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CONCLUSION ON PESTICIDES PEER REVIEW

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Updated peer review of the pesticide risk assessment of the active substance pydiflumetofen

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Abstract

The conclusions of the EFSA following the peer review of the initial risk assessments carried out by the competent authority of the rapporteur Member State, France, and co-rapporteur Member State, Austria, for the pesticide active substance pydiflumetofen and the assessment of applications for maximum residue levels (MRLs) are reported. The context of the peer review was that required by Regulation (EC) No 1107/2009 of the European Parliament and of the Council. The conclusions were reached on the basis of the evaluation of the representative uses of pydiflumetofen as a fungicide field application on pome fruits, grapes, potato, fruiting vegetables, cucurbits and *Brassica* vegetables and updated following the request from Commission to consider additional information submitted and review the risk assessment. The reliable endpoints, appropriate for use in regulatory risk assessment and the proposed MRLs, are presented. Missing information identified as being required by the regulatory framework is listed. Concerns are reported where identified.

KEYWORDS

fungicide, maximum residue level, peer review, pesticide, pydiflumetofen, risk assessment

CONTENTS

SUMMARY

Pydiflumetofen is a new active substance for which, in accordance with Article 7 of Regulation (EC) No 1107/2009 of the European Parliament and of the Council, the rapporteur Member State (RMS), France, received an application from Syngenta Crop Protection AG on 25 March 2016 for approval. In addition, in accordance with Article 8(1)(g) of the Regulation, Syngenta Crop Protection AG submitted applications for maximum residue levels (MRLs) as referred to in Article 7 of Regulation (EC) No 396/2005. Complying with Article 9 of the Regulation, the completeness of the dossier was checked by the RMS and the date of admissibility of the application was recognised as being 30 May 2016.

An initial evaluation of the dossier on pydiflumetofen was provided by the RMS in the draft assessment report (DAR) and subsequently, a peer review of the pesticide risk assessment on the RMS evaluation was conducted by EFSA in accordance with Article 12 of Regulation (EC) No 1107/2009. EFSA published its conclusion on the peer review of the pesticide risk assessment of pydiflumetofen on 11 October 2019. The European Commission sent a mandate to EFSA, dated 30 August 2022, with a request to review the risk assessment as regards the persistence, the ED properties for non-target organisms, the genotoxicity of the metabolites 2,4,6-TCP and SYN547891, the toxicological relevance of impurities and information on the commercial scale production. The following conclusions are derived.

The uses of pydiflumetofen according to the representative uses as a fungicide on field application for pome fruits, grapes, potato, fruiting vegetables, cucurbits and *Brassica* vegetables 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 pydiflumetofen or the representative formulation. In the area of identity, physical and chemical properties and analytical methods, data gaps were identified for addressing the extraction efficiency of the monitoring methods for the plant matrices and additional validation data for determination of the active substance in muscle.

Regarding the mammalian toxicology area, a data gap was identified to further address the toxicological relevance of three individual impurities present in the technical specification in comparison with the toxicological profile of the parent compound. Another data gap was identified to clarify the genotoxic potential of the metabolite 2,4,6-TCP leading to an issue not finalised. In addition, the potential adversity related to succinate dehydrogenase inhibitors (SDHI) fungicidal mode of action (MOA) in humans is inconclusive.

Data gaps related to residue trials in Brussels sprout, kohlrabi and to the isomeric behaviour in livestock studies were identified for the residue section. In addition, pydiflumetofen is a highly persistent compound, and therefore, the need of MRLs for rotational crops might be necessary. As regards for the MRL application, MRLs were proposed only in cases the data were sufficient to support the intended good agricultural practice (GAP). The consumer risk assessment for animal commodities should be regarded as provisional due to insufficient toxicological data on 2,4,6-TCP. In addition, the consumer risk assessment from the consumption of drinking water is also not finalised.

Pydiflumetofen exhibited very high persistence in soil both in laboratory and in field studies, and also high persistence in water/sediment studies. The data available on environmental fate and behaviour are sufficient to carry out the required environmental exposure assessments at EU level, with the notable exception that a data gap was identified for information on the effect of water treatment processes on the nature of residues of both the active substance and its identified metabolites potentially present in surface, when surface water is abstracted for drinking water. This gap leads to the consumer risk assessment from the consumption of drinking water being not finalised for all the representative uses.

In the area of ecotoxicology, some data gaps were identified for the risk assessment for bees. A high risk to earthworms was concluded for pydiflumetofen for the uses in grapes at 200 g a.s./ha (data gap). A low risk to earthworm-eating mammals via secondary poisoning could not be concluded for pydiflumetofen for the uses in grapes at 200 g a.s./ha (data gap).

Regarding **humans** and **non-target organisms**, based on the available evidence, ED criteria 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, are not met for the oestrogen, androgen, thyroid and steroidogenesis (EATS)-modalities for humans, wild mammals and non-mammalian species.

BACKGROUND

Regulation (EC) No 1107/2009 of the European Parliament and of the Council[1] (hereinafter referred to as 'the Regulation') lays down, inter alia, the detailed rules as regards the procedure and conditions for approval of active substances. This regulates for the European Food Safety Authority (EFSA) the procedure for organising the consultation of Member States and the applicant for comments on the initial evaluation in the draft assessment report (DAR), provided by the rapporteur Member State (RMS), and the organisation of an expert consultation, where appropriate.

In accordance with Article 12 of the Regulation, EFSA is required to adopt a conclusion on whether an active substance can be expected to meet the approval criteria provided for in Article 4 of the Regulation (also taking into consideration recital (10) of the Regulation) within 120 days from the end of the period provided for the submission of written comments, subject to an extension of 30 days where an expert consultation is necessary, and a further extension of up to 150 days where additional information is required to be submitted by the applicant in accordance with Article 12(3).

Pydiflumetofen is a new active substance for which, in accordance with Article 7 of the Regulation, the RMS, France (hereinafter referred to as the 'RMS'), received an application from Syngenta Crop Protection AG on 25 March 2016 for approval of the active substance pydiflumetofen. In accordance with Article 8(1)(g) of the Regulation, Syngenta Crop Protection AG submitted applications for maximum residue levels (MRLs) as referred to in Article 7 of Regulation (EC) No 396/2005. [2] Complying with Article 9 of the Regulation, the completeness of the dossier was checked by the RMS and the date of admissibility of the application was recognised as being 30 May 2016.

The RMS provided its initial evaluation of the dossier on pydiflumetofen in the DAR, which was received by EFSA on 25 July 2017 (France, 2017). The DAR included a proposal to set MRLs, in accordance with Article 11(2) of the Regulation. The peer review was initiated on 27 September 2017 by dispatching the DAR for consultation of the Member States and the applicant, Syngenta Crop Protection AG, for consultation and comments. EFSA also provided comments. In addition, EFSA conducted a public consultation on the DAR. The comments received were collated by EFSA and 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 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 12(3) of the Regulation were considered in a telephone conference between EFSA and the RMS, on 25 January 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 environmental fate and behaviour.

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 where this took place, were reported in the final column of the evaluation table.

In accordance with Article 12 of the Regulation, EFSA should adopt a conclusion on whether pydiflumetofen can be expected to meet the approval criteria provided for in Article 4 of the Regulation, taking into consideration recital (10) of the Regulation, and give a reasoned opinion concerning MRL applications as referred to in Article 10(1) of Regulation (EC) No 396/2005. A consultation on the conclusions arising from the peer review of the risk assessment and on the proposed MRLs took place with Member States via a written procedure in November 2018.

In addition, a targeted written consultation with Member States took place in August 2019 subsequent to the completion of the peer review of the updated endocrine assessment conducted by EFSA in line with the new scientific criteria for the determination of endocrine-disrupting properties, as laid down in Commission Regulation (EU) 2018/605.[3]

EFSA published its conclusion on the peer review of the pesticide risk assessment of pydiflumetofen on 11 October 2019 (EFSA, 2019c). Following discussions, the Standing Committee on Plants, Animals, Food and Feed considered that the assessment conducted for the persistence of the substance may not be fully suitable for volatile substances like pydiflumetofen.[4] Furthermore, EFSA had identified certain data gaps including for the assessment of endocrine-disrupting (ED) properties as the new scientific criteria to identify endocrine-disrupting properties had become applicable in November 2018 (and thus after the submission of the application which was declared admissible on 28 April 2016). Consequently, Member States found it necessary to consider additional studies related to the persistence and to address the data gaps identified by EFSA in its conclusion, in order to be able to take an informed decision on a possible approval. The rapporteur Member State, France, agreed to consider additional studies on persistence as well as additional information as regards the ED properties for non-target organisms,

[1]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, p. 1–50.

