity study in rats and rabbits. An uncertainty factor of 100 was applied. This ARfD would cover acute effects observed in the acute neurotoxicity studies at 500 mg/kg bw. The same basis applies to the systemic **acute acceptable operator exposure level** (AAOEL). A correction factor of 56% for systemic bioavailability is needed to derive the AAOEL of 0.56 mg/kg bw. It is noted that during the previous peer review an ARfD and AAOEL were not set (EFSA, 2007).

The agreed systemic **acceptable operator exposure level** (AOEL) is 0.2 mg/kg bw per day on the basis of the relevant short-term NOAEL of 33 mg/kg bw per day in the 1-year study in dogs based on decreased body weight gain in females and body weight loss in males, liver effects in males and females; and increased total cholesterol in males at 297 mg/kg bw per day. An uncertainty factor of 100 was applied. A correction factor of 56% for systemic bioavailability is needed to derive the AOEL. The AOEL is also supported by an overall NOAEL of 37 mg/kg bw per day in rat (derived from short-term and long-term rat studies). It is noted that during the previous peer review a different AOEL was set (0.59 mg/kg bw per day, EFSA, 2007).

Fludioxonil met the criteria for endocrine disruption (ED) (see Section 6); overall, the toxicological reference values (ADI, AOEL, AAOEL and ARfD) are not impacted by the newly submitted 2-generation reproductive toxicity study (i.e. reference values set at the Pesticides Peer Review Experts' Meeting PREV 01 – Session 2 (April 2019) are confirmed). The lowest NOAEL for the ED endpoint is 58 mg/kg bw per day (see Section 6). Therefore, the toxicological reference values are considered covering the endocrine effects.

The RMS estimated **non-dietary exposure** (i.e. operator, worker, bystander and resident) considering dermal absorption values of fludioxonil in 'A8207M' of 0.4% for the concentrate and in 'A8240D' of 0.1% for the concentrate, and 5% and 8%, respectively, for the dilutions as input values.

Considering the representative uses with 'A8207M' as fungicide in **cereals**, the maximum estimated operator exposure was below the AOEL (13% of the AOEL) with the use of personal protective equipment (PPE, i.e. gloves) during seed treatment according to the Generic SeedTropex Model. Worker exposure (i.e. fork lift truck drivers) was below the AOEL

(0.04% of the AOEL). Bystander and resident exposures to dust from treated seed during sowing activities, in relation to the amount of active substance that might be present in this dust, are far below the AOEL.

Considering the representative uses with 'A8240D' as fungicide in **grapes**, **pome fruits**, **strawberries (outdoor)** and **strawberries (indoor)**, the maximum estimated operator exposure was below the AOEL/AAOEL (strawberries indoor) without the use of PPE according to the Dutch Greenhouse Model. Maximum worker exposure was below the AOEL (82% of the AOEL, grapes) without the use of PPE according to the EFSA Model. Maximum bystander and resident exposure was below the AOEL/AAOEL (pome fruits, outdoors, resident child all pathways) according to the EFSA Model.

Fludioxonil met the criteria for endocrine disruption (see Section 6); the applicant did not submit an assessment of negligible exposure for the representative uses (see Background section and Section 6).

The RMS assessed the toxicological profile of **metabolites**, found as residues in plants or animal matrices or in groundwater, based on experimental data, QSAR analysis, grouping and read-across. The majority of experts agreed on the grouping, as proposed by the RMS[11]:

Group 1: Fludioxonil is the lead compound and its toxicological profile (genotoxicity and general toxicity) cover metabolites SYN518576, SYN518577, SYN518578 and their glucuronide and sulfate conjugates. Regarding CGA173506 lactic acid (SYN551031), the majority of experts agreed that it is unlikely to be genotoxic and for the general toxicity further justification should be provided to support read-across from parent (a data gap is not proposed taking into account the low exposure under the representative uses assessed, see Section 3). Regarding metabolite CGA192155, although not included in the group 1, results from the 90-day rat study indicated that its toxicological profile is qualitatively similar to the parent and it is considered not more toxic than the parent. Therefore, reference values of the parent can apply to this metabolite.

Group 2: CGA339833 and CGA308103 are the lead compounds and their toxicological profile cover CGA344624, CGA344623 and SYN518581. These metabolites are considered unlikely to be genotoxic. For CGA339833 an ADI of 0.29 mg/kg bw per day was established, based on a NOAEL of 58 mg/kg bw per day from a 90-day study in rats and an uncertainty factor of 200 to account for the use of a short- term toxicity study. This ADI can apply to this group of metabolites. The toxicological profile of the Group 2 metabolites is qualitatively different from that of the parent.

Group 3: CGA265378 is the lead compound and its toxicological profile would cover SYN518579 and SYN518579 tautomer. These metabolites are considered unlikely to be genotoxic. For general toxicity, a conclusion cannot be drawn based on the data provided (a **data gap** is proposed for the lead compound, CGA265378, see Sections 3 and 9.1). An assessment of CGA265378 as groundwater metabolite is not triggered for the representative uses.

Group 4: CGA335892 is the lead compound. For glucuronide conjugate of CGA335892, read-across to CGA335892 is accepted. No conclusion can be drawn for genotoxicity (additional alerts compared to parent from QSAR analysis) and general toxicity (nevertheless a data gap is not proposed given the expected low exposure according to the representative uses, see Section 3).

A group was not proposed for the following metabolites: CGA227731, CGA308565 and SYN518580. The majority of experts agreed with the RMS' assessment to consider metabolite CGA227731 as genotoxic in vitro and in vivo (mutagenic in the Ames test-strain TA1537 and in the liver in the in vivo Comet assay), leading to **an issue that could not be finalised** (see **data gap** in Section 3 regarding exposure and Section 9.1). CGA308565 is unlikely to be genotoxic and of low acute oral toxicity to rats. For SYN518580, no conclusion can be drawn for genotoxicity (additional alerts compared to parent from QSAR analysis) and general toxicity. Considering the representative uses and the assessment of the metabolism of fludioxonil in primary crops, no further data are needed for CGA308565, however a **data gap** has been identified to further address the genotoxicity potential for SYN518580 (see Sections 3 and 9.1).

Fludioxonil is not classified for reproductive toxicity in the existing Annex VI entry of the CLP Regulation.[12] However, based on the newly submitted 2-generation toxicity study following the stop of the clock to address endocrine disruption, EFSA agreed with the RMS that the criteria for classification according to Regulation (EC) No 1272/2008[12] may be met for **reproductive toxicity**, category 2, having an impact on the relevance assessment of **groundwater metabolites CGA192155**, **CGA339833**, which were concluded as non-relevant groundwater metabolites when considering the existing Annex VI entry of the CLP Regulation for fludioxonil. However, the above considerations on the active substance would indicate the metabolites would be considered relevant unless it is demonstrated that they do not share the reproductive toxicity potential of fludioxonil (see also Sections 4 and 7). EFSA noted that the ECHA RAC Opinion from 2017 did not consider this newly submitted 2-generation toxicity study.[13]

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).

[11]See further details on experimental data, QSAR analysis, grouping and read-across under expert's consultation point 2.11 in the report of the Pesticides Peer Review Experts' Meeting PREV 01 – Session 2 (April 2019) (EFSA, 2024).

[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 fludioxonil. 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.

Fludioxonil was discussed at the Pesticides Peer Review Experts' Meeting PREV 04 in April 2019.

