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CONCLUSION ON PESTICIDES PEER REVIEW

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

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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 Poland and co-rapporteur Member State France for the pesticide active substance flufenacet are reported. In addition, the assessment of the confirmatory data following the Article 12 maximum residue limit (MRL) review of Regulation (EC) No 396/2005 is also reported. The context of the peer review was that required by Commission Implementing Regulation (EU) No 844/2012. The conclusions were reached on the basis of the evaluation of the representative use of flufenacet as a herbicide on winter cereals. Confirmatory data following the Article 12 MRL review were assessed. The reliable end points, appropriate for use in regulatory risk assessment and the assessment of confirmatory data following the Article 12 MRL review, are presented. Missing information identified as being required by the regulatory framework is listed. Concerns are reported where identified.

KEYWORDS

Art 12 confirmatory data, flufenacet, herbicide, 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. Flufenacet is one of the active substances listed in Regulation (EU) No 686/2012.

In accordance with Article 1 of the Regulation, the rapporteur Member State (RMS), Poland and co-rapporteur Member State (co-RMS), France, received an application from Bayer CropScience for the renewal of approval of the active substance flufenacet. In addition, Bayer CropScience submitted an application for the assessment of confirmatory data following the Article 12 maximum residue limit (MRL) review of Regulation (EC) No 396/2005. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicant, the co-RMS (France), the European Commission and the European Food Safety Authority (EFSA) about the admissibility.

An initial evaluation of the dossier on flufenacet 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 use of flufenacet according to the representative uses as a herbicide on wheat, barley and rye as proposed at EU level results in a sufficient herbicidal efficacy against the target weeds according to the representative uses proposed at the European Union (EU) level.

The assessment of the data package revealed no issues that could not be finalised or that need to be included as critical areas of concern with respect to **identity, physical–chemical and technical properties** of the active substance and the representative formulation and **analytical methods**.

In the area of **mammalian toxicology** and non-dietary exposure, critical areas of concern were not identified. A data gap regarding the toxicological assessment of a groundwater metabolite (FOE trifluoroethanesulfonic acid) leads to the groundwater relevance assessment not being finalised.

In the area of **residues**, several data gaps have been identified resulting in the consumer risk assessment not finalised. The confirmatory data following Article 12 MRL review have been addressed.

The data available on **environmental fate and behaviour** for flufenacet and its transformation products 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 the water treatment process chlorination (other than the non-formation of haloacetonitriles and halonitromethanes) on the nature of residues potentially present in surface water and groundwater, when surface water or groundwater are 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. With the available FOCUS modelling, groundwater exposure (80th percentile annual average recharge concentrations moving below 1 m) above the parametric drinking water limit of 0.1 µg/L was indicated for the groundwater metabolites FOE oxalate, FOE sulfonic acid, FOE methylsulfone, FOE trifluoroethanesulfonic acid and trifluoroacetic acid. The groundwater metabolite relevance assessment was not finalised for any of these metabolites except for FOE methylsulfone, which was concluded as being not relevant. The non-relevance could not be concluded for the other metabolites due to the data gaps identified in the area of residues and a data gap in toxicology.

In the area of **ecotoxicology** a critical area of concern for aquatic organisms (algae) was identified. High risk was also identified for some of the representative uses for birds, bees and earthworms.

An assessment not finalised was identified as the formulation for the representative uses contains the active substance diflufenican and the RMS assessment report did not include exposure and risk assessments for this active substance from the representative uses. It is noted that EFSA used information from a previous EFSA assessment of diflufenican to conclude on human non-dietary exposure assessment to the product for representative uses.

Regarding the assessment of the **endocrine disruption** (ED) properties, overall, it was concluded that, for humans and wild mammals, flufenacet meets the criteria for the thyroid (T)-modality 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. Flufenacet was not considered to meet the ED criteria for the oestrogen, androgen and steroidogenesis (EAS)-modalities for humans and non-target organisms.

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 Poland and co-RMS France received an application from Bayer CropScience for the renewal of approval of the active substance flufenacet. In addition, Bayer CropScience submitted an application for the assessment of confirmatory data following the Article 12 maximum residue level (MRL) review of 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 (France), the European Commission and EFSA about the admissibility.

The RMS provided its initial evaluation of the dossier on flufenacet in the RAR, which was received by EFSA on 7 June 2017 (Poland, 2017). The RAR included an assessment of the confirmatory data identified in the context of the MRL review under Article 12 of Regulation (EC) No 396/2005.

In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicant, Bayer CropScience, for consultation and comments on 20 September 2017. EFSA also provided comments. In addition, EFSA conducted a public consultation on the RAR. EFSA collated and forwarded all comments received to the European Commission on 24 November 2017. 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 26 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, environmental fate and behaviour and ecotoxicology.

The outcome of the telephone conference, together with EFSA's further consideration of the comments, is reflected in the conclusions set out in column 4 of the reporting table. All points that were identified as unresolved at the end of the comment evaluation phase and which required further consideration, including those issues to be considered in 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, were reported in the final column of the evaluation table.

Commission Regulation (EU) 2018/605[5] introduced new scientific criteria for the determination of endocrine-disrupting (ED) properties, applicable as of 10 November 2018 to all applications for the approval/renewal of active substances, including pending applications. The peer review on the active substance flufenacet was already in an advanced stage at the time of entry into force of the new criteria, and an assessment of the ED potential in line with the EFSA/ECHA (2018) guidance document for this substance was not available. Therefore, EFSA has performed an assessment of the ED properties of the active substance flufenacet in line with the EFSA/ECHA (2018) guidance for further consideration in the peer review.

Following a consultation with Member States in the Pesticides Peer Review Experts' meeting 05 Mammalian toxicology–Ecotoxicology (joint session on endocrine disruption) (7–8 May 2019), it was considered necessary to apply an additional

[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, p. 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. OJ L 278, 8.11.2018, p. 3–6.

[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, p. 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, p. 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, p. 33–36.

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, are met.

Therefore, in accordance with the provisions of Commission Regulation (EU) No 2018/1659, in June 2019, the applicant was given the opportunity to submit, within a period of up to 30 months, additional information to address the approval criteria set out in point 3.6.5 and/or 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) No 2018/605, and/or documentary evidence demonstrating that flufenacet may be used such that exposure is negligible, and/or the conditions for application of the derogation under Article 4(7) of Regulation (EC) No 1107/2009 are met. The additional information submitted by the applicant was subsequently evaluated by the RMS.

A public consultation on the revised RAR on the endocrine properties assessment made available by the RMS after the 30-month clock stop (Poland, April, 2022) was conducted in May–August 2022. All comments received, including those from the applicant, Member States and EFSA, were collated in the format of a reporting table and were considered during the finalisation of the peer review. As a result of the public consultation, the need for an additional experts' consultation in the area of mammalian toxicology and ecotoxicology was identified.

The toxicity of the metabolite trifluoroacetic acid (TFA) was the subject of a notification falling under Article 56 of Regulation (EC) No 1107/2009 concerning information on potentially harmful or unacceptable effects, submitted on 7 January 2021 to EFSA, the European Commission and Member States by the notifier Bayer of the REACH registration dossier on TFA and the REACH lead registrant and producer of TFA under Regulation (EC) No 1907/2006 (which later became the TFA task force - BASF, Bayer, Corteva, Syngenta). The notification concerned adverse developmental effects in rabbits after exposure to the metabolite TFA observed in a development toxicity study. In view of determining the human relevance of these developmental effects specific to rabbits, follow-up in vitro and in vivo studies were carried out under Regulation (EC) No 1907/2006. Since at the time of conducting the peer review process on the renewal of approval of flufenacet, these follow-up investigations were still ongoing, the data submitted as part of this Article 56 notification were not taken into account in this present conclusion.