[2]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, p. 1–16.

[3]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, p. 33–36.

[4]With a measured vapour pressure of 1.84×10^{-7} at 20°C and Henry's law constant of 1.05×10^{-4} Pa m^3 mol^{-1} FOCUS (2008) air guidance considers significant volatilisation from soil would not occur.

the genotoxicity of the metabolites 2,4,6-TCP and SYN547891, the toxicological relevance of impurities and information on the commercial scale production. The applicant submitted such additional information and the rapporteur Member State indicated that the revised DAR had been prepared. In accordance with the views of the Member States in the Standing Committee on Plants, Animals, Food and Feed and under consideration of Art 31 of the General Food Law,[5] the European Commission sent a mandate to EFSA dated 30 August 2022 in accordance with Article 31 of Regulation (EC) No 178/2002 with a request to organise a peer review and update its above-mentioned conclusion for all the areas where the rapporteur Member State has updated the DAR, taking into account in particular the physico-chemical properties of the active substance.

EFSA was requested to update its conclusion as the results of this mandate within 8 months from delivery of the updated DAR and LoEP from the RMS with the revised assessments, which were received by EFSA on 2 September 2022 (France, 2022).

This conclusion report summarises the outcome of the peer review of the risk assessment on the active substance and the representative formulation evaluated on the basis of the representative uses of pydiflumetofen as a fungicide on field application for pome fruits, grapes, potato, fruiting vegetables, cucurbits and *Brassica* vegetables as proposed by the applicant and updated following the request from Commission to review the risk assessment as regards the persistence, the ED properties for non-target organisms, the genotoxicity of the metabolites 2,4,6-TCP and SYN547891, the toxicological relevance of impurities and information on the commercial scale production. In accordance with Article 12(2) of Regulation (EC) No 1107/2009, risk mitigation options identified in the DAR and considered during the peer review are presented in the conclusion. MRLs were assessed for outdoor uses in various crops as proposed in Appendix A and the import tolerance on soya beans. Furthermore, this conclusion also addresses the assessment required from EFSA under Article 12 of Regulation (EC) No 396/2005, provided the active substance will be approved under Regulation (EC) No 1107/2009 without restrictions affecting the residue assessment. In the event of a non-approval of the active substance or an approval with restrictions that have an impact on the residue assessment, the MRL proposals from this conclusion might no longer be relevant and a new assessment under Article 12 of Regulation (EC) No 396/2005 will be required. A list of the relevant end points for the active substance and the formulation and the proposed MRLs is provided in Appendix A.

In addition, a key supporting document to this conclusion is the peer review report (EFSA, 2019a, 2023), 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 DAR;
- the reporting table (25 January 2018);
- the evaluation tables (November 2018 and July 2019);
- 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 EFSA addendum on endocrine assessment;
- the comments received on the updated DAR;
- the consolidated commenting table with comments received on the revised DAR containing the RMS evaluations in the context of the mandate to review of the risk assessment of pydiflumetofen;
- the comments received on the draft EFSA conclusion and the updated EFSA conclusion.

Given the importance of the DAR including its revisions (France, 2018, 2022), the peer review report including its update (EFSA, 2019a, 2023) and the EFSA addendum on endocrine assessment (EFSA, 2019b), all these documents are considered as background documents to this conclusion.

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

Pydiflumetofen is the ISO common name for 3-(difluoromethyl)-*N*-methoxy-1-methyl-*N*-[(*RS*)-1-methyl-2-(2,4,6-trichlorophenyl)ethyl]-1*H*-pyrazole-4-carboxamide (IUPAC).

The representative formulated product for the evaluation was 'A19649B', a suspension concentrate (SC) containing 200 g/L pydiflumetofen.

The representative uses evaluated were spray applications for the control of various fungal diseases in pome fruits, grapes, potato, fruiting vegetables, cucurbits, *Brassica* vegetables in the EU. Full details of the GAPs can be found in the list of end points in Appendix A.

Data were submitted to conclude that the representative uses of pydiflumetofen proposed at EU level result in a sufficient fungicidal efficacy against the target organisms, following the guidance document SANCO/10054/2013 - rev. 3 (European Commission, 2013).

[5]Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety OJ L 31, 1.2.2002, p. 1–24.

CONCLUSIONS OF THE EVALUATION

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

The following guidance documents were followed in the production of this conclusion: SANCO/3029/99-rev. 4 (European Commission, 2000a), SANCO/3030/99-rev. 4 (European Commission, 2000b) and SANCO/825/00-rev. 8.1 (European Commission, 2010).

Batch data from the industrial production plant were submitted and it was proposed the current reference specification to be updated based on these data. The minimum purity of the active substance as manufactured is 980 g/kg. The technical pydiflumetofen is produced as a racaemic mixture. It should be noted that evaluation of the toxicological relevance of some impurities is open. In addition, data for the presence of an impurity in the batches are required (data gap, see Sections 2 and 8). As a consequence, new data such as spectral data, content of the impurities before and after the storage of the formulation and methods for analysis of the relevant impurities in the formulation might be required. The batches used in the (eco) toxicological assessment support the newly proposed and original reference specifications (See Sections 2 and 5).

The product is stable after storage at ambient temperature. The main data regarding the identity of pydiflumetofen and its physical and chemical properties are given in Appendix A.

Adequate methods are available for the generation of pre-approval data required for the risk assessment. Methods of analysis are available for the determination of the active substance in the technical material and in the representative formulation.

The residue definition for monitoring in plant and animal matrices was defined as pydiflumetofen. The QuEChERS multiresidue enforcement method with liquid chromatography with tandem mass spectrometry (LC-MS/MS) can be used for the determination of residues of pydiflumetofen in high water content, high acid content, high oil content and dry crop matrices with a limit of quantification (LOQ) of 0.01 mg/kg. A data gap was, however, identified to address the extraction efficiency of the method. The QuEChERS multiresidue method with LC-MS/MS can be used for the determination of the residues of pydiflumetofen in animal matrices (fat, liver, milk and eggs) with an LOQ of 0.01 mg/kg; however, a data gap was identified for additional validation data for the determination of pydiflumetofen in muscle. An LC/MS/MS method also exists for the determination of 2,4,6-trichlorophenol (free and conjugates) in animal commodities (muscle, fat, kidney, milk and eggs) with an LOQ of 0.01 mg/kg.

Appropriate LC-MS/MS methods exist for monitoring pydiflumetofen in the environmental compartments with LOQs of 0.5 µg/kg in soil, 0.05 µg/L in ground and surface water and 30 µg/m^3 in the air, respectively.

The QuEChERS multiresidue method with LC-MS/MS can be used for the determination of the residues of pydiflumetofen in blood with an LOQ of 0.01 mg/kg. An LC/MS/MS method also exists for the determination of 2,4,6-trichlorophenol (free and conjugates) in blood with an LOQ of 0.01 mg/kg.

2 | MAMMALIAN TOXICITY

The following guidance documents were followed in the production of this conclusion: SANCO/221/2000-rev. 10-final (European Commission, 2003), SANCO/10597/2003-rev. 10.1 (European Commission, 2012), Guidance on dermal absorption (EFSA PPR Panel, 2012), Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products (EFSA, 2014b) and Guidance on the Application of the CLP Criteria (ECHA, 2017).

Pydiflumetofen was discussed at the Pesticides Peer Review Experts' Meeting 182 in September 2018, at the Pesticides Peer Review Experts' Meeting 05 (joint Mammalian toxicology – Ecotoxicology meeting) in May 2019, and at the Pesticides Peer Review Experts' Teleconference 98 in March 2023.

The technical specification is supported by the toxicological assessment based on additional genotoxicity testing performed with a spiked batch of pydiflumetofen (with levels of impurities above their specification). For three significant impurities, a robust assessment of the general toxicity profile has not been provided, and therefore, their toxicological relevance cannot be concluded (data gap, see Section 8). For one theoretical impurity, if demonstrated to be present in the technical batches (see Section 1), the assessment of its toxicological relevance will have to be further clarified.[6] All analytical methods used in the toxicological studies have been considered validated by the RMS for the identification and quantification of pydiflumetofen and its metabolites.