The metabolism of fludioxonil was investigated in fruit crops (grapes, tomatoes, peaches) and leafy crops (lettuces, whole plant of spring onions) following foliar treatment and in root crops (potatoes), pulses and oilseeds (cotton, soyabean) and cereals (rice, wheat) following seed treatment, using either the phenyl or the pyrrole ^{14}C-labelling form of fludioxonil. In the fruit and leafy crops, fludioxonil was found to be the predominant compound of the total radioactive residues (12%–87% TRR in edible parts). Numerous metabolites were identified individually at very minor proportions in all crops and accounted as sum for max 21% TRR (spring onion whole plant). The concentration of some of these metabolites accounted for levels at or above 0.05 mg/kg in grapes, peaches, whole plant of spring onions and in lettuces. The metabolite CGA265378 is expected to occur at concentrations > 0.05 mg/kg at PHI 0 day and 0.04 mg/kg at PHI 7 days in leafy crops from the metabolism data and therefore a data gap was identified to address the general toxicity for CGA265378 (see Sections 2 and 9.1). It is also noted that though metabolite SYN518580 was recovered in very low proportions in grapes (< 1% TRR), quantifiable residues (> 0.01 mg/kg) might be expected based on the metabolism study and the GAP-compliant residue trials on grapes. Since its genotoxic potential could not be ruled out, a **data gap** has been identified to address the genotoxicity potential of SYN518580 (see Sections 2 and 9.1). Following seed treatment, the total residues were very low in potato tubers and in cereal grain (< 0.01 mg/kg) and in cotton and soya bean seeds and in cereal straw (up to 0.015 mg/kg). The parent compound was recovered only in potato tubers and peels (up to 44% TRR). Other metabolites were tentatively identified in feed items at a trace level (< 0.01 mg/kg). Throughout all the crops, fludioxonil was considered as a relevant marker of the total residues and the **residue definition for enforcement** was set as fludioxonil for all categories of crops following foliar and seed treatment. The metabolism studies on fruits did not provide information on residues at the GAP relevant early pre-harvest intervals (PHIs) of the representative uses (3 to 21 days) but only at longer PHIs. Whilst this shortcoming will not impact the qualitative metabolic pattern, it will not allow to estimate the quantitative contribution of metabolites to the overall dietary exposure at the relevant PHIs and thus to derive robust conversion factors for monitoring to risk assessment. Therefore, a complete datasets of residue trials compliant with the representative uses and analysing fludioxonil alone, and fludioxonil and all its metabolites that can be oxidised to metabolite 2,2-difluoro-*2H*-1,3-benzodioxole-4-carboxylic acid (CGA192155), expressed as fludioxonil, and supported by acceptable storage stability data and validated analytical methods (**data gap**, see Section 9.1) are required. The **residue definition for risk assessment** is provisionally proposed as 'sum of fludioxonil and its metabolites oxidised to metabolite 2,2-difluoro-*2H*-1,3-benzodioxole -4-carboxylic acid (CGA192155), expressed as fludioxonil' for primary crops following foliar and seed treatment. The inclusion of the metabolites in the residue definition should be revisited in the light of the outstanding residue trials.

Confined rotational crops metabolism studies were triggered (field soil DT_{90} Fludioxonil: 34–790 days). The metabolism of fludioxonil in rotational crops was similar to the metabolic pattern depicted in primary crops with an extensive degradation of fludioxonil. As for the significant residue levels of metabolite CGA227731 observed in cereal forage and straw (11% and 22% TRR, respectively) and considering its genotoxicity potential (see Section 2), sufficient rotational crops field trials covering the Northern and Southern zones of Europe to determine the magnitude of CGA227731 residues in cereal forage, grain and straw at the different standard plant back intervals (PBIs) covering the maximum PECsoil for fludioxonil and supported by validated methods and acceptable storage stability data are required (**data gap**, see Section 9.1). In the absence of these data, the residue definition for monitoring and risk assessment in rotational crops is set by default to fludioxonil.

Fludioxonil remained stable under the standard hydrolysis conditions representative of pasteurisation, baking/brewing/boiling and sterilisation.

A sufficient number of valid residue field trials analysing only for fludioxonil for all representative uses are available, except for the uses on strawberries. It is noted that a **data gap** has been identified for a complete dataset of residue trials compliant with all representative uses analysing for fludioxonil alone, and fludioxonil and all its metabolites that can be oxidised to CGA192155, expressed as fludioxonil, (see above). EFSA takes note that new seed treatment studies with barley grain, which were not submitted during the peer review, are already available. Furthermore, it is noted that only a single storage stability study on grapes and representative of the high-acid content matrices was provided and in order to comply with the current data requirements, an additional storage stability study on a crop representative of the high-acid content commodities is required (**data gap**, see Section 10).

In the metabolism studies conducted in goat and laying hens with [pyrrole-^{14}C] labelled fludioxonil, the compound was extensively degraded except in ruminant fat and poultry muscle (83% TRR and 29% TRR, respectively). The toxicity of all the identified metabolites was addressed except for CGA335892 free and sulfate conjugates. However, the residues of this metabolite in egg yolk are expected to be at a trace level (< 0.01 mg/kg) considering the representative uses and the authorised European uses (Article 12 MRL review; EFSA, 2011) and therefore further toxicity data are not required. In case of future uses with feed items, the need to request these data for this compound should be reconsidered accordingly. Overall, these studies were considered as sufficiently valid to derive the **residue definition** for **enforcement** and **risk assessment** for products of animal origin as 'sum of fludioxonil and its metabolites oxidised to metabolite 2,2-difluoro-*2H* -1,3-benzodioxole-4-carboxylic acid (CGA192155), expressed as fludioxonil'. Feeding studies are not triggered for poultry. Based on the available and acceptable feeding study on lactating goats, MRLs were proposed at the LOQ of the common moiety method (0.01 mg/kg) for milk and tissues. It is also highlighted that the analytical method for the determination of the common moiety residues is considered suitable to release conjugated residues observed in the metabolism studies.

Considering the representative use on wheat and the expected low residue situation in wheat grain following seed treatment, a metabolism study in fish is not required.

According to the representative uses on grapes and strawberries, treatment may occur at flowering and the data requirement to determine the residues in pollen and bee products for human consumption resulting from residues taken up by honeybees from crops at blossom should be addressed for these crops. Residue trials on winter oilseed rape were provided for the determination of fludioxonil residues in honey. Given that the trials were underdosed, additional residue trials on a crop representative of a worst-case scenario with respect to potential residues in honey and conducted at an appropriate dose rate of application should be provided; the residue situation in the rotational crops should also be considered in the overall assessment to determine the residues of fludioxonil in pollen and bee products (**data gap**, see Section 10).

In view of the identified data gaps to finalise the residue definitions for risk assessment in primary and in rotational crops, a provisional dietary intake calculation has been carried out considering the risk assessment input values for fludioxonil for the representative uses respectively on pome fruit (apples, pears), strawberries, table and wine grapes, wheat and oats and for milk and ruminants' tissues. The calculated chronic intake accounted for 6.0% (NL toddler) and for 5.3% (DE child) of the ADI when considering EFSA PRIMo rev. 3.1 and 2A, respectively; whilst the highest acute intake was 27% and 24% (both from table grapes) of the ARfD when considering EFSA PRIMo rev. 3.1 and 2A, respectively.

Although CGA192155 and CGA339833 were concluded as non-relevant groundwater metabolites when considering the existing Annex VI entry of the CLP Regulation[14] for fludioxonil, the criteria for classification according to Regulation (EC) No 1272/2008 for these two metabolites may be met for reproductive toxicity, category 2, see Sections 2, 4 and 7. A consumer risk assessment through drinking water was carried out based on the default assumptions laid down in the WHO Guidelines (WHO, 2017) for drinking water quality for (a) a 60-kg adult drinking 2 L of water per day, (b) a 10-kg child drinking 1 L of water per day and (c) a 5-kg bottle-fed infant drinking 0.75 L of water per day. The TMDI was shown to be below 1% of the ADI derived respectively for all three population groups. The concentrations of the unidentified groundwater metabolites MF2 and D9 were indicated to be above 0.1 µg/L but a groundwater relevance assessment could not be conducted (see **data gaps** in Sections 4 and 9.1). The consumer risk assessment is also not finalised as appropriate information to address the effect of water treatment processes on the nature of the residues that might be present in surface water and groundwater, when surface water or groundwater are abstracted for drinking water is missing (see **data gap** in Sections 4 and 9.1).