A final consultation on the conclusions arising from the peer review of the risk assessment and on the confirmatory data following the Article 12 MRL review, took place with Member States via a written procedure in May–June 2024.

This conclusion report summarises the outcome of the peer review of the risk assessment of the active substance and the formulation for representative uses, evaluated on the basis of the representative use of flufenacet as a herbicide on winter cereals, as proposed by the applicant. In accordance with Article 12(2) of Regulation (EC) No 1107/2009, risk mitigation options identified in the RAR and considered during the peer review are presented in the conclusion. Confirmatory data following the Article 12 MRL review were assessed. A list of the relevant end points for the active substance and the formulation and the assessment of confirmatory data following the Article 12 MRL review is provided in Appendix B. In addition, the considerations as regards the cut-off criteria for flufenacet 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 (26 January 2018 and 9 September 2022[6]);
- the evaluation table (24 July 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 EFSA ED assessment[7];
- the comments received on the draft EFSA conclusion completion according to Commission Implementing Regulation (EU) No 2018/1659.

Given the importance of the RAR, including its revisions (Poland, 2017, 2022, 2023), the peer review report (EFSA, 2024), and the EFSA ED assessment (EFSA, 2019), all these documents are considered as background documents to this conclusion and thus are made publicly available.

It is recommended that this conclusion 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.

[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]ED assessment performed by EFSA before the timepoint of the ED additional information request (stop of the clock). The ED assessment including evaluation of the newly provided additional information on the endocrine disruption properties following the ED clock stop is available in the revised RAR (Poland, 2023) with the final outcome presented in the current EFSA Conclusion (see Section 6).

THE ACTIVE SUBSTANCE AND THE PRODUCT FOR THE REPRESENTATIVE USES

Flufenacet is the ISO common name for 4′-fluoro-*N*-isopropyl-2-{[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]oxy}acetanilide (IUPAC).[8]

The formulated product for the representative uses was 'DFF+FFA SC 600', a suspension concentrate (SC) containing 400 g/L flufenacet and 200 g/L diflufenican.[9]

The information on the active substance and the formulation 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,[10] nor considered as an active substance in accordance with Regulation (EC) No 1107/2009. Details on the composition of the formulation cannot be reported in conclusions because of the provisions in Article 63(2)(d) of Regulation (EC) No 1107/2009, however this information was fully available and evaluated during the peer review. A proposal for classification of the formulation according to Regulation (EC) 1272/2008 was provided by the applicant and assessed by the RMS (please see Volumes 3 CP of the RAR).

The representative uses evaluated were spray applications on wheat, barley and rye (pre- and early post emergence) to control annual grasses and broad-leaved weeds. Full details of the GAPs can be found in the list of end points in Appendix B.

Data were submitted to conclude that the use of flufenacet results in a sufficient herbicidal efficacy against the target weeds according to the representative uses proposed at EU level, following the guidance document SANCO/2012/11251-rev. 4 (European Commission, 2014b).

CONCLUSIONS OF THE EVALUATION

General aspects

With regard to the mammalian toxicity information available for the formulation for representative uses 'DFF+FFA SC 600', studies were performed for acute toxicity endpoints. With regard to the co-formulants contained in 'DFF + FFA SC 600', sufficient toxicological data were available for all components, but one (present at levels well below 10% of the formulation). EFSA considered that the available toxicological information for this component does not sufficiently address the genotoxicity and repeated dose toxicity potential of 'DFF+FFA SC 600' over short- and long-term exposure and may be considered for further assessment. It is noted that collected information (not covering all endpoints), including the existing approved uses other than plant protection products, under EU regulated frameworks, did not highlight any additional concern (see Section 10). Regarding ecotoxicology, suitable data with the formulation for representative uses were available for the assessment of non-target organisms according to the requirements of Regulation (EU) No 284/2013.[11] Based on the available toxicity data, it is noted that the formulation for representative uses is not more acutely toxic than the active substance. No chronic data with the formulation for representative uses were available with the exception of algae, aquatic plants, earthworms, soil macro-organisms. Therefore, available data for the individual components were retrieved. No additional chronic data were found, except for one of the components for which chronic data with fish and invertebrates were available. Overall, pending on the outcome on the data gap identified in mammalian toxicology for one component in the formulation for representative uses, further consideration to non-target organisms may be necessary.

A search of the scientific peer-reviewed open literature on the active substance and its relevant metabolites, dealing amongst others with side-effects on human health was conducted by the applicant; however, the assessment of the reliability and relevance of the literature on human health was not reported by the RMS in the RAR, leading to a data gap (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 flufenacet is based on batch data from industrial plant production and quality control data. The proposed minimum purity of the technical material is 970 g/kg. Toluene is considered as a relevant impurity with a maximum level of 1 g/kg. It should be noted that the assessment of the toxicological relevance of the other impurities is not concluded (see Section 2) and consequently, new data such as spectral data, content of the impurities in the

[8]It should be noted that flufenacet, some of its metabolites (those indicated with an * in Appendix D) and diflufenican are identified as compounds that meet the definition of per- and polyfluoroalkyl substances (PFAS) based on their chemical structure (https://echa.europa.eu/hot-topics/perfluoroalkyl-chemicals-pfas).

[9]Peer review process for the renewal of the approval is ongoing (EFSA-Q-2016-00266).

[10]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, p. 7–26.

[11]Commission Regulation (EU) No 284/2013 of 1 March 2013 setting out the data requirements for plant protection products, in accordance with 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 93, 3.4.2013, p. 85–152.

formulation before and after the storage and methods for analysis of the relevant impurities in the formulation might be required. There is no FAO specification available for flufenacet.

The batches used in the toxicological assessment support the proposed renewal specification (see Section 2). The information to support the compliance of the batches used in ecotoxicological studies with the proposed renewal specification and the original reference specification was considered insufficient (see Section 5). It is proposed that the reference specification of the first approval (that was based on the data from the pilot plant scale production) be updated (i.e. higher minimum purity of the active substance, new relevant impurity and lower levels for some of the significant impurities).

The main data regarding the identity of flufenacet and its physical and chemical properties are given in Appendix B. A data gap for the content of the relevant impurity before and after the storage of the plant protection product was identified (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 in the formulation for the representative uses and for the determination of the respective impurities in the technical material. However, a data gap for a method for determination of toluene in the formulation was defined (see Section 10).

The components of the residue definition (flufenacet (sum of all metabolites containing the N-fluorophenyl-*N*-isopropyl moiety, expressed as flufenacet)) in food and feed of plant origin can be monitored by high performance liquid chromatography with a tandem mass spectrometry (HPLC–MS/MS) with a limit of quantification (LOQ) of 0.05 mg/kg for straw and 0.01 mg/kg for the other commodity groups, both expressed as flufenacet.

The components of the residue definition (flufenacet (sum of all metabolites containing the N-fluorophenyl-*N*-isopropyl moiety, expressed as flufenacet)) in food of animal origin can be determined by gas chromatography–mass spectrometry (GC–MS) after derivatisation of the common moiety 4-fluoro-N-isopropylaniline to 2,2,2-trifluoro-N-(4-fluorophenyl)-N-isopropylacetamide with LOQs of 0.05 mg/kg in muscles, kidney, fat and eggs, 0.01 mg/kg in milk and 0.02 mg/kg in liver, all expressed as flufenacet.

Flufenacet in soil can be monitored by HPLC–MS/MS with a LOQ of 2 µg/kg. Flufenacet in drinking and surface water can be monitored by HPLC–MS/MS with a LOQ of 0.05 µg/L. It should be noted that the residue definition for surface water is open (see Section 5) and as a consequence new monitoring methods might be required in case additional components are included. A method for monitoring residues in air that covers the proposed residue definition is required (data gap, see Section 10).