Pydiflumetofen is rapidly and extensively absorbed after oral administration, it is widely distributed, metabolised and excreted predominantly in faeces via biliary excretion. A residue definition for body fluids and tissues was established as pydiflumetofen and its metabolite 2,4,6-trichlorophenol (2,4,6-TCP, free and conjugated). An *in vitro* interspecies comparative metabolism study did not reveal evidence of the occurrence of unique human metabolites.

Low acute toxicity was observed when pydiflumetofen was administered by the oral, dermal or inhalation routes, no skin or eye irritation or skin sensitisation potential were attributed to the active substance; in addition, no potential for phototoxicity was observed in an *in vitro* 3T3 standard fibroblast cell line Neutral Red Uptake phototoxicity assay.

Reduced body weight and liver toxicity (increased weight and histopathological changes) were the most sensitive effects of pydiflumetofen toxicity upon short- to long-term dietary exposure. The relevant short- and long-term No-Observed

[6]See experts' consultation 2.3 at the Report of the Pesticides Peer Review Experts' Teleconference 98 (EFSA, 2023).

Adverse Effect Levels (NOAELs) are 17.5 and 9.2 mg/kg body weight (bw) per day, respectively, from the 90-day and 18-month studies in mice. An increased incidence of liver tumours was observed in mice; key events of constitutive androstane receptor (CAR) activation and hepatocellular proliferation were demonstrated to occur in *in vitro* mouse hepatocyte cultures, but not in human material. The mode of action (MOA) (CAR activation) was concluded to be of low relevance to humans and pydiflumetofen was considered unlikely to pose a carcinogenic hazard to humans. In March 2019, in accordance with Regulation (EC) No 1272/2008,[7] the Risk Assessment Committee (RAC) of ECHA adopted the opinion proposing harmonised classification and labelling[8] at EU level of pydiflumetofen as **Carc. 2, H351**, 'suspected of causing cancer' (ECHA, 2019) and the Regulation (EC) No 1272/2008 was therefore amended accordingly with Regulation (EU) 2021/849.[9] The RMS highlighted the potential adversity related to succinate dehydrogenase inhibitors (SDHI) fungicidal MOA in human. This would include severe human neurological diseases and the carcinogenic potential linked to the SDH inhibition (Benit et al., 2018) in which *in vitro* data showed that the human enzyme is inhibited by SDHIs with IC_{50} values in the µM range). The item was presented in its general terms by the RMS. The experts concluded that a concern and relevance to humans cannot be excluded and the assessment of these issues was considered inconclusive (data gap, however, it is noted that there is no validated methodology to address the issue[10]). A minority of experts, including the RMS, considered the *in vitro* chromosome aberration (CA) assay in human lymphocytes assay as equivocal, and would have requested additional information to exclude a genotoxic potential. The majority of experts considered the *in vitro* study negative, supported by the negative studies *in vivo*, with sufficient evidence of bone marrow exposure and pydiflumetofen was concluded unlikely to be genotoxic.[11] Pydiflumetofen does not meet the trigger for a photomutagenicity study, and therefore, the photomutagenicity testing is not required.

In the multigeneration study in rats, the only effect observed was a significant delay in sexual maturation in the F_1 generation. In March 2019, the ECHA RAC proposed classification of pydiflumetofen as **Repro 2, H361f**, 'Suspected of damaging fertility' (ECHA, 2019) and the Regulation (EC) No 1272/2008 was therefore amended accordingly with Regulation (EU) 2021/849.[9] In the rabbit developmental toxicity study, an increased incidence of one skeletal variant (rib costal cartilage interrupted) was observed although without signs of maternal toxicity. The NOAEL for this effect was established at 10 mg/kg bw per day while the maternal NOAEL was 500 mg/kg bw per day. A critical NOAEL for acute effects was established at 30 mg/kg bw per day for early reduction of maternal body weight gain and food consumption in the developmental toxicity study in rats. Signs of acute neurotoxicity were seen in females at high dose levels (300 mg/kg bw). No signs indicative of immunotoxicity were identified in the overall data package.

Toxicological studies have been provided on **metabolites** relevant to consumer exposure, i.e. NOA449410, SYN508272 (M700F007), SYN545547, SYN548263, SYN547897 and 2,4,6-TCP and are reported in Appendix A. Toxicological reference values were derived for NOA449410 and SYN508272.[12] A genotoxic potential could be excluded for metabolites SYN545547, SYN548263, SYN547897 and SYN547891. Regarding **2,4,6-TCP**, the metabolite was found to produce carcinogenic effects in rats and mice and is classified as Carc. 2, H351 'suspected of causing cancer' according to Annex VI of Regulation (EC) No 1272/2008. The results of gene mutation studies in bacteria, cultured mammalian cells and Big Blue transgenic rats indicate that 2,4,6-TCP does not induce gene mutations. Other *in vitro* data and limited *in vivo* data show that 2,4,6-TCP has the potential to induce structural chromosome aberrations and/or aneugenic effects. No robust *in vivo* study on the induction of chromosome aberrations and/or aneugenicity by 2,4,6-TCP is available (data gap, see Section 8). Derivation of toxicological reference values for 2,4,6-TCP was also discussed by the experts, their applicability is pending on the clarification of its genotoxic potential.[13]

The acceptable daily intake (**ADI**) of pydiflumetofen is 0.09 mg/kg bw per day based on the NOAEL of 9.2 mg/kg bw per day for reduced body weight and hepatotoxicity in the 18-month study in mice, applying an uncertainty factor (UF) of 100. The acceptable operator exposure level (**AOEL**) is 0.1 mg/kg bw per day based on the NOAEL of 10 mg/kg bw per day for the increased incidence of variations in the developmental toxicity study in rabbits applying an UF of 100; no correction needed regarding the oral absorption. The acute reference dose (**ARfD**) and the acute acceptable operator exposure level (AAOEL) are 0.3 mg/kg bw per day based on the NOAEL of 30 mg/kg bw per day for reduction of maternal body weight gain and food consumption during the first days of treatment in the developmental toxicity study in rats, applying an UF of 100.

Regarding the representative formulation, A19649B, a suspension concentrate (SC) formulation containing 200 g/L pydiflumetofen, dermal absorption was established at 0.2% for the concentrated formulation and 11% worst-case in-use spray dilution (0.033 g/L) based on pro-rata correction on the triple pack approach (rat *in vivo* and comparative *in vitro* dermal absorption study on human and rat skin). Estimated **non-dietary exposure** according to the EFSA calculator did not indicate exceedance of either the AOEL or the AAOEL for all representative exposure scenarios, even when no personal protective equipment but workwear, arms and legs covered, is taken into consideration for operators and workers. Since no isomeric ratio change has been observed in plant metabolism studies and the environment (see Sections 3 and 4), there is no need to further investigate the differential toxicity of the different isomers of pydiflumetofen. It is noted that the isomer ratio has not been investigated in the animal metabolism studies (see Section 3); therefore, for other uses than the representative ones, this issue may have to be revised.

[7]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, 1–1355.

[8]It should be noted that classification is formally proposed and decided in accordance with Regulation (EC) No 1272/2008.

[9]Commission Delegated Regulation (EU) 2021/849 of 11 March 2021 amending, for the purposes of its adaptation to technical and scientific progress, Part 3 of Annex VI to Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures. OJ L 188, 28.5.2021, p. 27–43.

[10]See experts' consultation 2.6 at the Pesticides Peer Review Experts' Meeting 182 (EFSA, 2019a).

[11]See experts' consultation 2.1 at the Pesticides Peer Review Experts' Meeting 182 (EFSA, 2019a).

[12]See experts' consultation 2.7 at the Pesticides Peer Review Experts' Meeting 182 (EFSA, 2019a).

[13]See experts' consultation 2.1 at the Report of the Pesticides Peer Review Experts' Teleconference 98 (EFSA, 2023).

3 | RESIDUES

The assessment in the residue section is based on the OECD guidance document on overview of residue chemistry studies (OECD, 2009), the OECD publication on MRL calculations (OECD, 2011), the European Commission guideline document on MRL setting (European Commission, 2011) and the Joint Meeting on Pesticide Residues (JMPR) recommendations on livestock burden calculations (JMPR, 2004, 2007).