Fludioxonil met the criteria for endocrine disruption (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 rates of dissipation and degradation in the environmental matrices investigated were estimated using FOCUS (2006) kinetics guidance. In soil laboratory incubations under aerobic conditions in the dark, fludioxonil exhibited high to very high persistence, forming no major (> 10% applied radioactivity (AR)) metabolites. One unidentified chromatographically resolved fraction ascribed the code **MF2** that accounted for up to 7.7% AR in one soil triggered the need to be identified and, if applicable, have soil transformation rates and soil adsorption values made available. Such information was not available. Consequently, a **data gap** was identified (see Section 9.1). Mineralisation of the pyrrole and phenyl ring ^{14}C radiolabels to carbon dioxide accounted for 28%–45% AR after 363–364 days. The formation of unextractable residues (not extracted by acetone followed by acetonitrile/water or acetonitrile/water or acetone/water) for these radiolabels accounted for 26%–29% AR after 362–363 days. In laboratory soil photolysis investigations fludioxonil was transformed faster than in the dark incubations forming the major photolysis transformation products **CGA265378** (max. 11% AR) and **SYN545245** (max. 29% AR), both of which exhibited very low persistence, **CGA192155** (max. 27% AR), which exhibited moderate persistence and **CGA339833** (max. 13% AR) which exhibited low to moderate persistence. All these persistence indications were derived from soil laboratory incubations with the metabolites as test substance under aerobic conditions in the dark. One unidentified chromatographically resolved fraction ascribed the code **D9** that accounted for up to 7.3% AR triggered the need to be identified and, if applicable, have soil transformation rates and soil adsorption values made available. Such information was not available. Consequently, a **data gap** was identified (see Section 9.1). In anaerobic soil incubations fludioxonil was essentially stable. Fludioxonil exhibited slight mobility in soil. CGA192155 and CGA339833 exhibited very high soil mobility. Data are missing on the soil adsorption of CGA339833 (information on two more soils outstanding, **data gap**), CGA265378 and SYN545245 (where reliable data were not available, **data gap**). Consequently, relevant data gaps were identified (see Section 10). For fludioxonil and CGA192155 there was no indication that soil adsorption was pH dependent. In satisfactory field dissipation studies carried out at 10 European sites (six in Germany, two in Switzerland, one each in France and Italy, spray application to the soil surface on bare soil plots in late spring) fludioxonil exhibited low to high persistence. Sample analyses were only carried out for the parent fludioxonil. For three of these German field trial sites DT_{50} values were accepted as being reasonable estimates of bulk soil degradation (where surface processes including photolysis had been excluded) when using the EFSA (2014b) DegT50 guidance. The field data kinetic endpoints from these three sites were combined with laboratory incubation values to derive the modelling endpoint for parent fludioxonil.

In laboratory incubations in dark aerobic natural sediment water systems, fludioxonil exhibited very high persistence. In an irradiated sediment water study the major metabolite CGA192155 (max. 12% AR in water and 6% AR in sediment) was

[14]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.

formed. The unextractable sediment fraction (not extracted by acetonitrile/water) was a major sink for the pyrrole ring ^{14}C radiolabel, accounting for 36%–43% AR at 100 days. Mineralisation of this radiolabel accounted for only 6%–10% AR at 100 days. The necessary surface water and sediment exposure assessments (predicted environmental concentrations (PEC) calculations) were carried out for the metabolites CGA192155, CGA265378, CGA339833, SYN545245, unidentified MF2 and unidentified D9 using the FOCUS (FOCUS, 2001) step 1 and step 2 approach (version 3.2 of the Steps 1–2 in FOCUS calculator). For the active substance fludioxonil, appropriate step 3 (FOCUS, 2001) and step 4 calculations were available.[15] The step 4 calculations appropriately followed the FOCUS (FOCUS, 2007) guidance, with no-spray drift buffer zones of up to 15 m being implemented (representing a 62%–86% spray drift reduction) and also for just vines and the run-off scenarios combined no-spray drift buffer zones with vegetative buffer strips of up to 10 m combined with 50% spray drift reduction (representing a 68%–89% spray drift reduction plus reducing solute flux in run-off by 60% and erosion runoff of mass adsorbed to soil by 85%), being implemented. The SWAN tool (version 4.0.1) was appropriately used to implement these mitigation measures in the simulations.

For the representative protected use including permanent greenhouses and the active substance and CGA192155, the necessary surface water and sediment exposure assessments (PEC calculations) were carried out using the WATERSTREAMS/GEMS model (v. 3.3.2) for a scenario for spray application to strawberries in a permanent greenhouse for a soil-less growing system, in line with what is outlined in EFSA (2014a) guidance. Only results for the surface water were reported in the RAR.

The necessary groundwater exposure assessments were appropriately carried out using FOCUS (European Commission, 2014a) scenarios and the models PEARL 4.4.4, PELMO 5.5.3 and MACRO 5.5.4.[16] The potential for groundwater exposure from the representative uses by fludioxonil, CGA265378 and SYN545245 above the parametric drinking water limit of 0.1 µg/L was concluded to be low in geoclimatic situations that are represented by all 9 FOCUS groundwater scenarios. For the identified metabolite **CGA192155**, this groundwater modelling indicated that the drinking water limit was not exceeded for the seed treatment uses and the foliar spray use on strawberries. The modelling gave indications that annual average recharge concentrations moving below 1m would be above 0.1 µg/L at the Piacenza scenario for the use on pome fruit (0.106 µg/L) and the Hamburg, Piacenza and Porto scenarios for the use on vines (0.223–0.392 µg/L). For the identified metabolite **CGA339833** (for which a data gap for further adsorption data was identified), the drinking water limit was not exceeded for the seed treatment uses. There were indications that these concentrations would be above 0.1 µg/L for the Hamburg, Jokioinen and Kremsmuster scenarios for the use on strawberries (0.528–3.356 µg/L) and for all the scenarios for pome fruit (0.131–4.016 µg/L) and vines (0.555–3.213 µg/L). CGA192155 and CGA339833 were concluded as non-relevant groundwater metabolites, when considering the existing Annex VI entry of the CLP Regulation for fludioxonil, see Sections 2, 3 and 7. However EFSA agreed with the RMS that the criteria for classification according to Regulation (EC) No 1272/2008[17] may be met for **reproductive toxicity**, category 2, see Sections 2 and 7. Consequently, unless it is demonstrated that groundwater metabolites do not share the reproductive toxicity potential of fludioxonil, it may be that all groundwater metabolites need to be considered relevant. For the unidentified possible metabolite ascribed as MF2 these concentrations were indicated to be above 0.1 µg/L at all FOCUS scenarios for all the representative uses (0.303–28.8 µg/L). For the unidentified possible metabolite ascribed as D9 these concentrations were indicated to be above 0.1 µg/L at all FOCUS scenarios for the representative uses on strawberries, pome fruit and vines (2.27–23.6 µg/L). It should be noted that substance properties were not available for these two possible unidentified metabolites, so these concentration estimates are derived using conservative default assumptions. As the identity and exact number of these compounds is not known, it was not possible to conduct a groundwater relevance assessment (see Section 7). This leads to the identification of an **assessment not finalised** (see Section 9.1).

The applicant did not provide appropriate information to address the effect of water treatment processes on the nature of the residues that might be present in surface water and groundwater, when surface water or groundwater are 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 risk assessment was based on the following documents: European Commission (2002), SETAC (2001), EFSA (2009), EFSA PPR Panel (2013) and EFSA (2013).

Fludioxonil was discussed at the Pesticides Peer Review Experts' meeting PREV 03 (April 2019) and TC 123 (November 2023).

For the representative uses in strawberry, applications are foreseen in both field and protected structures. In the RAR it is clarified that protected structures are permanent structures but also plastic/net shelters, shade houses and walk-in tunnels.

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

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

[17]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.

Thus, the exposure assessment for the use in protected non-permanent structures (e.g. plastic/net shelters, etc) is considered similar to the outdoor uses. For the use in permanent structure, low risk to all non-target organisms, except aquatic organisms, is anticipated since exposure is considered to be minimal and low risk can be concluded for those groups.

The batches used in the ecotoxicological studies are not considered compliant with both the original and newly proposed reference **specifications** (**data gap**, see Section 10).

Acute and long-term studies were available with **birds and mammals** and the active substance. Acute data on mammals were also available with the two representative formulations.

Based on the available data, low acute and chronic risk to birds was concluded for the relevant routes of exposure, i.e. dietary, secondary poisoning and contaminated water.

Low acute risk to mammals was concluded for all the representative uses. The selection of the long-term endpoint was discussed at the Pesticides Peer Review TC 123 considering the new studies submitted in the context of the assessment for endocrine disruption.[18] Based on the agreed endpoint, low long-term risk to mammals was concluded for all the representative uses.

Acute and chronic toxicity data were available for all the **aquatic taxa** with the active substance. Acute and (semi) chronic data with sediment dwellers were available for fludioxonil. Toxicity data with the formulation 'A8207M' were only available with algae and aquatic invertebrates. The formulation 'A8240D' was only tested with algae. Considering that algae are not the most sensitive aquatic species, it was not possible to evaluate whether fludioxonil may be more toxic when formulated.

Acute toxicity data with fish were available for the pertinent surface water metabolites: CGA192155 and CGA339833. Acute toxicity data with aquatic invertebrates were available for CGA192155, CGA339833, SYN545245 and CGA265378. Toxicity data with algae were available for CGA192155, CGA339833, SYN545245. For the metabolite CGA192155 acute and chronic data were available with sediment dwellers.