HPLC–MS/MS method can be used for monitoring of flufenacet and FOE thiadone residues in body fluids with a LOQ of 50 µg/L (as parent equivalents). A method for monitoring residues in body tissues that covers the proposed residue definition is required[12] (data gap, see Section 10).

2 | MAMMALIAN TOXICITY

The toxicological profile of the **active substance** flufenacet was discussed at the Pesticides Peer Review Experts' Meeting 179 (June 2018) and TC 99 (March 2023) and assessed based on the following guidance documents: European Commission (2003a, 2012), EFSA PPR Panel (2012), and ECHA (2017).

The batches used in toxicity studies were representative of the proposed renewal reference specification[13] for the active substance and associated impurities (see Section 1). Toluene is a relevant impurity but not of concern at the maximum levels of the proposed specification (i.e. 1 g/kg). For other impurities, a conclusion cannot be drawn based on the limited data reported in the RAR (data gap, see Section 10). The analytical method used in toxicity studies were considered fit for purposes.

In **toxicokinetic** studies, flufenacet was extensively and rapidly absorbed. Oral absorption was estimated to be greater than 90%. There was no evidence for accumulation. Excretion of flufenacet was predominantly through urine. The main metabolic pathway identified was cleavage of the molecule, glutathione conjugation of the arylacetamide moiety and degradation of the thiadiazole ring. No unique human metabolite is expected based on a comparative in vitro metabolism study with rat and human microsomes.

In **acute toxicity** studies, the substance has moderate acute toxicity when administered orally, and low acute toxicity when administered dermally or by inhalation to rats. It is not a skin or eye irritant but a skin sensitiser. Flufenacet is not phototoxic in the 3T3 NRU-PT test. However, flufenacet is mainly a UVB absorber and the 3T3 NRU-PT test might not be suitable to test UVB absorber leading to a data gap (see Section 10).

In **short-term** oral toxicity studies with rats, mice and dogs, the target organs of toxicity were liver, thyroid, kidney, the haematopoietic and nervous system. The relevant overall short-term oral no observed adverse effect level (NOAEL) is 1.14 mg/kg bw per day (1-year dog study).

Based on available genotoxicity studies the substance is unlikely to be genotoxic. Photomutagenicity testing is not required.

[12]See MS comments on draft EFSA conclusion (EFSA, 2024).

[13]An assessment on whether the batches used in toxicity studies were representative of the original specification was not presented in the RAR (however, considering the compliance with the new reference specification a data gap was not identified).

In **long-term toxicity** and **carcinogenicity** studies with rats and mice the target organs of toxicity were liver, thyroid, eye and kidney. The rat was the most sensitive species. The relevant long-term lowest observable adverse effect level (LOAEL) is 1.2 mg/kg bw per day (2-year rat study; a NOAEL could not be derived). The substance showed no carcinogenic potential in both species.

Reproductive toxicity studies included a screening test, a 2-generation study and a comparative thyroid assay (CTAs). The relevant NOAELs of 6.6 mg/kg bw per day for parental and offspring toxicity were identified in the CTAs whereas the relevant NOAEL of 37.45 mg/kg bw per day for reproductive toxicity was identified in the 2-generation study. Fertility and overall reproductive performance were not impaired; reduced body weights/body weight gains, changes in thyroid hormones and in thyroid histopathology were observed in both dams and/or offspring in the CTAs. In this study, no higher sensitivity of the pups was observed when compared to adults for changes in thyroid hormones (THs), thyroid stimulating hormone (TSH) and thyroid histopathology. In the **developmental toxicity** studies, there was no evidence of teratogenicity and the relevant maternal NOAELs are 25 mg/kg bw per day for the rat and 5 mg/kg bw per day for the rabbit. Based on reduced body weight and skeletal variations in rat and rabbit, the developmental NOAEL is 25 mg/kg bw per day for both species.

Flufenacet induced axonopathy and axon swelling in the 1-year dog study and in toxicity studies in rats. The metabolite FOE thiadone (M09, thiadiazole moiety) could be responsible for these effects (at least in dogs). In the developmental neurotoxicity (DNT) study, the agreed maternal NOAEL is 1.7 mg/kg bw per day, based on the reduced bodyweight gain and reduced food consumption, whereas the developmental LOAEL is 1.7 mg/kg bw per day (a NOAEL could not be derived), based on the reduced body weight and body weight gain and delayed development (eyes opening). Morphometric changes in the linear measurements of the caudate putamen area were also observed in female rats at PND 72 from the low dose of 1.7 mg/kg bw per day and considered adverse (see Section 6).

The pesticide mode of action of flufenacet involves inhibition of the biosynthesis of very long chain fatty acids. This mechanism could operate in mammals and could be involved in the neurotoxicity and other toxicity findings observed in several species associated to lipotoxicity and metabolism of fatty acids, although no specific studies are available on mammals. Potential for **immunotoxicity** was not observed in the available toxicity studies.

The reassessment of the toxicological profile of flufenacet leads to a revision of the existing[14] acceptable operator exposure level (AOEL) and acceptable daily intake (ADI) but the acute reference dose (ARfD) remained the same (not based on the same study) (European Commission, 2003b). An acute acceptable operator exposure level (AAOEL) is newly proposed as it was not derived during the first peer review process.

The agreed **ADI** is 0.004 mg/kg bw per day on the basis of the relevant long-term LOAEL of 1.2 mg/kg bw per day in the 2-year study in rats based on renal pelvic mineralisation. An additional uncertainty factor (UF) of 3 (because of the use of a LOAEL) in addition to the standard UF of 100 was applied.

The agreed **ARfD** is 0.017 mg/kg bw on the basis of the maternal NOAEL of 1.7 mg/kg bw per day in the DNT study in rats based on body weight decrease during the first days of treatment observed at 3 mg/kg bw per day. An UF of 100 was applied.

The agreed systemic **AOEL** is 0.006 mg/kg bw per day on the basis of the developmental LOAEL of 1.7 mg/kg bw per day in the DNT study in rats based on the reduced body weight and body weight gain, on the delayed development (eyes opening) and changes in the linear measurements of the caudate putamen area in female rats at PND 72. An additional UF of 3 (because of the use of a LOAEL) in addition to the standard UF of 100 was applied.

The **AAOEL** is 0.017 mg/kg bw on the same basis as the ARfD.

Flufenacet met the criteria for endocrine disruption (ED) (see Section 6); overall, the toxicological reference values (ADI, AOEL, AAOEL and ARfD) are not impacted. The lowest NOAEL for the ED endpoint is 2.19 mg/kg bw per day (see Section 6). Therefore, the toxicological reference values are considered covering the endocrine effects.

The RMS and EFSA estimated **non-dietary exposure**[15] to flufenacet (i.e. operator, worker, bystander and resident) considering dermal absorption values of flufenacet in 'DFF+FFA SC 600' of 0.2% for the concentrate and of 5% for the dilution as input values.[16]

Considering the representative uses of 'DFF+FFA SC 600' as a herbicide in winter cereals the maximum estimated operator exposure was below the AOEL (37% of the AOEL) without the use of personal protective equipment (PPE) according to the German Model. According to the EFSA Guidance (EFSA, 2014) operator exposure was below the AOEL (47.7%) and AAOEL (99.7%) without the use of personal protective equipment PPE, while in the case gloves and coverall are worn, the above values are respectively 7% of the AOEL and 28.5% of the AAOEL. Worker exposure (scouting) was below the AOEL without the use of gloves (47% of the AOEL, EUROPOEM model). Bystander and resident exposure was below the AOEL (maximum 9.3% of the AOEL; adult bystander, 1 meter buffer distance, German model[17]). According to the EFSA Guidance

[14]ADI of 0.005 mg/kg bw per day and AOEL and ARfD of 0.017 mg/kg bw (per day) (European Commission, 2003b).