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

Metabolism studies in primary crops were conducted with pyridine and phenyl labelled pydiflumetofen in fruits crop (tomatoes), cereals (wheat) and pulses and oilseeds (rapeseed) via foliar application and one pyridine labelled via soil application. Pydiflumetofen was found as the major compound in different investigated crops accounting for up to 97% total radioactive residues (TRRs) (in fruits), 82% TRRs (grains) and 63% TRRs (rapeseeds). Although in the study design on fruit some deviations were noted in terms of application time BBCH (83–86) vs. BBCH (51–89) and the preharvest interval (PHI) of 14 days vs. PHI 65 days when compared with the representative GAP, since the parent remained the predominant compound also at longer PHI (up to 97% TRRs in tomatoes), all the metabolism studies were considered acceptable. The residue definitions for monitoring and risk assessment are proposed as pydiflumetofen covering all crop groups.

Confined rotational metabolism studies were conducted with both labelled pydiflumetofen at all three PBI at max rate of 408 g/ha covering three crop groups (roots, leafy, cereals). In rotational crops besides pydiflumetofen accounting for up to 78% TRR in leafy, SYN547891 was also found in wheat forage and immature lettuce only (12% TRR). Although, SYN547891 is not expected to be persistent and its level of occurrence is low compared with the parent, however still > 10% of TRRs in food items, its genotoxic profile was addressed (see Section 2). Currently, SYN547891 was not included in the risk assessment residue definition for rotational crops and therefore the same residue definitions as for primary crops are applicable. However, since pydiflumetofen is highly to very highly persistent compound with DT50 = 8540 days (see Section 4), the accumulation of the substance has to be taken into account for the assessment of the rotational crop field studies. It is noted that the possible isomerisation during the metabolism studies in primary and rotational crops of pydiflumetofen was investigated showing no isomeric ratio change.

The stability of pydiflumetofen residues when stored at −18°C was demonstrated for 23 months in all plant commodity categories. In animal matrices, besides pydiflumetofen, the stability of 2,4,6-TCP residues was also demonstrated up to 12 months.

Under the standard hydrolysis conditions representative of processing (pasteurisation, backing, sterilisation), pydiflumetofen was considered to be hydrolytically stable.

Fully compliant livestock metabolism studies with both labelled pydiflumetofen were available for ruminants and poultries. In poultries, the predominant compounds were 2,4,6-TCP found in all matrices except liver (maximum 68% TRRs in eggs) while pydiflumetofen was found in all matrices, the maximum TRRs in fat 47% TRRs in eggs white. In addition, NOA449410 was also found in eggs white up to 15% TRRs while SYN508272 was found in eggs white up to 34% TRRs and in muscle up to 46% TRRs. In ruminants, parent is again the predominant compound, accounting for maximum 74% TRRs in fat, milk (16% TRRs), muscle (24% TRRs), fat (74% TRRs) and 2,4,6-TCP in milk (43% TRRs), additional metabolites such as SYN548264 in milk 29% TRRs, SYN548263 in kidney 17% TRRs, SYN508272 up to 18% TRRs in muscle, while NOA449410 accounted for 12% TRRs in kidney. Although SYN508272 was recovered at significant levels (> 10% TRRs in muscle, eggs, milk) and is also of lower toxicity compared to the parent (see Section 2), since the dosing levels were significantly higher compared to the expected exposure intake (792N for poultries and 43N for ruminants), only parent compound and 2,4,6-TCP were considered relevant for residue definitions. Therefore, for monitoring, all the experts including EFSA agreed to propose the residue definition as pydiflumetofen while for risk assessment, the residue definition was proposed as pydiflumetofen and 2,4,6-TCP for all livestock commodities. It should be noted, however, that 2,4,6-TCP was found to produce carcinogenic effects and its genotoxic potential was inconclusive (see Section 2). The new data submitted were not sufficient to conclude on the genotoxicity of 2,4,6-TCP (see Section 2); thus, it cannot be concluded on the expression of the risk assessment residue definition. It should be noted that possible change in the isomeric ratio was not investigated in livestock studies and is necessary, considering also that the metabolic pattern is different when compared with plants (data gap).

Although pydiflumetofen is fat soluble and potato is fish feed item but with low residue levels detected (< 0.01 mg/kg), currently a metabolism study in fish is not triggered. In addition, it should be noted that the bioconcentration fish study submitted in Section 5 cannot support the fish metabolism study.

3.1 | Representative use residues

As regards the representative uses on apples, pears, grapes (table and wines), tomatoes, cucumbers, courgettes, melon, watermelon, potatoes, broccoli, cauliflower, kale and head cabbage sufficient number of GAP compliant trials are available while for Brussels sprouts and kohlrabi sufficient residue trials to support the representative GAP in SEU are needed (data gap). All the available trials are supported by storage stability data and validated analytical methods and MRL proposals were derived (see Appendix A). An MRL of 0.01 (MRL is proposed at the LOQ.) mg/kg was proposed also in honey, based on the submitted trials. Processing trials were also available; therefore, processing factors were proposed for several crops (see Appendix A).

A total of six rotational field trials (4 SEU and 2 NEU) covering all three PBI conducted at the maximum dose rate of 600 g/ha were available in spinach, carrots and barley. Samples were analysed for pydiflumetofen only, and the residue levels

were up to 0.09 mg/kg in barley straw at second PBI in SEU trials. In the NEU trials conducted in maize, soybean, spinach, carrots and radish, the residue levels were found up to 0.04 mg/kg at the first PBI in radish roots. Although the max PEC soil was not covered, these rotational field trials are considered acceptable, however due to the accumulation of pydiflumetofen in the soil, setting of MRLs might become necessary for rotational crops.

The dietary burden intake was triggered for poultries and ruminants, therefore laying hens and lactating cattle feeding studies analysing for pydiflumetofen and 2,4,6-TCP covered by the storage stability and validated analytical method were provided. Hence, MRL for animal commodities were also proposed.

The overall consumer risk assessment was conducted by using EFSA PRIMo rev.2 and it covers the residues of pydiflumetofen only in plant (representative uses). However, for the animal commodities, since the risk assessment residue definition includes also 2,4,6 TCP for which the genotoxic potential cannot be ruled out (see Section 2), the consumer risk assessment for animal commodities could not be finalised. The chronic (theoretical maximum daily intake (TMDI)) was calculated for maximum 9.4% of ADI (wine grapes, FR diet) and the acute consumer intakes (IESTI) accounted for 46% (kale, NL diet). An updated consumer risk assessment was conducted by using PRIMo 3.1 with TMDI accounting for 9% of ADI (table grapes) and highest IESTI accounting for 30% of ARfD (kale). It should be noted, however, that if 2,4,6-TCP is not genotoxic, no consumer intake risk for the animal commodities is expected since the feeding studies demonstrated that the residue levels at 1 N rate are by far below 0.01 mg/kg. The consumer risk assessment from the consumption of drinking water is also not finalised considering the lack of appropriate information to address the effect of water treatment processes on the nature of residues of pydiflumetofen and its possible metabolites, potentially present in surface water, when surface water is abstracted for drinking water (see Section 4).

3.2 | Maximum residue levels

Maximum residue levels (MRLs) were assessed for outdoor uses in pome fruits quince, medlar and loquat, potatoes (sweet, yams), peppers (Sweet & Bell peppers), aubergines, okra, gherkins, pumpkins, Chinese cabbage/p-tsai and for protected uses on fruiting vegetables (tomatoes, peppers, aubergines, okra, cucumber, courgette, gherkins, melon, watermelon, pumpkin) and the import tolerance on soyabean. All the intended uses were sufficiently supported by residue trials validated by the analytical method and storage stability studies; therefore, MRL proposals have been derived. For the crops where the uses were intended for indoor and outdoor, the MRL was derived based on the most critical residue situation (e.g. indoor uses) (see the detailed assessment in Appendix A).

For the livestock assessment, besides the representative uses, soyabean was also included in the dietary burden intake calculation since it is listed in the European livestock diet. However, its contribution to the total dietary burden is very low; thus, the expected residue levels in the animal commodities at the 1N rate remained by far below 0.01 mg/kg.

The consumer risk assessment using EFSA PRIMO rev 2 was conducted for all the uses where MRLs could be derived, except animal commodities and the EU representative uses whenever more critical. The chronic maximum TMDI was calculated for 10% of ADI (wine grapes, FR all population) and acute consumer intakes (IESTI) (accounted and 46% of ARfD kale, NL diet). The results from an updated consumer risk assessment by using PRIMo 3.1 were TMDI accounting for 10% of ADI (table grapes) and highest IESTI accounting for 30% of ArfD (kale). For MRL application, a refined chronic consumer intake calculation (IEDI) was also calculated by using input values from the residue levels in crops as they are consumed (STMR), processing factors whenever applicable and the toxicological end point (ADI). Therefore, the maximum IEDI accounted for 2% of the ADI (tomatoes, WHO cluster diet B).