Based on the available data and risk assessment, low risk to **aquatic organisms** was concluded for the **active substance** for the representative uses on wheat and oat. For the representative uses on grapes, low risk (acute and chronic) to fish and aquatic invertebrates was concluded by using FOCUS PECsw step 3&4 with the implementation of appropriate mitigation measures (see Section 8) for the majority of the FOCUS exposure scenarios. For the representative uses on pome fruit, low risk (acute and chronic) to fish and aquatic invertebrates was concluded by using FOCUS PECsw step 3&4 with the implementation of mitigation measures (see Section 8). Low risk to aquatic organisms was concluded for the representative outdoor and protected uses on strawberry excluding permanent greenhouses by using FOCUS step 3 PECsw. For the representative uses on strawberry in permanent greenhouses, low risk to aquatic organisms was concluded by using appropriate mitigation measures (see Section 8). Low risk to algae and sediment dwellers was concluded by using FOCUS PECsw step 1&2 for all the representative uses. Low risk to aquatic organisms was concluded for the all the pertinent **metabolites and representative uses**. For the possible metabolites (unidentified chromatographically resolved fractions ascribed as D9 and MF2), high risk could not be excluded based on a screening risk assessment for the representative uses on pome fruit, strawberry (except soil-less growing systems) and grapes (table and wine) (**data gap**, see Section 10).

A study on bioconcentration (BCF) in fish was available. Some deficiencies were noted (e.g. only one concentration tested, lack for lipid normalisation, BCF kinetic not calculated as recommended in the relevant OECD guideline).[19] However, the study was overall considered suitable for risk assessment.

Acute toxicity data on **honey bees** were available with the active substance and the formulations for representative uses. Chronic toxicity studies and toxicity studies with honeybee larvae were only available with the 2 formulations for representative uses. Based on the available data and risk assessment both according to European Commission (2002) and EFSA (2013), low risk was concluded to honey bees for all the representative uses and the relevant routes of exposure.

Data on potential sub-lethal effects and data on metabolites occurring in pollen and nectar were not available (**data gap**, see Section 10). Data on accumulative effects and toxicity data on wild bees were not available.

Extended laboratory studies were available for **non-target arthropods**. Based on those data, a low in-field and off-field risk was assessed for all the uses evaluated.

The risk to **earthworms** from exposure to fludioxonil and soil metabolites CGA192155, CGA339833, SYN545245, CGA265378, MF2 and D9 was assessed as low for all the uses evaluated.

Toxicity data with **soil macroorganisms other than earthworms**, i.e. collembola and soil mites, were only available with the formulated products and the pertinent metabolites. The reproduction study on *Folsomia candida* performed with the seed treatment formulation ('A8207M') was discussed by the experts. Overall, the experts agreed that the EC_{10}, extrapolated and below the lowest tested concentration, should be used in the risk assessment instead of the NOEC. Based on the available data, the risk to soil macroorganisms other than earthworms from exposure to both formulations and soil metabolites CGA192155, CGA339833, SYN545245, CGA265378, MF2 and D9 was assessed as low for all uses evaluated. It is noted that the active substance when formulated in the product 'A8207M' was indicated to be more toxic than in the formulation for representative uses 'A8240D'.

The risk to **soil microorganisms** (nitrogen transformation) was assessed as low for fludioxonil and metabolites CGA192155, CGA339833, SYN545245, CGA265378, MF2 and D9 for all uses evaluated.

The risk to **non-target terrestrial plants** and **biological methods of sewage treatment** were assessed as low for all uses evaluated.

[18]See experts' consultation point 5.10 in the Report of the Pesticides Peer Review Experts' TC 123 (November 2023) (EFSA, 2024).

[19]See experts' consultation point 5.5 in the Report of the Pesticide Peer Review Experts' Meeting 03 (April 2019) (EFSA, 2024).

6 | ENDOCRINE DISRUPTION PROPERTIES

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

With regard to the assessment of the endocrine disruption potential of fludioxonil **for humans** according to the ECHA/EFSA guidance (2018), in determining whether fludioxonil 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 fludioxonil with the EAS and T signalling pathways using the available evidence in the data set.

The **T-modality** has been considered sufficiently investigated and a pattern of T-mediated adversity was not identified. Therefore, based on the available and sufficient data set, it was concluded that the ED criteria are not met for the T-modality (Scenario 1a of the ECHA/EFSA ED Guidance, 2018).

A pattern of **EAS-mediated** adversities i.e. delayed sexual maturation (increased age at balanopreputial separation) in F1 generation, decreased anogenital distance index (AGDI) in F1a and F2a males, increased mean length of the oestrus cycle in F1 females, was observed for fludioxonil in a sufficiently investigated data set. Effects on 'sensitive to, but not diagnostic of EAS' parameters[20] i.e. increased number of ovarian small follicles, decreased number of implantation scars, decreased percentage of post-implantation loss and decreased mean number of pups born, also contributed to the assessment. Evidence of endocrine activity was observed in the OECD TG 458 Androgen Receptor Trans Activation (ARTA) assay (i.e. AR antagonism), OECD TG 456 steroidogenesis assay (i.e. decrease in testosterone synthesis and increase in estradiol synthesis) and in the OECD TG 441 Hershberger assay (i.e. weak anti-androgenic effect could occur based on the data pattern). The observed pattern of EAS-mediated adversities suggests an anti-androgenic mode of action (MoA). However, other MoAs, affecting steroidogenesis and/or oestrogenic pathways, are also plausible based on the available evidence. In addition, literature studies are also supporting the evidence of a weak antagonism of the androgen receptor (e.g. Yeast androgen screen (YAS) Assay, MDA-kb2 Assay and AR-EcoScreen Assay) and of a weak oestrogen receptor agonism (e.g. yeast oestrogen screen (YES) assay, ERalpha and ERbeta CALUX assay).

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 fludioxonil (Scenario 1b of the ECHA/EFSA ED Guidance, 2018).

In the studies conducted with fludioxonil, the lowest adverse effect level (LOAEL), where EAS-mediated adversity (i.e. delayed sexual maturation) was observed in F1a males, is 175 mg/kg bw per day from a two-generation reproductive toxicity study in the rats. A no observed adverse effect level (NOAEL) of 58 mg/kg bw per day is derived based on this effect. In the same study, a statistically significant and treatment-related decrease in ano-genital distance index (AGDI) is recorded in F1 male animals starting from the low dose of 58 mg/kg bw per day; however, due to the uncertainty in the interpretation of the dose–response relationships, this effect has not been taken into account for setting the NOAEL for EAS-mediated adversities.[21]

The outcome of the assessment reported above for humans also applies to **wild mammals as non-target organisms for the EATS-modalities**, i.e. fludioxonil is not considered an endocrine disruptor through the T-modality, while it showed interference with the (hypothalamus-pituitary-gonad (HPG)) axis (endocrine disruptor through the EAS-modalities). The EAS-adversity identified was considered relevant at the level of population,[22] 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**, the following studies were available:

Study	Guideline	Relevant for investigation of ED properties through
Amphibian Metamorphosis Assay (AMA)	OECD TG 231	T-modality

[20]Refer to ECHA/EFSA (2018) ED guidance, chapter 3.1.1: Sensitive to, but not diagnostic of, EATS – parameters measured in vivo that may contribute to the evaluation of adversity, however, due to the nature of the effect and the existing knowledge as described in OECD GD 150, these effects cannot be considered diagnostic on their own of any of the EATS modalities. Nevertheless, in the absence of more diagnostic parameters, these effects might provide indications of an endocrine MoA that might warrant further investigation. This includes parameters from OECD CF level 3, 4 and 5 in vivo assays and labelled in OECD GD 150 as endpoints potentially 'sensitive to, but not diagnostic of, EATS modalities'.

[21]See experts' consultation point 2.16 in the Report of the Pesticides Peer Review Experts' TC 118 (November 2023) (EFSA, 2024).

[22]See experts' consultation point 5.9 in the Report of the Pesticides Peer Review Experts' TC 118 (November 2023) (EFSA, 2024).

Study	Guideline	Relevant for investigation of ED properties through
Fish Short-Term Reproduction Assay (FSTRA)	OECD TG 229	EAS-modalities
Fish Sexual Development Test according	OECD TG 234	
Fish Full life cycle toxicity test[23] (FFLCT)	USEPA 850.1500	

Overall, the effects observed in the AMA are more likely attributable to systemic toxicity and therefore concluded that the study did not show a pattern of interference with the hypothalamus-pituitary-thyroid (HPT) axis.[24]

The available fish studies, as reported above, showed all a consistent pattern of effects i.e. change in female gonad histopathology, reduced secondary sex characteristics in males, reduced fecundity.