[15]The acute exposure estimates for operators (% of AAOEL) and the exposure estimates for all pathways for resident and bystander have been calculated by EFSA (EFSA, 2014) following a comment made by DE during the written procedure on the draft conclusion and background documents (EFSA, 2024).

[16]The dermal absorption values were agreed during the experts' meeting checking the raw data. Please refer to the report of the meeting, experts' consultation 2.14 (EFSA, 2024).

[17]It is noted that the original German approach (Martin et al., 2008) is no longer scientifically supported. Nevertheless, bystanders and resident exposure is not expected to be above the AOEL according to other models including the UK approach since exposure according to the EFSA model is below the AOEL for all exposure groups (maximum 87% of AOEL, child resident, sum of all pathways, 2–3 m distance). Therefore, the figures according to Martin et al., 2008 are given for informative purposes only.

(EFSA, 2014), exposure estimates are below the (A)AOEL for resident and bystander, child and adult (maximum 87% of AOEL, child resident, sum of all pathways, 2–3 m distance and 27.5% of AOEL, adult resident, sum of all pathways, 2–3 m distance). The RMS provided additional calculations according to the EFSA Guidance (EFSA, 2014) in the RAR indicating exposure below the (A)AOEL for all exposure groups (Poland, 2023). It is noted that the RMS did not conduct a combined exposure assessment for flufenacet and diflufenican. The non-dietary exposure estimates for diflufenican assessed during the peer review (EFSA, 2007) for the same representative uses indicated exposure below the AOEL[18] for diflufenican (3.3% of the AOEL according to German model for operator, worker exposure 3% of the AOEL according to EUROPOEM model and 0.1% of the AOEL according to Lloyd & Bell, 1983). Given that the same representative use was assessed during the peer review on diflufenican, similar models were used and the resulting % of the respective AOELs; EFSA considered it unlikely that combined exposure to both flufenacet and diflufenican would be of concern considering potential additive effects.

During the Pesticides Peer Review Experts' Meeting 179, only the genotoxic potential of metabolites FOE oxalate (M01), FOE sulfonic acid (M02) and FOE methylsulfone (M07) was discussed. No further discussion took place on the assessment of metabolites during the experts' meeting given that a complete RMS' assessment was only provided after the experts' meeting. The following assessment reflects EFSA's view. EFSA noted that a Member State[19] considered that the grouping and read-across as proposed by EFSA should be further substantiated (particularly, the toxicological impact of the non-common moiety of each compound was not discussed).

Toxicological studies were submitted for some of the **metabolites** found in groundwater or as residues in crops or livestock. The toxicological profile of these metabolites was assessed based on grouping and read-across. The evidence supporting grouping and read-across was based on the mammalian metabolism of the parent, the common moiety, toxophore and specific experimental data[20] on the metabolites.

Metabolite FOE oxalate (M01) is not a rat metabolite. It is unlikely to be genotoxic. It is less bioavailable than the parent and it is rapidly excreted from rats/mammals without undergoing metabolic conversion. For grouping of metabolites it could be considered one of the representative plant metabolites arising from the *N*-fluorophenyl-*N*-isopropyl moiety of the parent compound flufenacet.

Metabolite FOE sulfonic acid (M02) is a minor rat metabolite. It is of low acute oral toxicity and it is unlikely to be genotoxic. It is poorly absorbed after oral administration. For grouping of metabolites it is also considered as one of the representative plant metabolites arising from the *N*-fluorophenyl-*N*-isopropyl moiety of the parent compound flufenacet.

Metabolite FOE methylsulfone (M07) is a minor rat metabolite. It is unlikely to be genotoxic. No further toxicity studies are available. For grouping it is considered within the group of metabolites containing the *N*-fluorophenyl-*N*-isopropyl moiety.

Metabolite FOE-thioglycolate sulfoxide (M04) is not mutagenic in the bacterial gene mutation assay. For grouping it is considered within the group of metabolites containing the *N*-fluorophenyl-*N*-isopropyl moiety.

Considering experimental data on metabolites containing the *N*-fluorophenyl-*N*-isopropyl moiety (Metabolite FOE oxalate (M01), FOE sulfonic acid, FOE-thioglycolate sulfoxide and FOE methylsulfone) and taking into account that some major rat metabolites (FOE S-oxo cysteine (M12) and FOE des-i-propyl methylsulfone (M15)) contain the *N*-fluorophenyl-*N*-isopropyl moiety or are derived from this moiety, these metabolites (M01, M02, M04, M07, M12, M15) are considered unlikely to be of higher toxicity than the parent. In case it is needed, their toxicity can be considered covered by that of the parent (i.e. reference values of the parent apply to these metabolites if needed).

Experimental data supported that the metabolite FOE thiadone (M09) could be responsible for some of the effects observed for flufenacet treatment at high doses (i.e. the thiadiazole moiety could be considered a toxophore). It is of moderate acute oral toxicity and it does not show any mutagenic potential in the Ames test. It might be considered a major rat metabolite (close to 10%; higher than 20% when considering two of its conjugated downstream metabolites M26 and M24), thus, it is considered covered by the toxicity of the parent compound. The conjugated metabolites of FOE thiadone (oxalylacetic acid conjugate (M26)), glucuronic acid conjugate (M24), *N*-glucoside conjugate (M25) and malonylalanyl conjugated (M34)[21]) are considered covered by the toxicity of FOE thiadone and therefore, by the parent compound (i.e. reference values of the parent apply to these metabolites if needed).

The metabolite trifluoroacetic acid (TFA) is a groundwater metabolite and is found as well in crops and livestock. In the environment and in crops it is present with a counter ion. Toxicological studies have been conducted using the salt of trifluoroacetic acid, e.g. sodium trifluoroacetate. Trifluoroacetate is a major rat metabolite coming from the degradation of the thiadiazole moiety (around 10%). Sodium trifluoroacetate is of low acute oral toxicity and neither mutagenic nor clastogenic; however, aneugenicity was not investigated (data gap, see Section 10). Reference values for consumer risk assessment have been previously peer reviewed by EFSA. An ADI of 0.05 mg/kg bw per day (expressed as sodium trifluoroacetate) was derived and an ARfD was deemed unnecessary (EFSA, 2017). According to the latest scientific state of the art (EFSA Scientific Committee, 2021[22]) the derivation of reference values could be affected by the conclusion on aneugenicity.

[18]EFSA noted that during the renewal of diflufenican the same AOEL value for diflufenican was kept (i.e. 0.11 mg/kg bw per day) (EFSA-Q-2016-00266).

[19]Flufenacet_MS comments on draft EFSA conclusion (EFSA, 2024).

[20]It is noted that there are no repeated toxicity data on metabolites other than for trifluoroacetic acid.

[21]It is noted that M25 and M34 are N-conjugated compounds and according to the RAR, hydrolysis to the aglycon is not expected. However, it is not expected that these conjugates will be of higher toxicity than M09.

[22]The Standing Committee on Plants, Animals, Food and Feed agreed that the EFSA GD should apply to dossiers submitted from 1 January 2023 onwards, in the context of (renewal of) approval of active substances under Regulation (EC) No 1107/2009.

However, this has not been discussed during the peer review of flufenacet since the EFSA Scientific Opinion on the guidance on aneugenicity assessment (2021) was not available at the time of the dossier submission and experts' consultation (June 2018). In addition, a CLH proposal for reproductive toxicity has been sent to the ECHA,[23] based on a new developmental toxicity study,[24] having a potential impact on the relevance assessment as a groundwater metabolite (see Section 7) and as a residue (since the effects observed in the developmental toxicity may trigger the need to set an ARfD).

The metabolite FOE trifluoroethanesulfonic acid (M44) is coming from the degradation of the thiadiazole moiety but not formed in rat. It is unlikely to be genotoxic. Available data did not allow read-across from the parent). No further toxicity studies are available allowing to set reference values leading to a data gap and groundwater relevance assessment that could not be finalised, see Section 9.1.1.