4 | ENVIRONMENTAL FATE AND BEHAVIOUR

Pydiflumetofen was discussed at the Pesticides Peer Review Experts' Teleconference (TC) 190 in September 2018.

The enantiomeric composition of pydiflumetofen did not change during the degradation studies.

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, pydiflumetofen exhibited very high persistence, forming no major (> 5% applied radioactivity (AR)) metabolites. Mineralisation of the pyrazole and phenyl rings ^{14}C radiolabel to carbon dioxide accounted for 3.2%–5.3% AR after 120 days, respectively. The formation of unextractable residues (not extracted by acetonitrile/ammonium acetate, and acetonitrile/water acidified to pH 3) for these radiolabels accounted for 8.1%–33% AR after 120 days. In anaerobic and photolysis soil incubations, pydiflumetofen was essentially stable, with no major (> 5% applied radioactivity [AR]) metabolites.

Pydiflumetofen exhibited low to slight mobility in soil. Adsorption endpoints were derived also for surface water/sediment metabolite SYN545547, which exhibited medium to low mobility (K_{Foc} 322–759 mL/g), and aquatic photolysis metabolite NOA449410, which exhibited very high mobility in soil (K_{Foc} 0.3–6.1 mL/g). It was concluded that the adsorption of pydiflumetofen and its water metabolites was not pH dependent.

In satisfactory European field dissipation studies (target dose rate applied 204 g/ha) carried out at one site in Germany, one in Italy, two sites in France, one site in Spain and one in the UK (spray application to the soil surface on bare soil plots in late spring, soils covered with sand after the application), pydiflumetofen exhibited very high persistence. Sample analyses were only carried out for the parent pydiflumetofen. Field study $DegT_{50}$ values were derived following normalisation

to FOCUS reference conditions (20°C and Pf2 soil moisture) following the EFSA (2014a) $DegT_{50}$ guidance. The field data endpoints were not combined with lab values to derive modelling endpoints. In three further field soil dissipation studies (target dose rate applied 200 g/ha) carried out at one site in northern Germany, one in Portugal and one in Southern France (spray application to the soil surface on bare soil plots in early summer pre-sown with grass seed which subsequently emerged), pydiflumetofen exhibited high to very high persistence. Because of the very high persistence of pydiflumetofen, the dissipation and degradation numerical values estimated in the majority of investigations are more uncertain than usual due to their extrapolation beyond the study durations and other factors that can be found detailed in the report of the Pesticides Peer Review Experts' TC 190. At three of the field trial sites with the bare soil plot design and 2 with the grass emerged plot design, soil cores down to 1 m were sampled at intervals of 4–7 years after the only application of pydiflumetofen. The plots had been cultivated and cropped by the land owners after the initial experiments had finished. At four of the five trial sites, pydiflumetofen soil residues remained above the LOQ (0.5 µg/kg wet soil) in core depth segments (discretised every 10 cm) down to 50 cm. In 10 cm segments approximating to typical tillage depths (top 30 cm), quantifiable pydiflumetofen was present at between 1.2 and 19 µg/kg wet soil.

In laboratory incubations in dark natural sediment water systems under aerobic conditions, pydiflumetofen exhibited high persistence, forming the major metabolite SYN545547 (max. 2.3% AR in water and max. 12.3% AR in sediment, exhibiting moderate to very high persistence). The unextractable sediment fraction (not extracted by acetonitrile/water) under aerobic conditions was the major sink for the pyrazole and phenyl rings ^{14}C radiolabel, accounting for 10.1%–16.2% AR at study end (100 days). Mineralisation of these radiolabels accounted for only 0.9% AR at the end of the study. The rate of decline of pydiflumetofen in a laboratory sterile aqueous photolysis experiment was slow relative to that which occurred in the water phase of aerobic sediment water incubations, but it was fast compared to that which occurred in the whole system. No chromatographically resolved component (excluding pydiflumetofen) accounted for > 5% AR. Irradiation of phenyl and pyrazole-labelled pydiflumetofen in sterile natural water resulted in formation of the major photodegradation products SYN548261 (max. 7.3% AR) and NOA449410 (max. 5.4% AR). The necessary surface water and sediment exposure assessments (predicted environmental concentrations (PEC) calculations) were carried out for the metabolites SYN545547, SYN548261 and NOA449410, 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 pydiflumetofen, appropriate step 3 (FOCUS, 2001) and step 4 calculations were available.[14] The step 4 calculations were carried out only for representative uses on grapes and pome fruits and appropriately followed the FOCUS (FOCUS, 2007) guidance, with no-spray drift buffer zones of up to 10 m being implemented (representing a 91%–93% spray drift reduction). However, these step 4 calculations were not used for refining the risk assessment (see Section 5).

The necessary groundwater exposure assessments were appropriately carried out using FOCUS (European Commission, 2014) scenarios and the models PEARL 4.4.4, PELMO 5.5.3 and MACRO 5.5.4. The potential for groundwater exposure from the representative uses by pydiflumetofen above the parametric drinking water limit of 0.1 µg/L was concluded to be low in geoclimatic situations that are represented by all nine FOCUS groundwater scenarios for pydiflumetofen for the standard 20 years of simulations. However, these standard calculations resulted to be not sufficient to cover the groundwater risk assessment for such a highly persistent substance, since PEC_{GW} simulations done using longer periods were not able to depict the plateau phase of pydiflumetofen for all representative uses and showed increasing trends. Therefore, additional simulations considering annual applications of pydiflumetofen during 60 years were used in order to assess the long-term groundwater exposure for pydiflumetofen. Although these calculations were not performed using the standard FOCUS shells of the groundwater models, it was agreed that they are needed to illustrate that due to the persistence of pydiflumetofen, groundwater exposure from the active substance for the representative uses is likely to occur in the long term. For the representative uses on grapes, the 80th percentile annual average recharge concentrations leaving the top 1 m soil layer were estimated to be > 0.1 µg/L in all seven scenarios (2 × 200 g/ha) and in six of seven scenarios (2 × 40 g/ha) for pydiflumetofen. For the representative uses on pome fruit, the 80th percentile annual average recharge concentrations leaving the top 1 m soil layer were estimated to be > 0.1 µg/L at eight of nine scenarios for pydiflumetofen. For the representative uses on brassicas and kohrabi, the 80th percentile annual average recharge concentrations leaving the top 1 m soil layer were estimated to be > 0.1 µg/L at three of seven scenarios for pydiflumetofen. For the representative uses on cucurbits, tomatoes and potatoes concentrations expressed on this basis were estimated to be < 0.1 µg/L at all scenarios.

The soil exposure assessment was carried out for pydiflumetofen using the worst-case non-normalised field DT_{50}. Furthermore, since pydiflumetofen is a very highly persistent compound, PEC accumulation was calculated for all intended uses from the sum of background PEC soil over many years (plateau concentration) and initial PEC soil. A plateau concentration in soil was not reached in a short time period, and then, the calculations over a period of 100 years were used for the risk assessment. Due to the very high persistence of pydiflumetofen, the PEC in soil calculations are more uncertain than usual.

Following the current regulatory framework, pydiflumetofen products should be authorised only for uses where groundwater concentrations would be < 0.1 µg/L. Therefore, when addressing the effect of water treatment processes on the nature of residues the consideration needed is only for surface water abstraction. The applicant did not provide appropriate information to address the effect of water treatment processes on the nature of the residues of both the active substance and its identified metabolites that might be present in surface water, when surface water is abstracted for

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

drinking water. This has led to the identification of a data gap (see Section 7) and results in the consumer risk assessment not being finalised (see Section 9).

The PEC in soil, surface water, sediment and groundwater covering the representative uses assessed can be found in Appendix A 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).

Pydiflumetofen was discussed at the Pesticides Peer Review Experts' Meeting 05 (joint Mammalian toxicology – Ecotoxicology meeting) in May 2019.

The information to support the compliance of the batches used in the ecotoxicological studies with the technical specification was considered sufficient.

Acute oral toxicity data on **birds and mammals** were available with the active substance pydiflumetofen and the representative formulation. Short-term dietary, subchronic and reproduction toxicity data on birds and a two-generation study in rats with pydiflumetofen were reported. Based on the available data and risk assessment, low acute and long-term risk from dietary exposure to birds and mammals was concluded for all the representative uses.

Ecotoxicologically relevant metabolites were not found in plant material.