When considering all the mammalian and non-mammalian data together, a clear pattern of adversity and endocrine activity across species and taxa suggesting an anti-androgenic MoA[25] could be identified.

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, it can be concluded that fludioxonil meets the ED criteria and therefore it is an endocrine disruptor, leading to a critical area of concern (see Section 9.2).

The applicant provided information aimed at demonstrating that the exposure of humans and the environment to fludioxonil was negligible under realistic conditions of use, for uses as a fungicide in ornamentals in permanent (high technology) greenhouses, i.e. a non-representative use which was not part of the dossier for renewal of approval. Since the legislation does not provide for changes to the representative uses during the renewal process which were not part of the supplementary dossier submitted for the renewal, the RMS summarised the information provided by the applicant in the final RAR (France, 2024), but did not assess it in detail, due to its incompatibility with the regulatory framework. An assessment of the potential for negligible exposure for any of the representative uses is not available.

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
Fludioxonil (all uses)	The risk to earthworms, other soil macroorganisms and soil microorganisms was assessed as low
Unidentified MF2 (all uses except soil-less growing systems)	The risk to earthworms, other soil macroorganisms and soil microorganisms was assessed as low
CGA192155 (all non seed treatment uses)	The risk to earthworms, other soil macroorganisms and soil microorganisms was assessed as low
CGA265378 (all non seed treatment uses)	The risk to earthworms, other soil macroorganisms and soil microorganisms was assessed as low
CGA339833 (all non seed treatment uses)	The risk to earthworms, other soil macroorganisms and soil microorganisms was assessed as low
SYN545245 (all non seed treatment uses)	The risk to earthworms, other soil macroorganisms and soil microorganisms was assessed as low
Unidentified D9 (all non seed treatment uses except soil-less growing systems)	The risk to earthworms, other soil macroorganisms and soil microorganisms was assessed as low

Note: The 'all non seed treatment uses' indication is given because these are soil photolysis metabolites that will not be formed when seed is drilled and there is limited active substance exposure to light.

[23] The FFLCTT was not including all the parameters foreseen to be included in a Medaka Extended One Generation Test. Nevertheless, it was included in the weight of evidence.

[24] See experts' consultation point 5.8 in the Report of the Pesticide Peer Review Experts' TC 118 (November 2023) (EFSA, 2024).

[25] See experts' consultation point 5.9 in the Report of the Pesticide Peer Review Experts' TC 118 (November 2023) (EFSA, 2024).

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[c] Steps 3b and 3c	Consumer RA triggered Steps 4 and 5	Human health relevance
Fludioxonil (all uses)	No	Yes	–	–	Yes
Unidentified MF2 (all uses except soil-less growing systems)	Worst case default values (soil DT50 and Koc) assessment Cereal seed treatment Yes 0.303–1.8 µg/L Foliar spray applications Yes 2.76–28.8 µg/L	Open	Not assessed (open) Proposed classification of the active substance as reprotoxic would indicate the metabolite would be considered relevant unless it is demonstrated that it does not share the reproductive toxicity potential of fludioxonil	Open	Open[c]
CGA192155 (all non seed treatment uses)	No strawberries Yes pome fruit 1/9 FOCUS scenarios 0.106 µg/L Yes vines 3/7 FOCUS scenarios 0.223–0.392 µg/L	No	No, when considering the existing Annex VI entry of the CLP Regulation for fludioxonil Unlikely to be genotoxic Proposed classification of the active substance as reprotoxic would indicate the metabolite would be considered relevant unless it is demonstrated that it does not share the reproductive toxicity potential of fludioxonil	Low consumer risk from representative uses (step 5) ADI of fludioxonil can apply[c]	No, when considering the existing Annex VI entry of the CLP Regulation for fludioxonil[c]
CGA265378 (all non seed treatment uses)	No	Assessment not triggered	Assessment not triggered Unlikely to be genotoxic Proposed classification of the active substance as reprotoxic would indicate the metabolite would be considered relevant unless it is demonstrated that it does not share the reproductive toxicity potential of fludioxonil	Assessment not triggered	Assessment not triggered
CGA339833 (all non seed treatment uses except soil-less growing systems)	Yes strawberries 3/4 FOCUS scenarios 0.528–3.356 µg/L Yes pome fruit 0.131–4.016 µg/L Yes vines 0.555–3.213 µg/L	No	No, when considering the existing Annex VI entry of the CLP Regulation for fludioxonil Unlikely to be genotoxic. Proposed classification of the active substance as reprotoxic would indicate the metabolite would be considered relevant unless it is demonstrated that it does not share the reproductive toxicity potential of fludioxonil	Low consumer risk from representative uses (step 5). ADI of 0.29 mg/kg bw per day[c]	No, when considering the existing Annex VI entry of the CLP Regulation for fludioxonil[c]
SYN545245 (all non seed treatment uses)	No	Assessment not triggered	Assessment not triggered	Assessment not triggered	Assessment not triggered
Unidentified D9 (all non seed treatment uses except soil-less growing systems)	Worst case default values (soil DT50 and Koc) assessment Yes 2.27–23.6 µg/L	Open	Not assessed (open) Proposed classification of the active substance as reprotoxic would indicate the metabolite would be considered relevant unless it is demonstrated that it does not share the reproductive toxicity potential of fludioxonil	Open[c]	Open[c]

Note: The 'all non seed treatment uses' indication is given because these are soil photolysis metabolites that will not be formed when seed is drilled and there is limited active substance exposure to light.

[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.

[c]Based on the newly submitted two-generation toxicity study after the stop the clock to address endocrine disruption, EFSA agreed with the RMS that the criteria for classification according to Regulation (EC) No 1272/2008 may be met for reproductive toxicity, category 2, having an impact on the relevance assessment of groundwater metabolites. RMS is invited to submit a CLH proposal to ECHA for potential revision of the current harmonised classification accordingly.

TABLE 3 Surface water and sediment.

Compound (name and/or code)	Ecotoxicology
Fludioxonil (all uses)	Low risk to aquatic organisms for all uses and the majority of FOCUS scenarios with the implementation of mitigation measures
CGA192155 (all uses)	Low risk to aquatic organisms
Unidentified MF2 (all uses except soil-less growing systems)	High risk could not be excluded for the representative uses pome fruit, strawberry (except soil-less growing systems) and grapes (table and wine) (data gap). Low risk for uses as seed treatments
CGA265378 (all non seed treatment uses)	Low risk to aquatic organisms
CGA339833 (all non seed treatment uses)	Low risk to aquatic organisms
SYN545245 (all non seed treatment uses)	Low risk to aquatic organisms
Unidentified D9 (all non seed treatment uses except soil-less growing systems)	High risk could not be excluded for the representative uses pome fruit, strawberry (except soil-less growing systems) and grapes (table and wine) (data gap). Low risk for uses as seed treatments

Note: The 'all non seed treatment uses' indication is given because these are soil photolysis metabolites that will not be formed when seed is drilled and there is limited active substance exposure to light.

TABLE 4 Air.

Compound (name and/or code)	Toxicology
Fludioxonil	Low acute inhalation toxicity to rats

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.

Representative use	Grapes, wine (F) Foliar	Grapes, table (F) Foliar	Pome fruit (apple and pear) (F) Foliar	Strawberry (F) Foliar	Strawberry (G) Foliar	Wheat (F) Seed treatment	Oat (F) Seed treatment
Operator exposure						Use of gloves is required	Use of gloves is required
Worker exposure							
Resident/ bystander exposure							
Risk to aquatic organisms	RMM equivalent to 15 m no-spray buffer zone or 10 m no-spray buffer zone +50% drift reduction using reducing nozzles[a]; RMM equivalent to 10 m no-spray buffer +10 m vegetative filter strip for the R4 scenario b; for the other scenarios the worst case is 10 m		RMM equivalent to 15 m no-spray buffer zone or 10 m no-spray buffer zone +50% drift reduction using reducing nozzles or 5 m no-spray buffer zone +75% drift reduction using		Soil-less system with filter rinsing water and 90% end of pipe mitigation or soil-less system without filter rinsing water and 70% end of pipe mitigation[c]		

TABLE 5 (Continued)

Representative use	Grapes, wine (F) Foliar	Grapes, table (F) Foliar	Pome fruit (apple and pear) (F) Foliar	Strawberry (F) Foliar	Strawberry (G) Foliar	Wheat (F) Seed treatment	Oat (F) Seed treatment
	no-spray buffer zone +50% drift reduction using reducing nozzles or 5 m no-spray buffer zone +75% drift reduction using reducing nozzles or 90% drift reduction using reducing nozzles[b]		reducing nozzles or 90% drift reduction using reducing nozzles				

[a]1 application at 500 g a.s./ha.