3 | RESIDUES

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

Flufenacet was discussed at the Pesticides Peer Review Experts' Meeting 180 in June 2018.

3.1 | Representative use residues

Metabolism in primary crops was investigated in studies with flufenacet radiolabelled in three different ring-positions (fluorophenyl ring and thiadiazole-ring in position 2 and position 5) in cotton, soybean (pulses and oilseeds category) applied pre-emergence, potato (root and tuber category) pre-and post-emergence; maize pre- and post-emergence / wheat (cereal/grass category) post-emergence. The data show a clear difference between the thiadiazole- and the fluorophenyl-label studies in terms of the identified residues regardless of pre- and post-emergence scenarios. In the studies with fluorophenyl-labelled flufenacet, metabolites containing the *N*-fluorophenyl-*N*-isopropyl moiety (e.g. FOE oxalate (M01), FOE sulfonic acid (M02) and FOE thioglycolate sulfoxide (M04)) were identified in significant proportions. In the study with 5-thiadiazole ^{14}C radiolabelled flufenacet almost exclusively trifluoroacetic acid (TFA) (M45) was identified and in the study with 2-thiadiazole ^{14}C radiolabelled flufenacet metabolites with the intact thiazoline ring (FOE thiadone N-glucoside (M25) and FOE thiadone malonylalanyl conjugate (M34)) were predominant. Confined rotational crop studies with all three labels confirm the metabolic pattern observed in primary crops. The presented limited field rotational crops studies analysing for *N*-fluorophenyl-*N*-isopropyl moiety bearing metabolites and for TFA are not acceptable as they have major deviations from guidelines and lead to data gaps.[25] The design of the new studies should address the persistence of FOE sulfonic acid (M02) and TFA and their potential to accumulate in soil. On the basis of the primary and rotational crop metabolism studies the **residue definition for risk assessment** is set as 'Flufenacet (sum of all metabolites containing the *N*-fluorophenyl-*N*-isopropyl moiety expressed as flufenacet)' and separately, 'trifluoroacetic acid'. This proposal to consider TFA is based on the newly available data from the rotational crop study with trifluoroacetic acid. Although TFA is the predominant residue, it is not a specific marker, therefore the **residue definition for enforcement** is set as 'Flufenacet (sum of all metabolites containing the *N*-fluorophenyl-*N*-isopropyl moiety expressed as flufenacet)'.

A sufficient number of critical GAP compliant residue trials for the northern and southern zone analysing for the sum of all compounds containing the *N*-fluorophenyl-*N*-isopropyl moiety and supported by storage stability data were provided for the representative uses on cereals. Results of trifluoroacetic acid from residue field trials for the representative uses were not provided (data gap, see Section 9.1.1) nor are data available to address the storage stability of TFA in all crops which can be grown in rotation (data gap, see Section 10). In view of the residue levels in cereals a data gap is set for a study addressing the fate of the *N*-fluorophenyl-*N*-isopropyl moiety under the standard hydrolysis conditions at processing (see Section 10). Processing factors for cereal based processes (milling, backing, brewing and distilling) were derived only for compounds containing the *N*-fluorophenyl-*N*-isopropyl moiety.

Metabolism studies in goat and hen were conducted with ^{14}C flufenacet (both labels) and with metabolites FOE oxalate, thiadone *N*-glucoside (only in goat) and trifluoroacetic acid. Shortcomings (except in the study with trifluoroacetic acid) were the too short dosing time of 3 days and consequently no plateau in milk and egg was reached. The oxalate metabolite was not metabolised in any matrix whilst flufenacet was extensively metabolised mainly in eggs, muscle and liver. Thiadone *N*-glucoside was hardly detected whilst thiadone was predominant in all goat matrices, except in milk. The **residue definition for enforcement** is set as 'Flufenacet (sum of all metabolites containing the *N*-fluorophenyl-*N*-isopropyl moiety expressed as flufenacet)' and for **risk assessment** as 'Flufenacet (sum of all metabolites containing the *N*-fluorophenyl-*N*-isopropyl moiety expressed as flufenacet)' and separately 'trifluoroacetic acid'. A ruminant feeding study was conducted with FOE oxalate. Although compliant with GLP and current guidance documents, no information on the storage duration of the samples was provided (data gap, see Section 10). Quantifiable residues of FOE oxalate were found

[23]EFSA noted that trifluoroacetic acid is currently under the registry of classification and labelling (CLH) intentions under ECHA remit and further data might become available. https://echa.europa.eu/it/registry-of-clh-intentions-until-outcome/-/dislist/details/0b0236e188e6e587.

[24]Prenatal Developmental Toxicity Study in rabbits (OECD 414) from REACh registration dossier https://echa.europa.eu/de/registration-dossier/-/registered-dossier/5203.

[25]See Data requirement 3.15 in the evaluation table Section 3 (EFSA, 2024).

in muscle, fat, liver and kidney but not in milk. For TFA, ruminant feeding studies were triggered and pending information on the coverage of the PECsoil also poultry feeding studies might become necessary. In the absence of feeding studies, dietary burden for this substance was calculated using the transfer factors, which were derived from the animal metabolism study. A data gap was identified to further address residue levels in pollen and in bee products for human consumption resulting from residues taken up by honeybees from rotated crops at blossom (see Section 10).

The consumer risk assessment for the proposed uses of flufenacet has to consider 4 sources of exposure for flufenacet and its fluorophenyl-metabolites and for TFA: contribution through primary plants, rotational crops, animal commodities and through drinking water. Chronic and acute consumer dietary intake assessments were provisionally performed taking into account respectively, the STMR and highest residues from rotational plant and animal dietary sources. It should be noted that the assessment is not finalised and only indicative (see Section 9.1.1) due to uncertainties related to the coverage of the PECsoil for TFA and the lack of actual residue data from limited rotational crop field trials for flufenacet and its *N*-fluorophenyl-*N*-isopropyl moiety bearing metabolites and for TFA, and actual residue data for TFA in cereals grown as primary crop (see data gaps above). The calculated theoretical maximum daily intake (TMDI) for flufenacet and its *N*-fluorophenyl-*N*-isopropyl moiety bearing metabolites accounts for 22% of the ADI (WHO cluster diet B) for cereals. The international estimated short-term intake (IESTI) for flufenacet and its fluorophenyl-metabolites is exceeded in several diets from sweet corn (726%) and wheat (143%) when considering the highest residue of 1.68 mg/kg found after first rotation in wheat grain and downscaled from the rotational crop metabolism study with [fluorophenyl-UL ^{14}C] labelled flufenacet. However, taking the highest residue in grain (0.11 mg/kg) found in the primary crop residue trials will result in an IESTI of 48% from sweet corn. For TFA, the calculated TMDI from the available rotational crop experiments accounts for 31% of the ADI (UK toddler) when ADI is expressed as sodium trifluoroacetate.

An assessment of exposure for the groundwater metabolites FOE oxalate, FOE sulfonic acid and TFA was performed for adults, infants and children based on the default assumptions laid down in the WHO Guidelines (WHO, 2017) for drinking water quality. Altogether, the two metabolites containing the *N*-fluorophenyl-*N*-isopropyl moiety contribute together to 10, 29 and 43% of the ADI of flufenacet for adult, child and infant, respectively. It is noteworthy that the FOE sulfonic acid was the major contributor to the ADI of flufenacet with 9, 27 and 41% of ADI for adult, child and infant, respectively. TFA contributes with 8, 23 and 35% of ADI for adult, child and infant, respectively (calculation based on sodium trifluoroacetate). For the groundwater metabolite FOE trifluoroethanesulfonic acid a consumer risk assessment is triggered. However, a toxicological reference value could not be set (data gap, see Sections 2 and 9.1.1).