Low risk to birds and mammals was concluded from exposure to contaminated water. Low risk via secondary poisoning was indicated except for earthworm-eating mammals for the representative use on grapes at 200 g a.s./ha (data gap). For the metabolite SYN54554, low risk via secondary poisoning was concluded for all representative uses.

Toxicity data were available on all the relevant taxa of **aquatic organisms** and the active substance pydiflumetofen while acute toxicity data for fish, daphnia and a study on algae were available on the representative formulation. Based on the available tier 1 data, low risk to algae, higher aquatic plants and sediment-dwelling organisms were concluded for all the representative uses of pydiflumetofen at FOCUS Step 1&2.

A low chronic risk to fish was concluded for all representative uses. However, a high acute risk to fish at FOCUS Step 3 was indicated for the majority of the relevant FOCUS scenarios (5 of 6) for the use in grapes at 200 g a.s./ha, in many (5 of 10) FOCUS scenarios for the use in pome fruit and in the FOCUS scenario D6 for the uses in tomatoes and brassicas. A low acute risk to fish was indicated for the remaining representative uses.

The chronic risk to aquatic invertebrates was low for all representative uses. However, a high acute risk to aquatic invertebrates at Step 3 was indicated for several FOCUS scenarios for the use in grapes (5 of 6) and in pome fruit (7 of 10) and in the FOCUS scenario D6 for the uses in tomatoes, potatoes, brassicas and cucurbits.

Therefore, acute risk assessment refinement for fish and aquatic invertebrates was needed and tier 2 acute RAC was presented. The acute tier 2 RAC for fish and invertebrates was based on species sensitivity distribution (SSD) approach. Based on these risk assessment refinements, a low acute risk was concluded to fish and aquatic invertebrates using FOCUS steps 1 & 2.

A low risk to aquatic organisms was concluded for the pertinent aquatic metabolites SYN545547, SYN548261 and NOA449410. A low risk to sediment dwellers was concluded for the metabolite SYN545547.

Acute oral and contact toxicity studies were available on honey**bees** for pydiflumetofen. Chronic data on adult honeybees and brood development were available with pydiflumetofen and the representative formulation. Three semi-field studies (i.e. OECD 75 tests) were also available to assess the effects on bee brood indicating no adverse effect for an application rate of 200 g a.s./ha.

The risk assessment was based on the calculation of acute oral and contact hazard quotients (HQs) according to the European Commission (2002) guidance document for honeybees. A low acute risk to adult honeybees was concluded considering these assessments.

A qualitative assessment of the bee brood data from the semi-field studies in flowering *Phacelia tanacetifolia* was also available. Although these studies have some limitations, the qualitative assessment can be considered suitable for concluding a low risk for the bee brood.

A tier 1 risk assessment considering all the other routes of exposure (e.g. chronic risk to honeybees, and different exposure scenarios), based on the EFSA (2013) was not available (data gap). No data were available for sublethal effect assessment (e.g. hypopharyngeal glands (HPG)) (data gap). No data and no risk assessments were available for the relevant plant metabolites potentially formed in pollen and nectar (data gap). No toxicity data and risk assessment were provided for bumblebees and solitary bees.

The Tier 1 and tier 2 toxicity tests on **non-target arthropods**, *Aphidius rhopalosiphi* and *Typhlodromus pyri*, were available with the representative formulation. A low in-field and off-field risk to non-target arthropods was concluded for all the representative uses, based on the available data.

Based on the available toxicity data with the representative formulation, a low risk to **earthworms** was identified for all the representative uses, with the exception of the uses in grapes at 200 g a.s./ha (data gap).

On the basis of the available data and risk assessment, a low risk to **soil macroorganisms** other than earthworms, **soil microorganisms**, **non-target terrestrial plants** and **organisms in sewage treatment plants** was concluded for all the representative uses.

6 | ENDOCRINE DISRUPTION PROPERTIES

Pydiflumetofen was discussed at the Pesticides Peer Review Experts' Meeting 05 (joint Mammalian toxicology – Ecotoxicology meeting) in May 2019. For non-target organisms other than wild mammals, further data were considered necessary[15] and a long-term stop of the clock was applied to complete the data package as laid down in Article 13(3a) of Regulation 844/2012, as amended by Commission Implementing Regulation (EU) No 2018/1659. An assessment of the endocrine disruption potential of Pydiflumetofen **for humans and non-target organisms** according to the ECHA/EFSA guidance (2018) was also made available.

With regard to the assessment of the endocrine disruption potential of pydiflumetofen **for humans** according to the ECHA/EFSA guidance (2018), the oestrogen, androgen, thyroid and steroidogenesis (EATS) modalities were considered sufficiently investigated and no adversity was observed.

Particularly, for the T-modality, minimal follicular cell hypertrophy was only observed in rat studies (90-day and two-generation), and it was not reproducible in studies at higher dose levels and longer duration in the same species and in studies performed in other species. Furthermore, thyroid effects were only observed concomitantly to liver effects. Therefore, based on the available evidence, pydiflumetofen was not showing a consistent pattern indicative of T-mediated adversity.

Regarding oestrogen, androgen and steroidogenesis (EAS) modalities, the EAS-mediated parameters were sufficiently investigated since an OECD TG 416 study performed with the latest version (OECD, 2001) was available and no EAS-mediated adversity was observed.

In conclusion, according to point 3.6.5 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605, pydiflumetofen is not an endocrine disruptor in humans.

The outcome of the assessment reported above for humans also applies to wild mammals as non-target organisms. For non-target organisms other than mammals, an Amphibian Metamorphosis Assay (AMA, OECD TG 231) and a Fish Short-Term Reproduction Assay (FSTRA, OECD TG 229) were available.

Both studies were discussed at the Pesticides Peer Review Experts' Teleconference 99 (joint Mammalian toxicology – Ecotoxicology meeting) in March 2023.

Regarding the T-modality, despite some uncertainties were observed in the available AMA, experts agree that the study could still be used in the ED assessment. Overall, based on the result of the AMA, no pattern of T-mediated endocrine activity was observed.

Regarding the EAS modalities, some positive findings were observed in female fish, i.e. decreased VTG at all concentrations, decreased fecundity, change in female gonad histopathology, i.e. increased oocyte atresia. However, some sources of uncertainties were identified in the study and in the overall ED assessment (see Table 1 below).

TABLE 1 Uncertainty analysis of the ED assessment for non-target organisms other than mammals for the EAS-modalities.

Line of evidence	Uncertainty	Comment
VTG measurements in fish	Decrease in females VTG was observed at all concentrations (flat concentration responses). However, only at the mid concentration, the decrease was statistically significant	The observed VTG decrease might not be treatment-related considering the lack of dose response (i.e. VTG concentrations are all in the same order of magnitude), which is not expected in case of a correlated effects dose, and the dose spacing of 10
Gonad histopathology	Change in the gonad histopathology of females (increased oocyte atresia) was observed at the low and high concentrations	Although an increased prevalence and severity of oocyte atresia is observed at the lowest and the highest concentrations, no oocyte atresia was observed at the intermediate concentration
Liver histopathology	Change in liver histopathology: Slight increase in the prevalence of individual cell necrosis/apoptosis (minimal to mild) in the livers of females exposed to the mid and high concentration and some basophilia	The findings in the liver histology (basophilia and necrosis) were considered normal physiological findings for actively reproductive females. Overall, the changes in the VTG levels cannot be due to liver toxicity
Evidence of EAS-mediated endocrine activity in the FSTRA	VTG decrease in females was statistically significant only at the intermediate concentration. A decrease in fecundity was observed only at the highest tested concentration. Change in gonad histopathology, i.e. increased oocyte atresia was observed only at the low and high concentrations	Overall, a clear pattern of endocrine activity and adversity was not identified in the study, i.e. at the intermediate concentration where the reduction in VTG was statistically significant, a decrease in fecundity and change in gonad histopathology would be expected. The decrease in fecundity observed at the high concentration was accompanied by increased prevalence and severity of oocyte atresia. However, a similar change was also observed at the low concentration, although in the absence of effects on fecundity
Criteria not met for mammals and humans	Potential difference in physiology and sensitivity between mammals and non-mammalian species Metabolism studies to explain different responses between vertebrate species are not available	Although there may be some physiological differences, it is also well known that the endocrine system is well conserved across vertebrates

[15]See experts' consultation 3 and 4 at the Pesticides Peer Review Experts' Meeting 05 (Mammalian toxicology-Ecotoxicology -Joint session on ED) (EFSA, 2019a).