[b]2 applications at 500 g a.s./ha.

[c]These conclusions apply to greenhouses (permanent). The use in non-permanent protected structures is considered similar to outdoor uses.

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 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.

1. The batches used in toxicity studies could not be concluded to be representative of the originally and newly proposed reference specification for the active substance fludioxonil and associated impurities, since for some impurities, the applicant did not provide enough information to exclude their relevance from the toxicological point of view (see Section 2).

   a. Ames test for an impurity is required (relevant for all representative uses evaluated; see Section 2 and Evaluation Table, expert consultation point 2.15 in EFSA, 2024)
   b. Scientific justification on the use of the acid form of an impurity in the toxicokinetic study (e.g. whether different absorption and/or distribution might be expected) should be provided (relevant for all representative uses evaluated; see Section 2 and Evaluation Table, expert consultation point 2.15 in EFSA, 2024).

2. The consumer dietary risk assessment could not be finalised in view of the identified data gaps to finalise the residue definition for risk assessment for primary and rotational crops and to address the magnitude of residues of metabolite CGA227731, considered genotoxic in vitro and in vivo, in cereal forage, grain and straw grown in rotation (see Section 3).

   a. Complete datasets of residue trials compliant with the representative uses and analysing respectively fludioxonil alone, and fludioxonil and all its metabolites that can be oxidised to metabolite 2,2-difluoro-*2H*-1,3-benzodioxole-4-carboxylic acid (CGA192155), expressed as fludioxonil, and supported by acceptable storage stability data and validated analytical methods are required (relevant for all representative uses evaluated; see Section 3).
   b. Toxicological information to address the toxicological profile of metabolite CGA265378 and to further address the genotoxicity potential of metabolite SYN518580 (relevant for the representative uses on strawberries, wheat and oats evaluated; see Sections 2 and 3).
   c. Sufficient rotational crops field trials covering the Northern and Southern zones of Europe to determine the magnitude of CGA227731 residues in cereal forage, grain and straw at the different standard PBIs, covering the maximum PECsoil for fludioxonil and supported by validated methods and acceptable storage stability data are required (relevant for the representative uses on strawberries, wheat and oats evaluated; see Section 3).

3. The consumer risk assessment from the consumption of drinking water was not finalised, whilst the nature of residues in drinking water is unknown, due to missing information to address the effect of water treatment processes on the nature

of residues present in surface water and groundwater, when surface water or groundwater are abstracted for use as drinking water (see Sections 3 and 4).

a. Information to address the effect of water treatment processes on the nature of residues present in surface water and groundwater, when surface water or groundwater are abstracted for drinking water was not available. Probably in the first instance, a 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 in groundwater and 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).

4. The groundwater exposure assessment was not finalised for the possible metabolites unidentified MF2 (all representative uses) and unidentified D9 (representative uses on strawberries, pome fruit and vines), consequently their groundwater relevance assessment is open (see Sections 4 and 7).

a. Information to demonstrate that unidentified metabolite fraction MF2 from aerobic laboratory soil incubations in Les Evouettes soil did not reach levels triggering identification and assessment was not available. If confirmed individual components exceed 5% AR, then the metabolite(s) would need identification and soil transformation rates, soil adsorption values and updated groundwater exposure assessments would need to be made available (relevant for all representative uses evaluated; see Section 4).
b. Satisfactory information to characterise the metabolite D9 from the pyrrole radiolabelled fludioxonil dosed soil photolysis study with air dried Somersham soil and definitely confirm the formation amounts of the region of interest (ROI) ascribed as D9 and clarify if this ROI was made up of a single or multiple components, was not available. If confirmed individual components exceed 5% AR, then the metabolite(s) would need identification and soil transformation rates, soil adsorption values and updated groundwater exposure assessments would need to be made available (relevant for the non seed treatment representative uses evaluated; see Section 4).

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:

5. Fludioxonil meets the ED criteria for the EAS-modalities 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 (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).

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.

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.

Representative use		Grapes, wine (F) Foliar	Grapes, table (F) Foliar	Pome fruit (apple and pear) (F) Foliar	Strawberry (F) Foliar	Strawberry (G)[e] Foliar	Wheat (F) Seed treatment	Oat (F) Seed treatment
Operator risk	Risk identified							
	Assessment not finalised							
Worker risk	Risk identified							
	Assessment not finalised							
Resident/ bystander risk	Risk identified							
	Assessment not finalised							
Consumer risk	Risk identified							
	Assessment not finalised	X[2,3]	X[2,3]	X[2,3]	X[2,3]	X[2,3]	X[2,3]	X[2,3]
Risk to wild non-target terrestrial vertebrates	Risk identified							
	Assessment not finalised							
Risk to wild non-target terrestrial organisms other than vertebrates	Risk identified							
	Assessment not finalised							
Risk to aquatic organisms	Risk identified	One out of five[c] FOCUS scenarios	One out of five[c] FOCUS scenarios					
	Assessment not finalised							
Groundwater exposure to active substance	Legal parametric value breached							
	Assessment not finalised							
Groundwater exposure to metabolites	Legal parametric value breached[a]	X	X	X	3/4 FOCUS scenarios	3/4 FOCUS scenarios[d]		
	Parametric value of 10 µg/L[b] breached							
	Assessment not finalised	X[4]	X[4]	X[4]	X[4]	X[4,d]	X[4]	X[4]

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 4 and 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]High risk identified only in case of two applications.

[d]Except for soil-less growing systems where groundwater exposure can be concluded as negligible.

[e]It was clarified in the RAR that the use was for all strawberry protected production systems i.e. greenhouses (permanent structures), walk-in tunnels and other protected structures.

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 three components, information on genotoxicity and repeated dose toxicity over the short- and long-term was not available for the components of the formulations for representative uses 'A8240D' and 'A8207M'. Therefore, in order to allow a final conclusion on the safety assessment of 'A8240D' and 'A8207M', genotoxicity and repeated dose toxicity data for these components (short- and long-term) 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 (relevant for all representative uses evaluated; see Section 'General aspects').
- Spectral data of the relevant impurity SYN549129 (relevant for all representative uses, see Section 1).
- Determination of the content of the relevant impurity SYN549129 in the formulations for representative uses before and after storage (relevant for all representative uses, see Section 1).
- Analytical method for the determination of the relevant impurity SYN549129 in the formulations for representative uses (relevant for all representative uses, see Section 1).
- Extraction efficiency of the QuEChERS multi-residue method for the determination of fludioxonil residues in plant commodities (relevant for all representative uses, see Section 1).
- An additional storage stability study on a crop representative of the high-acid content commodities to comply with the current OECD test guidelines (relevant for the representative uses on table and wine grapes and strawberries evaluated; see Section 3).
- Residue trials on a crop representative of a worst-case scenario with respect to potential residues in honey and conducted at an appropriate dose rate of application. The residue situation in the rotational crops should also be considered in the overall assessment to determine the residues of fludioxonil in pollen and bee products (relevant for the representative uses on table and wine grapes and strawberries evaluated; see Section 3).
- An OECD 106 guideline batch adsorption value for metabolite CGA339833 was only available for one soil. Information on two more soils would be needed to satisfy the regulatory requirement (relevant for non seed treatment representative uses; see Section 4).
- OECD 106 guideline batch adsorption studies for metabolites CGA265378 and SYN545245 were not available (relevant for non seed treatment representative uses but unnecessary for the representative uses evaluated where use of a default value (0 mL/g) was sufficient to finalise the assessments; see Section 4).
- The unknown metabolites (chromatographic peaks ascribed as #2 and #1) observed in the aerobic aquatic mineralisation study have not been characterised (information not needed to finalise the EU level, edge of field surface water exposure assessment for the representative uses being assessed; see evaluation table Section 4, data requirement 4.13 in the Peer Review Report; EFSA, 2024).
- If confirmed as being present in soil at levels triggering assessment (data gaps a. and b. in Section 9.1 point 4), additional information to address the exposure and risk to aquatic organisms for the metabolites making up MF2 and D9 (relevant for the representative uses in pome fruit, strawberry (except soil-less growing systems) and grapes (table and wine); see Sections 4 and 5).
- Additional information to address the sub-lethal effects of fludioxonil on bees (relevant for all representative uses evaluated; see Section 5).
- Additional information to address risk to bees when exposed to metabolites in pollen and nectar (relevant for all representative uses evaluated; see Section 5).
- Additional information to address the compliance of the batch used in some ecotoxicological studies with the original and newly proposed reference specifications (see Section 5).