It is noted that in the present assessment the ADI for flufenacet was lowered (see Section 2) and a different residue definition for risk assessment was proposed as newly available data from the rotational crop study with trifluoroacetic acid were considered. The established MRLs under Article 12 of Regulation (EC) No 396/2005 and the overall consumer exposure and risk assessment might need to be revised. Furthermore, a MRL of 0.15 mg/kg for wheat, barley and rye was calculated. Although the same data from residue trials as in the Article 12 MRL review (EFSA, 2012) were considered, the proposed MRL in the context of the renewal is now higher as a newer version of the OECD-EU-MRL calculator was used. The decision to update the MRL and harmonise it is left to risk managers.

3.2 | Confirmatory data following Article 12 MRL review

When reviewing the existing MRLs for flufenacet (EFSA, 2012), EFSA identified some information as unavailable (data gaps) and derived tentative MRLs for those uses which were not fully supported by data but for which no risk to consumers was identified. Tentative MRL proposals have been implemented in the MRL legislation by Commission Regulation (EU) No 1127/2014,[26] including footnotes related to the data gap:

- An analytical method for enforcement of flufenacet residues in acidic commodities (strawberries, blueberries, cranberries, currants, gooseberries).

The assessment of confirmatory data following the Article 12 MRL review is provided in Appendix B.

An analytical method for the quantification of the total residue of flufenacet arising from the *N*-isopropyl-4-fluorophenylacetamide portion of the molecule by HPLC-MS/MS for commodities of high-water content (cereal foliage), high-starch content (grain), dry (straw), high-acid content (orange fruit), high-protein content (dry bean seed) and high-fat content (rape seed) matrices is available and addresses this data gap.

4 | ENVIRONMENTAL FATE AND BEHAVIOUR

Flufenacet was discussed at the Pesticides Peer Review Experts' Meeting TC 178 in May 2018.

[26]Commission Regulation (EU) No 1127/2014 of 20 October 2014 amending Annexes II and III to Regulation (EC) No 396/2005 of the European Parliament and of the Council as regards maximum residue levels for amitrole, dinocap, fipronil, flufenacet, pendimethalin, propyzamide and pyridate in or on certain products. OJ L 305, 24.10.2014, p. 47–99.

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, flufenacet exhibited low to medium persistence, forming the major (> 10% applied radioactivity [AR]) metabolites FOE oxalate, FOE sulfonic acid (both max. 26% AR) and trifluoroacetic acid (max. 81% AR), which exhibited low to moderate, low to high and very high persistence, respectively. The metabolites FOE methylsulfone (max. 7.6% AR, moderate to high persistence), FOE thiadone and FOE trifluoroethanesulfonic acid (both max. ca. 6% AR with low to moderate persistence) all reached levels that triggered exposure assessment. Mineralisation of the phenyl ring ^{14}C radiolabel to carbon dioxide accounted for 2.7%–39% AR after 48–100 days. This range for the 5-thiadiazole ^{14}C radiolabel was 4.5%–6.5% AR after 120–121 days. The formation of unextractable residues (not extracted by water followed by acidified acetonitrile or acetonitrile followed by acidified acetonitrile/water with or without microwave heating) for these radiolabels, respectively accounted for 16%–64% AR after 48–100 days and 11%–17% AR after 120–121 days. In anaerobic soil incubations flufenacet degraded more slowly than under aerobic conditions forming no novel metabolites compared to those formed under aerobic conditions. Flufenacet was stable to photolysis at the soil surface. Flufenacet exhibited medium to low mobility in soil. FOE sulfonic acid, FOE oxalate, FOE trifluoroethanesulfonic acid and trifluoroacetic acid all exhibited very high mobility. FOE methylsulfone exhibited high to medium mobility, whilst FOE thiadone exhibited very high to high soil mobility. There was no evidence that the adsorption of any of these compounds was pH dependent. In reliable field soil dissipation studies carried out at six sites in Germany, four in northern France, four in southern France and two in Italy (spray application to the soil surface on bare soil plots in spring or autumn, with plots either maintained bare or in which maize, sunflower or soya bean crops subsequently germinated or post emergence application to winter wheat) flufenacet exhibited moderate to medium persistence whilst FOE sulfonic acid exhibited high persistence. Sample analyses were carried out for the parent flufenacet, FOE alcohol, FOE oxalate and FOE sulfonic acid only. The levels determined for the metabolites, except FOE sulfonic acid were low and were insufficient to enable kinetic fitting except for FOE oxalate but from just one trial site. According to the data requirements FOE methylsulfone should have been investigated in soil field experiments, but this had not been done in the available experiments (data gap, see Section 10). The exposure assessments for the EU representative uses have been completed without this information using the available laboratory endpoints. Field study $DT_{50/90}$ values just represent dissipation as neither the study designs nor the kinetic fitting approach enabled a $DegT_{50}$ that eliminated surface processes to be estimated. The available weather data were also not conducive for normalising the field results to reference soil moisture and temperature conditions.

In lysimeter studies of 3 years duration carried out in Germany with applications in the first 2 years of 480 g/ha (2N) with flufenacet labelled in the phenyl ring, all chromatographically resolved identified components in leachate accounted for <0.1 µg/L, as annual average concentrations except for FOE sulfonic acid which was present at 0.149–0.589 µg/L. In comparable lysimeter studies where application in the first year was 480 g/ha but that in the second was 180 g/ha (0.75N) all chromatographically resolved identified components in leachate accounted for <0.1 µg/L, as annual average concentrations except for FOE sulfonic acid which was present at 1.355–1.616 µg/L over the first year. In the second year these FOE sulfonic acid concentrations were <0.1 µg/L.

In laboratory incubations in dark aerobic natural sediment water systems, flufenacet exhibited moderate persistence, forming the metabolites FOE thiadone (max. 82% AR in water and 4% in sediment), FOE methylsulfide (max. 8% AR in water and 3.5% in sediment), FOE methylsulfone (max. 6.5% AR in water and 1.4% in sediment), FOE oxalate (max. 4.8% AR in water and 0.6% in sediment) and FOE sulfonic acid (max. 3% AR in water and 0.6% in sediment). The unextractable sediment fraction (not extracted by acidified acetonitrile) was a sink for the phenyl ring ^{14}C radiolabel, accounting for 28–46% AR at study end (157 days). This range for the 2-thiadiazole ^{14}C radiolabel was 2%–7% AR (156 days). Mineralisation of the phenyl ring ^{14}C radiolabel accounted for only 1.5%–3.5% AR at the end of the study. This range for the 2-thiadiazole ^{14}C radiolabel was 15%–15.3% AR. Flufenacet was essentially stable in a laboratory sterile aqueous photolysis experiment. The necessary surface water and sediment exposure assessments (Predicted environmental concentrations (PEC) calculations) were carried out for the metabolites FOE oxalate, FOE sulfonic acid, FOE methylsulfone, FOE thiadone, FOE methylsulfide, FOE trifluoroethanesulfonic acid and trifluoroacetic acid 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 flufenacet, appropriate step 3 (FOCUS, 2001) calculations were available.[27] The available FOCUS surface water step 4 calculations had not used the final agreed soil degradation and adsorption values for flufenacet (data gap, the values used were slightly more conservative than the agreed values) but appropriately followed the FOCUS (FOCUS, 2007) guidance, with no-spray drift buffer zones of up to 20 m being implemented for the drainage scenarios (representing a 91%–93% spray drift reduction), and combined no-spray buffer zones with vegetative buffer strips of up to 20 m (reducing solute flux in run-off by 80% and erosion runoff of mass adsorbed to soil by 95%) being implemented for the run-off scenarios. The SWAN tool (version 4.0.1) was appropriately used to implement these mitigation measures in the simulations. However, risk managers and others may wish to note that whilst run-off mitigation is included in the step 4 calculations available, the FOCUS (FOCUS, 2007) report acknowledges that for substances with K_{Foc} < 2000 mL/g (i.e. flufenacet), the general applicability and effectiveness of run-off mitigation measures had been less clearly demonstrated in the available scientific literature than for more strongly adsorbed compounds.