Overall, although the ED assessment presented some uncertainties, as presented in the table above, the level of such uncertainties was not considered so high as to prevent the conclusion that it is unlikely that pydiflumetofen may be an endocrine disruptor for non-target organisms other than mammals for EAS-modalities.

Based on the above considerations, it is concluded that pydiflumetofen does not meet the ED criteria for EATS-modalities for non-target organisms as laid down in point 3.8.2 of Annex II of Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605.

7 | OVERVIEW OF THE RISK ASSESSMENT OF COMPOUNDS LISTED IN RESIDUE DEFINITIONS TRIGGERING ASSESSMENT OF EFFECTS DATA FOR THE ENVIRONMENTAL COMPARTMENTS (TABLE 2–5)

TABLE 2 Soil.

Compound (name and/or code)	Persistence	Ecotoxicology
Pydiflumetofen (SYN545974)	High to very high persistence Single first order and bi-phasic kinetics DT_{50} 398–2380 days (DT_{90} 1320–7640 days; laboratory conditions at 20°C, pF2 soil moisture) European sand covered field studies single first order and bi-phasic kinetics DT_{50} 29–8540 days (DT_{90} 1820–> 10,000 days) European field dissipation studies on grass emerged plots single first-order and bi-phasic kinetics DT_{50} 23–1310 days (DT_{90} 755–4360 days)	Low risk to earthworms for all the representative uses, except for the uses in grapes at 200 g a.s./ha (data gap)

TABLE 3 Groundwater.

Compound (name and/or code)	Mobility in soil	> 0.1 µg/L at 1 m depth for the representative uses[a]	Pesticidal activity	Toxicological relevance
Pydiflumetofen (SYN545974)	Low to slight mobility K_{Foc} 1165–2206 mL/g	Yes (following annual applications during 60 years): Grapes, 2 × 200 g/ha: 7/7 FOCUS scenarios (**0.19–1.54** µg/L) Grapes, 2 × 40 g/ha: 6/7 FOCUS scenarios (0.08–**0.20** µg/L) Pome fruit: 8/9 FOCUS scenarios (< 0.001–**2.67** µg/L) Brassicas: 3/7 FOCUS scenarios (< 0.001–**1.87** µg/L)	Yes	Yes

[a]FOCUS scenarios or relevant lysimeter.

TABLE 4 Surface water and sediment.

Compound (name and/or code)	Ecotoxicology
Pydiflumetofen (SYN545974)	Low risk for aquatic organisms
SYN545547 (water/sediment)	Low risk for aquatic organisms
NOA449410 (aqueous photolysis)	Low risk for aquatic organisms
SYN548261(aqueous photolysis)	Low risk for aquatic organisms

TABLE 5 Air.

Compound (name and/or code)	Toxicology
Pydiflumetofen (SYN545974)	Rat LC_{50} inhalation > 5.11 mg/L air/4 h (nose only) – no classification required

8 | DATA GAPS

This is a list of data gaps identified during the peer review process, including those areas in which a study may have been made available during the peer review process but not considered for procedural reasons (without prejudice to the provisions of Article 56 of Regulation (EC) No 1107/2009 concerning information on potentially harmful effects).

- Data on the presence of one impurity in the technical batches (relevant for all representative uses evaluated; see Section 1).
- The extraction efficiency of the QuEChERS multiresidue enforcement method with LC-MS/MS for the determination of residues of pydiflumetofen in plant matrices should be addressed (relevant for all representative uses evaluated; see Section 1).
- Additional validation data for the QuEChERS multiresidue enforcement method for the determination of pydiflumetofen in muscle (relevant for all representative uses evaluated; see Section 1).
- The toxicological relevance of three individual impurities present in the technical specification in comparison with the toxicological profile of the parent should be further addressed (relevant for all representative uses evaluated; see Section 2).
- Since the metabolite 2,4,6-TCP has the potential to induce structural chromosome aberrations and/or aneugenic effects (based on *in vitro* data and limited *in vivo* data), a combined *in vivo* Comet/micronucleus assay (conducted according to the OECD TG 489/474 should be provided (relevant for the representative uses that could be also feed items (apple, potato, brassica and kohlrabi)); see Sections 2 and 3).
- The potential adversity related to SDHI fungicidal MOA in humans is inconclusive; there is currently no validated methodology to address this issue (relevant for all representative uses evaluated; see Section 2).
- Sufficient residue trials, validated by storage stability and analytical methods to support the representative GAP in SEU, are needed (relevant for Brussels sprout and kohlrabi; see Section 3).
- The possible change in isomeric ratio was not investigated in livestock studies and is necessary, considering also that the metabolic pattern is different when compared with plants (relevant for potatoes and kale; see Section 3).
- An assessment of the effect of water treatment processes on the nature of residues present in surface water, when surface water is abstracted for drinking water is not available. In the first instance, a consideration of the processes of ozonation and chlorination would appear appropriate. If an argumentation is made that concentrations at the point of abstraction for drinking water purposes will be low, this argumentation should cover metabolites predicted to be in surface water as well as the active substance. Should this consideration indicate 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 Section 4).
- Based on EFSA (2013), a tier 1 risk assessment considering all other routes of exposure to pydiflumetofen (e.g. chronic risk to honeybees and different exposure scenarios) should be provided (relevant for all representative uses evaluated; see Section 5).
- Based on EFSA (2013), assessment of sublethal effect (e.g. HPG) (relevant for all representative uses evaluated; see Section 5).
- Information to assess the risk to honeybees due to plant metabolites occurring in pollen and nectar should be provided (relevant for all representative uses evaluated; see Section 5).
- Further information to refine the risk assessment via secondary poisoning for earthworm-eating mammals are needed (relevant representative uses grapes; see Section 5).
- Further information to refine the risk assessment for earthworms are needed (relevant representative uses grapes at 200 g a.s./ha); see Section 5).

9 | CONCERNS

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 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.

1. The consumer risk assessment for animal commodities cannot be finalised since a genotoxic potential of 2,4,6-TCP cannot be ruled out (see Sections 2 and 3).
2. The consumer risk assessment is not finalised with regard to the unknown nature of residues that might be present in drinking water, consequent to water treatment following abstraction of surface water that might contain pydiflumetofen and its metabolites (see Sections 3 and 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.

Critical areas of concern were not identified.

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

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

TABLE 6 Overview of concerns reflecting the issues not finalised, critical areas of concerns and the risks identified that may be applicable for some but not for all uses or risk assessment scenarios.

Representative use		Pome fruit	Grapes (BBCH 67–89)	Grapes (BBCH 13–77)	Potato	Fruiting vegetables (tomato)	Edible cucurbit (cucumber, courgette)	Inedible cucurbit (melon, watermelon)	Brassica (broccoli, cauliflower, kale, brussels sprouts, cabbage)	Kohlrabi
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[1,2]	X[1,2]	X[1,2]	X[1,2]	X[1,2]	X[1,2]	X[1,2]	X[1,2]	X[1,2]
Risk to wild non-target terrestrial vertebrates	Risk identified		X							
	Assessment not finalised									
Risk to wild non-target terrestrial organisms other than vertebrates	Risk identified		X							
	Assessment not finalised									
Risk to aquatic organisms	Risk identified									
	Assessment not finalised									
Groundwater exposure to active substance	Legal parametric value breached	8/9 FOCUS scenarios	7/7 FOCUS scenarios	6/7 FOCUS scenarios					3/7 FOCUS scenarios	3/7 FOCUS scenarios
	Assessment not finalised									
Groundwater exposure to metabolites	Legal parametric value breached									
	Parametric value of 10 µg/L[a] breached									
	Assessment not finalised									