ABBREVIATIONS

a.s.	active substance
AAOEL	acute acceptable operator exposure level
AChE	acetylcholinesterase
ADE	actual dermal exposure
ADI	acceptable daily intake
AF	assessment factor
AMA	amphibian metamorphosis assay
AOEL	acceptable operator exposure level
AR	androgen receptor
AR	applied radioactivity
ARfD	acute reference dose
AST	aspartate aminotransferase (SGOT)
AUC	area under the blood concentration/time curve
bw	body weight
CI	confidence interval
CL	confidence limits
DAR	draft assessment report
DAT	days after treatment

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)
dw	dry weight
EAS	oestrogen, androgen and steroidogenesis modalities
EbC_{50}	effective concentration (biomass)
EC_{50}	effective concentration
ECHA	European Chemicals Agency
EEC	European Economic Community
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EMDI	estimated maximum daily intake
ER	oestrogen receptor
ER_{50}	emergence rate/effective rate, median
ETO	ecological threshold option
FAO	Food and Agriculture Organization of the United Nations
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
GAP	Good Agricultural Practice
GS	growth stage
HPLC–MS/MS	high-pressure liquid chromatography–tandem mass spectrometry
HR	hazard rate
IEDI	international estimated daily intake
IESTI	international estimated short-term intake
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
K_{doc}	organic carbon linear adsorption coefficient
K_{Foc}	Freundlich organic carbon adsorption coefficient
LD_{50}	lethal dose, median; dosis letalis media
LDD_{50}	lethal dietary dose; median
LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOQ	limit of quantification
MOA	mode of action
MRL	maximum residue level
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
OECD	Organisation for Economic Co-operation and Development
PEC	predicted environmental concentration
PEC_{air}	predicted environmental concentration in air
PEC_{soil}	predicted environmental concentration in soil
PHI	pre-harvest interval
PPE	personal protective equipment
QSAR	quantitative structure–activity relationship
RAC	regulatory acceptable concentration
RAR	renewal assessment report
REACH	Registration, Evaluation, Authorisation of Chemicals Regulation
SMILES	simplified molecular-input line-entry system
STMR	supervised trials median residue
TMDI	theoretical maximum daily intake
TRR	total radioactive residue
WHO	World Health Organization

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European Commission

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NOTE/UPDATE

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APPENDIX A

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

Properties		Conclusion[a]
CMR	Carcinogenicity (C)	Classification for carcinogenicity is not warranted (ECHA, 2017b)
	Mutagenicity (M)	Classification for germ cell mutagenicity is not warranted (ECHA, 2017b)
	Toxic for Reproduction (R)	No classification for reproductive toxicity is warranted (ECHA, 2017b). However, based on the newly submitted two-generation toxicity study after the stop the clock to address endocrine disruption, EFSA agreed with the RMS that the criteria for classification according to Regulation (EC) No 1272/2008 may be met for reproductive toxicity, category 2. EFSA noted that the ECHA RAC Opinion, 2017 could not have considered the newly submitted 2-generation toxicity study
Endocrine disrupting properties		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, it can be concluded that fludioxonil meets the ED criteria for humans and non-target organisms for the EAS-modalities. Fludioxonil was considered not to meet the ED criteria for the T-modality
POP	**Persistence** **Bioaccumulation** **Long-range transport**	Fludioxonil 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**	Fludioxonil is 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**	Fludioxonil is 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.2024.9047.

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[26] 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.

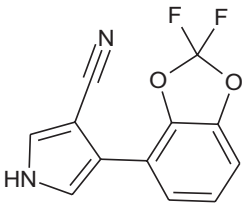
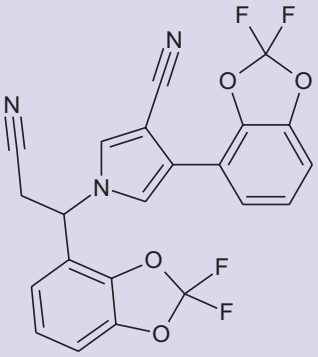
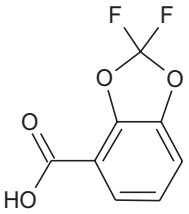
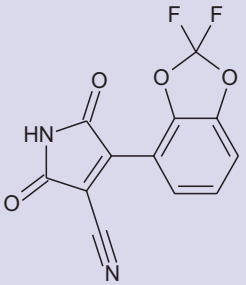
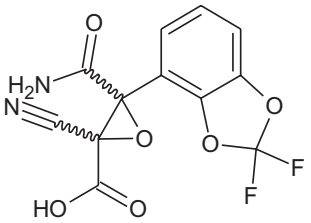
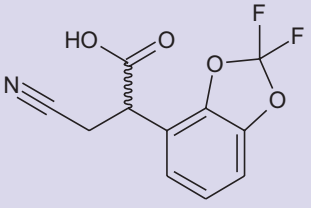
Wording	K_{oc} (either K_{Foc} or K_{doc}) mL/g
Very high mobility	0 to 50
High mobility	51 to 150
Medium mobility	151 to 500
Low mobility	501 to 2000
Slight mobility	2001 to 5000
Immobile	> 5000

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

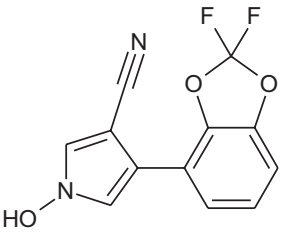
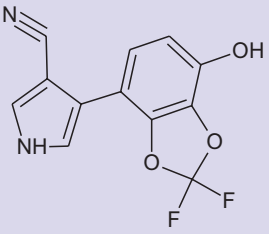
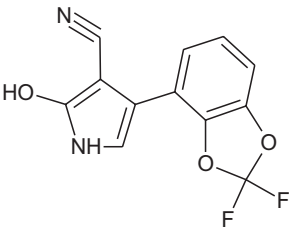
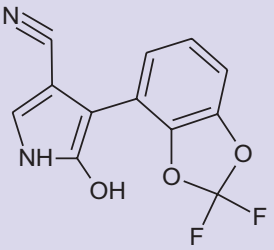
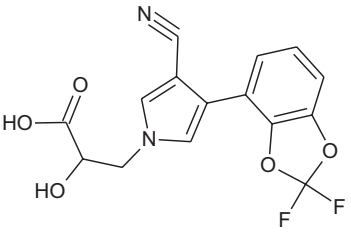
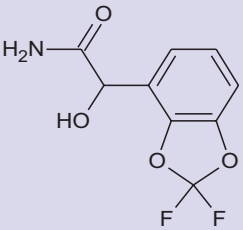
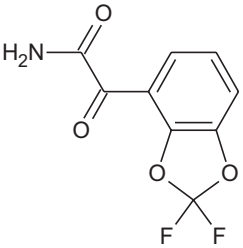
[26] For laboratory soil incubations normalisation was also to field capacity soil moisture (pF2/10kPa). For laboratory sediment water system incubations, the whole system DT values were used.

APPENDIX D

Used compound codes

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
Fludioxonil	4-(2,2-difluoro-1,3-benzodioxol-4-yl)-1*H*-pyrrole-3-carbonitrile N#Cc1c[NH]cc1c1cccc2OC(F)(F)Oc12 MUJOIMFVNIBMKC-UHFFFAOYSA-N	
SYN549129	1-[2-cyano-1-(2,2-difluoro-2*H*-1,3-benzodioxol-4-yl) ethyl]-4-(2,2-difluoro-2*H*-1,3-benzodioxol-4-yl)-1*H*-pyrrole-3-carbonitrile FC1(F)Oc2cccc(c2O1)c1cn(cc1C#N)C(CC#N)c1cccc2OC(F)(F)Oc12 LBMOUDBPLOAUCA-UHFFFAOYSA-N	
CGA192155*	2,2-difluoro-2*H*-1,3-benzodioxole-4-carboxylic acid O=C(O)c1cccc2OC(F)(F)Oc12 ZGAQVJDFFVTWJK-UHFFFAOYSA-N	
CGA265378*	4-(2,2-difluoro-2*H*-1,3-benzodioxol-4-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrole-3-carbonitrile N#CC=1C(=O)NC(=O)C=1c1cccc2OC(F)(F)Oc12 HWAHFPOFQKRSCB-UHFFFAOYSA-N	
CGA339833*	3-carbamoyl-2-cyano-3-(2,2-difluoro-2*H*-1,3-benzodioxol-4-yl)oxirane-2-carboxylic acid O=C(O)C1(C#N)OC1(c1cccc2OC(F)(F)Oc12)C(N)=O CIDOWFUMBJPVMD-UHFFFAOYSA-N	
SYN545245*	3-cyano-2-(2,2-difluoro-2*H*-1,3-benzodioxol-4-yl)propanoic acid O=C(O)C(CC#N)c1cccc2OC(F)(F)Oc12 KTKXZWYHYALRGX-UHFFFAOYSA-N	