The necessary groundwater exposure assessments were appropriately carried out using FOCUS (European Commission, 2014a) scenarios and the models PEARL 4.4.4 and PELMO 4.4.3.[28] The potential for groundwater exposure

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

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

from the representative uses by flufenacet and FOE thiadone 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. Metabolite FOE sulfonic acid was predicted to have 90th percentile annual average recharge concentrations moving below 1m depth above the parametric drinking water limit of 0.1 µg/L at all 9 FOCUS scenarios for all the representative uses. For metabolite FOE oxalate this situation was predicted for 4/9 FOCUS scenarios for autumn applications at 240 and 160 g/ha and 2/9 scenarios at 120 g/ha (spring applications at 160 and 120 g/ha were below 0.1 µg/L). For metabolite FOE methylsulfone this situation was predicted for autumn applications for 6/9 FOCUS scenarios at 240 g/ha, 5/9 scenarios at 160 g/ha and 2/9 scenarios at 120 g/ha. With spring applications this was predicted for 3/9 scenarios at 160 g/ha (below 0.1 µg/L at 120 g/ha). For metabolite FOE trifluoroethanesulfonic acid this situation was predicted for autumn applications for 7/9 FOCUS scenarios at 240, 6/9 scenarios at 160 and 120 g/ha. With spring applications this was predicted for 2/9 scenarios at 160 g/ha and 1/9 scenarios at 120 g/ha. Metabolite trifluoroacetic acid was predicted to have 90th percentile annual average recharge concentrations moving below 1m depth above 10 µg/L at all 9 FOCUS scenarios for autumn applications at 240 and 160 g/ha, and spring applications at 160 g/ha. This was the case for 7/9 scenarios for both autumn and spring applications at 120 g/ha. For all uses and all scenarios these concentrations were predicted to be above 0.1 µg/L. The groundwater relevance assessment for FOE trifluoroethanesulfonic acid could not be finalised whilst the available toxicological information was insufficient to set reference values (see Sections 2 and 9.1.1). The groundwater relevance assessment for FOE oxalate, FOE sulfonic acid and trifluoroacetic acid could not be finalised whilst the consumer risk assessment from both drinking water from groundwater sources and consumption from food commodities could not be finalised (see Sections 3 and 9.1.1). In addition, for trifluoroacetic acid the genotoxicity (aneugenicity) assessment is open, see Sections 2, 7 and 10.

The RMS presented appropriate information to address the effect of using ozone in 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. The conclusion of this consideration was that neither flufenacet nor any of its degradation products that trigger assessment (FOE oxalate, FOE sulfonic acid, FOE methylsulfone, FOE thiadone, FOE methylsulfide, FOE trifluoroethanesulfonic acid and trifluoroacetic acid), would be expected to undergo any substantial transformation due to ozone oxidation. The RMS also presented appropriate information to indicate it is unlikely that haloacetonitriles and halonitromethanes would be formed from any of these compounds by the water treatment processes for chlorination. However, the applicant has not addressed the potential for the formation of other possible chlorination transformation products. This has led to the identification of a data gap and results in the consumer risk assessment not being finalised (see Section 9.1.1).

The PEC in soil, surface water, sediment and groundwater for flufenacet and its metabolites that triggered assessment 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. PEC for diflufenican, included as a second active substance in the formulation for representative uses, and its transformation products are not available, leading to an assessment not finalised (see Section 9.1.1).

5 | ECOTOXICOLOGY

The risk assessment was based on the following documents: European Commission (2002a, 2002b), SETAC (2001), EFSA (2009), EFSA PPR Panel (2013) and EFSA (2013).

Several aspects of the risk assessment were discussed at the Pesticides Peer Review Experts' Meeting 181 in June 2018.

The metabolite trifluoroacetic acid was in the majority of the ecotoxicological studies tested as trifluoroacetate (Na salt). The risk assessment was performed by expressing hazard endpoints and exposure as acid equivalents.

The information to support the compliance of the batches used in ecotoxicological studies with the proposed renewal specification and the original reference specification was considered insufficient (data gap, see Section 10).

The representative formulation 'DFF+FFA SC 600' includes two active substances (flufenacet + diflufenican). It is acknowledged that a mixture risk assessment considering the two active substances in the formulation has not been presented, leading to an assessment not finalised (see Section 9.1.1).

Based on the available and agreed data and the Tier 1 risk assessment, low acute risk to **birds** was concluded for all the representative uses. Low long-term risk to birds was concluded for the representative use on wheat/barley at 160 g a.s./ha and on winter cereals (barley, wheat and rye) at 120 g a.s./ha. High chronic risk to birds was concluded for the representative uses on winter cereals (wheat, barley and rye) at 240 g a.s./ha. The available refinement based on the use of an experimentally derived DT_{50} was considered unreliable for use in risk assessment.[29]

Low acute and long-term risk to **mammals** was concluded for all the representative uses.

Acute and chronic toxicity data were available for the plant metabolite trifluoroacetic acid (TFA). Based on those data a low risk was concluded for all the representative uses. Many other metabolites were identified in plant metabolism studies. Considering all the available information such as metabolism in rat and hen and the available acute risk assessment for the parent, a low risk to birds and mammals when exposed to plant metabolites was concluded for all the representative uses.

[29]See expert consultation point 5.1 of the Pesticides Peer Review Experts' meeting 181 (EFSA, 2024).

A low risk for birds and mammals was concluded from exposure to contaminated water. A low risk via secondary poisoning was also concluded except for earthworm-eating birds for the representative uses on winter cereal (winter wheat, rye and barley) at 240 g a.s/ha. The available information to refine the risk was considered insufficient.[30]

Toxicity data were available for all the relevant aquatic taxa and the active substance flufenacet. The formulation for the representative uses was only tested with algae and aquatic macrophytes. Considering that algae and plants drive the risk assessment, this is considered acceptable. It has also to be noted that the risk assessment for algae was performed using the endpoint of the formulated product as surrogate of the active substances.[31] Based on the available Tier 1 data, a low risk for fish and aquatic invertebrates including sediment dwellers was concluded for all the representative uses of flufenacet by using FOCUS Step 2&3 PECsw, except for fish (chronic) in situation represented by the FOCUS scenario D2 for the representative uses on winter cereals (wheat, barley and rye) at 240 g a.s./ha. A high risk to algae was concluded for all the representative uses and the majority of the relevant FOCUS scenarios (eight out of nine). For the scenario D3, low risk to algae was concluded with the implementation of mitigation measures up to 20 m buffer zone for all representative uses. High risk to aquatic plants was concluded for eight out of nine relevant FOCUS scenarios for the representative uses on winter cereals (wheat, barley and rye) at 240 g a.s./ha and for six out of nine relevant FOCUS scenarios for the representative uses on wheat and barley at 160 g a.s./ha and for five out of nine FOCUS scenarios for the representative use on winter cereals (wheat, barley and rye) at 120 g a.s./ha. Mitigation measures up to 20 m buffer zone were needed to conclude a low risk for aquatic plants for the relevant FOCUS scenarios D3 and R1 for the representative uses on winter cereals (wheat, barley and rye) at 240 g a.s./ha and for the FOCUS scenarios R1, R3 and R4 for the representative uses on wheat and barley at 160 g a.s./ha and for the FOCUS scenarios R1 and R3 on winter cereals (wheat, barley and rye) at 120 g a.s./ha.[32] It has to be noted that the final agreed input values for flufenacet had not been used the available FOCUS surface water step 4 calculations and therefore the used values are slightly more conservative (see data gap in Section 4). To refine the risk assessment to algae and plants, a mesocosm study and a peak exposure study with *Lemna* sp. was available. The available mesocosm study was not considered suitable for its use in risk assessment due to many drawbacks.[33] Regarding the study with *Lemna* sp. under peak exposure conditions,[34] although the study was considered valid, a NOEC could only be derived. Since this is not in accordance with the recommendations given in the current Guidance Document (EFSA PPR Panel, 2013) for these types of studies, it was decided not to use it for risk assessment also considering that the NOEC was comparable to the Tier 1 endpoint.[34] Overall, considering the outcome of the Tier 1 risk assessment for algae a critical area of concern was identified (see Section 9.1.2). A chronic risk assessment to aquatic organisms covering the second active substance in the representative product was not available whilst PEC in surface water and sediment for diflufenican and its transformation products for the representative uses were not available (see Sections 4 and 9.1.1). However, a risk to algae is already indicated from exposure to flufenacet.