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

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

ABBREVIATIONS

3T3	standard fibroblast cell line (3-day transfer, inoculum 3×10^5 cells)
a.s.	active substance
AAOEL	acute acceptable operator exposure level
ADI	acceptable daily intake
AOEL	acceptable operator exposure level
AR	applied radioactivity
ARfD	acute reference dose
AST	aspartate aminotransferase (SGOT)
bw	body weight
CA	chromosome aberration
CAR	constitutive androstane receptor
DAR	draft assessment report
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
EATS	oestrogen, androgen, thyroid and steroidogenesis modalities
ECHA	European Chemicals Agency
EEC	European Economic Community
F_1	filial generation, first
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
HPG	hypopharyngeal glands
HQ	hazard quotient
IEDI	international estimated daily intake
IESTI	international estimated short-term intake
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
iv	intravenous
JMPR	Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
K_{Foc}	Freundlich organic carbon adsorption coefficient
LC	liquid chromatography
LC_{50}	lethal concentration, median
LC-MS	liquid chromatography–mass spectrometry
LC-MS-MS	liquid chromatography with tandem mass spectrometry
LOQ	limit of quantification
mm	millimetre (also used for mean measured concentrations)
mN	milli-newton
MOA	mode of action
MRL	maximum residue level
MS	mass spectrometry
NOAEL	no observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
Pa	pascal
PEC	predicted environmental concentration
PEC_{air}	predicted environmental concentration in air
PEC_{gw}	predicted environmental concentration in groundwater
PEC_{sed}	predicted environmental concentration in sediment
PEC_{soil}	predicted environmental concentration in soil
PEC_{sw}	predicted environmental concentration in surface water
pF2	pF value of 2 (suction pressure that defines field capacity soil moisture)
PHI	preharvest interval
ppm	parts per million (10^{-6})
r^2	coefficient of determination
RAC	regulatory acceptable concentration
SC	suspension concentrate
SD	standard deviation
SDHI	succinate dehydrogenase inhibitors
SSD	species sensitivity distribution

STMR	supervised trials median residue
TMDI	theoretical maximum daily intake
TRR	total radioactive residue
UF	uncertainty factor
WHO	World Health Organization

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CONFLICT OF INTEREST
If you wish to access the declaration of interests of any expert contributing to an EFSA scientific assessment, please contact interestmanagement@efsa.europa.eu.

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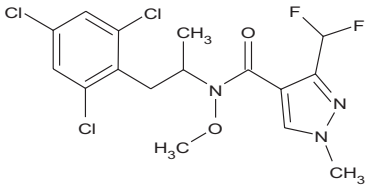
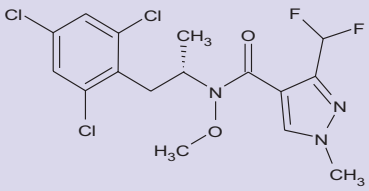
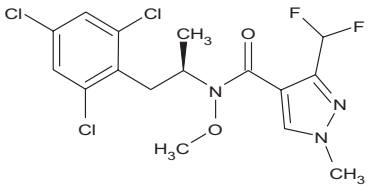
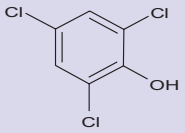
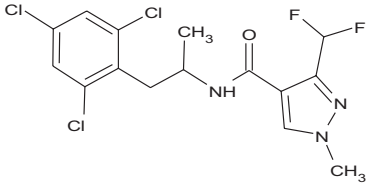
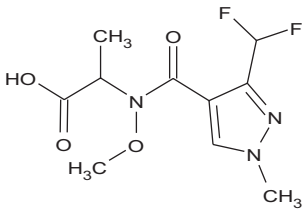
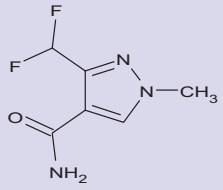
APPENDIX A

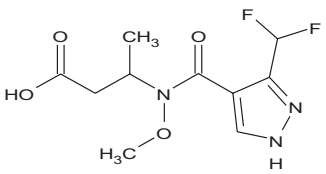
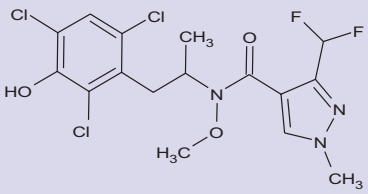
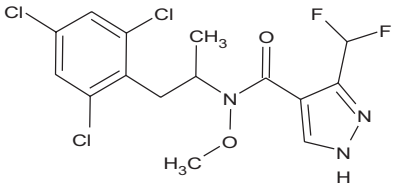
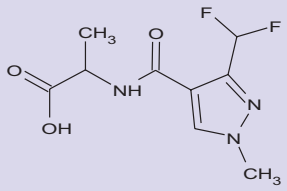
List of end points for the active substance and the formulation(s) for representative uses

Appendix A can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2024.8559

APPENDIX B

Used compound codes

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
Pydiflumetofen **SYN545974**	3-(difluoromethyl)-*N*-methoxy-1-methyl-*N*-[(*RS*)-1-methyl-2-(2,4,6-trichlorophenyl) ethyl]-1*H*-pyrazole-4-carboxamide FC(F)c1nn(C)cc1C(=O)N(OC)C(C)Cc1c(Cl)cc(Cl)cc1Cl DGOAXBPOVUPPEB-UHFFFAOYSA-N	
SYN546968	3-(difluoromethyl)-*N*-methoxy-1-methyl-*N*-[(*S*)-1-methyl-2-(2,4,6-trichlorophenyl) ethyl]-1*H*-pyrazole-4-carboxamide FC(F)c1nn(C)cc1C(=O)N(OC)[C@@H](C)Cc1c(Cl)cc(Cl) cc1Cl DGOAXBPOVUPPEB-QMMMGPOBSA-N	
SYN546969	3-(difluoromethyl)-*N*-methoxy-1-methyl-*N*-[(*R*)-1-methyl-2-(2,4,6-trichlorophenyl) ethyl]-1*H*-pyrazole-4-carboxamide FC(F)c1nn(C)cc1C(=O)N(OC)[C@H](C)Cc1c(Cl)cc(Cl)cc1Cl DGOAXBPOVUPPEB-MRVPVSSYSA-N	
2,4,6-trichlorophenol **(2,4,6-TCP)**	2,4,6-trichlorophenol Clc1cc(Cl)cc(Cl)c1O LINPIYWFGCPVIE-UHFFFAOYSA-N	
SYN545547 CSCD550897	3-(difluoromethyl)-1-methyl-*N*-[(2*RS*)-1-(2,4,6-trichlorophenyl)-2-propanyl]-1*H*-pyrazole-4-carboxamide FC(F)c1nn(C)cc1C(=O)NC(C)Cc1c(Cl)cc(Cl)cc1Cl AGBFDVZRSNTRHP-UHFFFAOYSA-N	
NOA449410 CSAA798670 R648993 M700F001	3-(difluoromethyl)-1-methyl-1*H*-pyrazole-4-carboxylic acid FC(F)c1nn(C)cc1C(=O)O RLOHOBNEYHBZID-UHFFFAOYSA-N	
SYN548261 AP3	*N*-{[3-(difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl] carbonyl}-*N*-methoxy-DL-alanine FC(F)c1nn(C)cc1C(=O)N(OC)C(C)C(=O)O YQGJQHCJONRMCU-UHFFFAOYSA-N	
SYN508272 M700F007	3-(difluoromethyl)-1-methyl-1*H*-pyrazole-4-carboxamide FC(F)c1nn(C)cc1C(N)=O XNXCINUKGNQCEZ-UHFFFAOYSA-N	

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
SYN548263	(3*RS*)-3-[{[3-(difluoromethyl)-1*H*-pyrazol-4-yl]carbonyl}(methoxy)amino]butanoic acid O=C(c1c[NH]nc1C(F)F)N(OC)C(C)CC(=O)O VQBGCHZNXMFNGM-UHFFFAOYSA-N	
SYN547897	3-(difluoromethyl)-*N*-methoxy-1-methyl-*N*-[(2*RS*)-1-(2,4,6-trichloro-3-hydroxyphenyl)-2-propanyl]-1*H*-pyrazole-4-carboxamide FC(F)c1nn(C)cc1C(=O)N(OC)C(C)Cc1c(Cl)cc(Cl)c(O)c1Cl ODEYONAEJYTJHV-UHFFFAOYSA-N	
SYN547891	3-(difluoromethyl)-*N*-methoxy-*N*-[(2*RS*)-1-(2,4,6-trichlorophenyl)-2-propanyl]-1*H*-pyrazole-4-carboxamide O=C(c1c[NH]nc1C(F)F)N(OC)C(C)Cc1c(Cl)cc(Cl)cc1Cl WAXZXWQXMFACEE-UHFFFAOYSA-N	
SYN548264	*N*-{[3-(difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl]carbonyl}-DL-alanine FC(F)c1nn(C)cc1C(=O)NC(C)C(=O)O DVRMRMCORDZSTP-UHFFFAOYSA-N	

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

[b]ACD/Name 2018.2.2 ACD/Labs 2018 Release (File version N50E41, Build 103230, 21 July 2018).

[c]ACD/ChemSketch 2018.2.2 ACD/Labs 2018 Release (File version C60H41, Build 106041, 7 December 2018).