(Continued)

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
CGA335892*	4-(2,2-difluoro-2*H*-1,3-benzodioxol-4-yl)-1-hydroxy-1*H*-pyrrole-3-carbonitrile N#Cc1cn(O)cc1c1cccc2OC(F)(F)Oc12 OTVSARSJPXPKIO-UHFFFAOYSA-N	
SYN518576*	4-(2,2-difluoro-7-hydroxy-2*H*-1,3-benzodioxol-4-yl)-1*H*-pyrrole-3-carbonitrile N#Cc1c[NH]cc1c1ccc(O)c2OC(F)(F)Oc12 MEGTXAJTJZODPX-UHFFFAOYSA-N	
SYN518577*	4-(2,2-difluoro-2*H*-1,3-benzodioxol-4-yl)-2-hydroxy-1*H*-pyrrole-3-carbonitrile N#Cc1c(O)[NH]cc1c1cccc2OC(F)(F)Oc12 BVCXNOCVYHENJL-UHFFFAOYSA-N	
SYN518578*	4-(2,2-difluoro-2*H*-1,3-benzodioxol-4-yl)-5-hydroxy-1*H*-pyrrole-3-carbonitrile N#Cc1c[NH]c(O)c1c1cccc2OC(F)(F)Oc12 HUSIGEYGZGWULP-UHFFFAOYSA-N	
CGA173506 lactic acid* (SYN551031)	3-[3-cyano-4-(2,2-difluoro-2*H*-1,3-benzodioxol-4-yl)-1*H*-pyrrol-1-yl]-2-hydroxypropanoic acid O=C(O)C(O)Cn1cc(C#N)c(c1)c1cccc2OC(F)(F)Oc12 JXJHRNRACRJPTN-UHFFFAOYSA-N	
CGA308103*	2-(2,2-difluoro-2*H*-1,3-benzodioxol-4-yl)-2-hydroxyacetamide NC(=O)C(O)c1cccc2OC(F)(F)Oc12 LOURJZKOYFFLRL-UHFFFAOYSA-N	
CGA344624*	2-(2,2-difluoro-2*H*-1,3-benzodioxol-4-yl)-2-oxoacetamide NC(=O)C(=O)c1cccc2OC(F)(F)Oc12 IKSJIDNOVDAETJ-UHFFFAOYSA-N	

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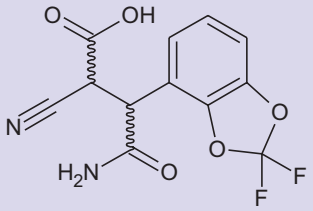
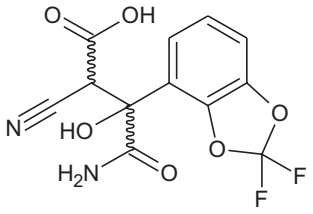
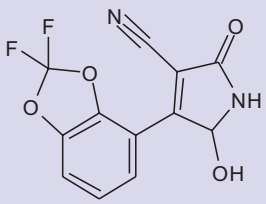
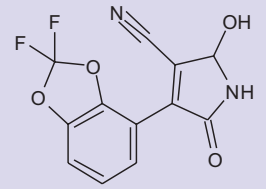
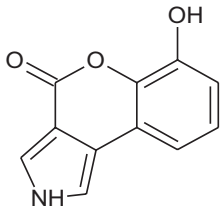
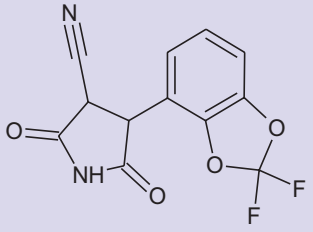
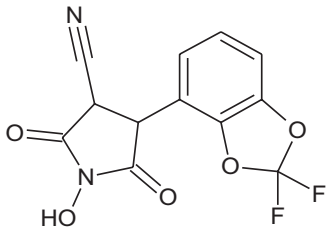
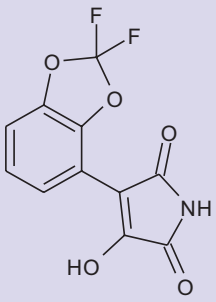
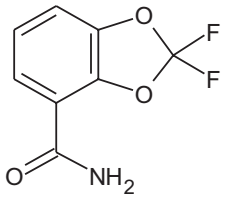
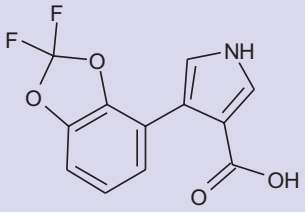
Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
CGA344623*	4-amino-2-cyano-3-(2,2-difluoro-2*H*-1,3-benzodioxol-4-yl)-4-oxobutanoic acid NC(=O)C(c1cccc2OC(F)(F)Oc12)C(C#N)C(=O)O QAYPGUMLQXOGDR-UHFFFAOYSA-N	
SYN518581*	4-amino-2-cyano-3-(2,2-difluoro-2*H*-1,3-benzodioxol-4-yl)-3-hydroxy-4-oxobutanoic acid NC(=O)C(O)(c1cccc2OC(F)(F)Oc12)C(C#N)C(=O)O NHBRJRFIPIPOGO-UHFFFAOYSA-N	
SYN518579* and **SYN518579 tautomer***	4-(2,2-difluoro-2*H*-1,3-benzodioxol-4-yl)-5-hydroxy-2-oxo-2,5-dihydro-1*H*-pyrrole-3-carbonitrile N#CC=1C(=O)NC(O)C=1c1cccc2OC(F)(F)Oc12 FGODVDFOKONXRQ-UHFFFAOYSA-N 4-(2,2-difluoro-2H-1,3-benzodioxol-4-yl)-2-hydroxy-5-oxo-2,5-dihydro-1H-pyrrole-3-carbonitrile N#CC=1C(O)NC(=O)C=1c1cccc2OC(F)(F)Oc12 VZIUETRWCWAMMM-UHFFFAOYSA-N	 
CGA227731	6-hydroxy[1]benzopyrano[3,4-*c*]pyrrol-4(2*H*)-one Oc1cccc2c1OC(=O)c1c[NH]cc21 VAMZFESDMDXBCB-UHFFFAOYSA-N	
CGA308565*	4-(2,2-difluoro-2*H*-1,3-benzodioxol-4-yl)-2,5-dioxopyrrolidine-3-carbonitrile O=C1NC(=O)C(C#N)C1c1cccc2OC(F)(F)Oc12 FSDHMXFTGSHLPL-UHFFFAOYSA-N	
SYN518580*	4-(2,2-difluoro-2*H*-1,3-benzodioxol-4-yl)-1-hydroxy-2,5-dioxopyrrolidine-3-carbonitrile O=C1N(O)C(=O)C(C#N)C1c1cccc2OC(F)(F)Oc12 MQRUOFNUHOGJJL-UHFFFAOYSA-N	

(Continued)

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
CGA260766*	3-(2,2-difluoro-2*H*-1,3-benzodioxol-4-yl)-4-hydroxy-1*H*-pyrrole-2,5-dione OC=1C(=O)NC(=O)C=1c1cccc2OC(F)(F)Oc12 OJBDAZBYGFTDSI-UHFFFAOYSA-N	
CGA340351*	2,2-difluoro-2*H*-1,3-benzodioxole-4-carboxamide NC(=O)c1cccc2OC(F)(F)Oc12 LJGCAWPZURVJEZ-UHFFFAOYSA-N	
CGA257777*	4-(2,2-difluoro-2*H*-1,3-benzodioxol-4-yl)-1*H*-pyrrole-3-carboxylic acid O=C(O)c1c[NH]cc1c1cccc2OC(F)(F)Oc12 WPLYHFDANIMBSH-UHFFFAOYSA-N	

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

[b]ACD/Name 2021.1.3 ACD/Labs 2021.1.3 (File Version N15E41, Build 123232, 07 July 2021).

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

*Metabolite meets the definition of per- and polyfluoroalkyl substances (PFAS) based on its chemical structure, however belongs to a PFAS subgroup excluded from the ECHA PFAS restriction proposal (https://echa.europa.eu/restrictions-under-consideration/-/substance-rev/72301/term).