A low risk to aquatic organisms was concluded for the pertinent aquatic metabolites FOE oxalate, FOE methylsulfone, FOE methylsulfide and FOE trifluoroethanesulfonic acid. Based on a screening assessment, high risk to algae could not be excluded for the metabolite FOE thiadone and to plants for the metabolite FOE sulfonic acid (data gap, see Section 10). In addition, for the representative uses on winter wheat, barley and rye at 240 g a.s./ha high chronic risk to fish could not be excluded for the metabolite TFA (data gap, see Section 10).

Acute toxicity data were available with the active substance for honey **bees** and the formulation for honey bees and bumble bees. In addition, chronic data for adult honey bees and larvae with the active substance and two higher tier studies (one study according to Oomen et al., 1992 and one according to OECD 75, OECD, 2014) were also available. However, no chronic toxicity studies were available with the formulation for representative uses which includes two active substances (data gap, see Section 10). Moreover, the higher tier studies were conducted with a formulation containing only flufenacet which is different than the representative one and therefore can only be considered as additional information. The acute risk assessment was conducted both according to the SANCO guidance on terrestrial ecotoxicology (European Commission, 2002a) and EFSA guidance (2013). Based on the available data and risk assessment, a low acute risk to honeybees and bumblebees and a low risk to honeybee larvae was concluded. However, high chronic risk was identified for adult honey bees when exposed to the treated crop for the representative uses on winter cereals (wheat, barley and rye) at 240 g a.s./ha and from exposure to flowering weeds for all the representative uses. It has to be noted, however, that based on new available knowledge (EFSA, 2023), cereals are not considered attractive to bees. To refine the risk occurring from flowering weeds, a study on occurrence of flowering weeds in cereals fields was available. Overall, on the basis of the available data, it was concluded that the total ground cover of flowering weeds in winter cereals could be considered generally unlikely to exceed the trigger of 10% suggested in the EFSA guidance (2013). Therefore, the exposure to bees via this scenario could be considered of low relevance for these uses, in particular considering that flufenacet is applied for weed control pre-and post-emergence. However, it has to be noted that based on new knowledge (EFSA, 2023), the weed scenario is considered relevant for the representative use in winter cereals at 120 g a.s./ha at BBCH ≥20.

[30]See expert consultation point 5.1 of the Pesticides Peer Review Experts' meeting 181 (EFSA, 2024).

[31]See expert consultation point 5.3 of the Pesticides Peer Review Experts' meeting 181 (EFSA, 2024).

[32]For the representative use on wheat and barley, spring application, at 160 g a.s./ha and 120 g a.s/ha low risk was identified for 5 out of 9 relevant FOCUS scenarios with the implementation of up to 20 m n-spray buffer zone. However, since the GAP includes both autumn application and spring application, the overall outcome (worst case) is summarised in the main text.

[33]See expert consultation point 5.4 of the Pesticides Peer Review Experts' meeting 181 (EFSA, 2024).

[34]See expert consultation point 5.4 of the Pesticides Peer Review Experts' meeting 181 (EFSA, 2024).

No data were available on accumulative effects and sub-lethal effects (data gap, see Section 10). In addition, no data were available on wild bees other than bumble bees. Acute toxicity data on honeybees and the metabolite TFA were available. Based on those data, a low acute risk to honeybees was concluded. No information on other metabolites potentially formed in pollen and nectar was available (data gap, see Section 10).

Based on the Tier 1 risk assessment, a high risk for **non-target arthropods** was concluded. Extended laboratory studies and aged residues studies were available on different species. Those demonstrated that an aging time of 28 days is needed to show a potential for recovery of the most sensitive species. Based on this information and considering that a low off-field risk was concluded allowing for in-field re-colonisation, low risk for non-target arthropods is concluded.

Based on the available toxicity data with the formulation for the representative uses, a high risk for **earthworms** was identified for all the representative uses. A field study with the formulation for representative uses, conducted in October in Germany was available showing recovery of the earthworm population within 1 year after the treatment at an application rate of 240 g a.s./ha. Based on this study, a low risk is concluded for all the representative uses. However, uncertainty exists because the representative uses cover also application performed in spring while the study was conducted in autumn. Therefore, although the application rates of some of the representative uses (at 160 g a.s./ha and 120 g a.s./ha) are lower than the one tested in the field study, earthworm populations in spring may be more active and effects of flufenacet may be potentially more detrimental. Therefore, low risk to earthworms could not be concluded for the representative uses on wheat and barley at 160 g a.s./ha and on winter cereals (wheat, barley and rye) at 120 g a.s./ha (since those include both autumn and spring applications) based on the available data.

A low risk for other **soil macro-organisms** than earthworms and **soil microorganisms** was concluded for flufenacet. A risk assessment for diflufenican was not available whilst PEC in soil for diflufenican for the representative uses were not available (see Sections 4 and 9.1.1).

A low risk for soil organisms when exposed to the pertinent flufenacet soil metabolites was concluded. A risk assessment for diflufenican soil transformation products was not available whilst PEC in soil for these transformation products for the representative uses were not available (see Sections 4 and 9.1.1).

Based on the available data and the probabilistic risk assessment, low risk to **non-target terrestrial plants** was concluded with the implementation of 5 m buffer zone or 50% drift reduction for the representative uses on winter cereals (wheat, barley and rye) at 240 g a.s./ha and the representative use on wheat and barley at 160 g a.s./ha. For the representative use on winter cereals (wheat, barley and rye) at 120 g a.s./ha low risk is concluded without mitigation measures. It has to be noted that the conclusion is based on the use of the endpoint for the formulated product which includes 2 active substances. When the endpoint is recalculated in terms of content of flufenacet, the results are slightly more conservative.

Low risk to organisms involved in the **biological methods for sewage treatment** was concluded.

6 | ENDOCRINE DISRUPTION PROPERTIES

With regard to the assessment of the endocrine disruption (ED) potential of flufenacet **for humans and non-target organisms** according to the ECHA/EFSA ED guidance (2018), in determining whether flufenacet 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 flufenacet with the EAS- and T- signalling pathways using the available evidence in the dataset. Several aspects of the ED assessment were discussed at the Pesticides Peer Review Joint Experts' Meeting 05 (May 2019) and TC 99 (March 2023) including a follow-up written procedure (October 2023).

For humans, the **T-modality** was considered sufficiently investigated and a pattern of T-mediated adversity i.e. changes in thyroid weight and thyroid histopathology, and T-mediated endocrine activity i.e. changes in THs and TSH, were observed in studies of different duration and in different species (i.e. rat, mouse and dog). In mouse and dog, T-mediated adversity was observed at doses overcoming the maximum tolerated dose (MTD) but changes in endocrine activity were consistently reported at doses below the MTD.

In addition, the comparative thyroid assays (CTAs) conducted in the rat, support the conclusion that there is a perturbation of the hypothalamic pituitary thyroid (HPT) axis in the sensitive population. This was observed in dams and foetuses at gestation day (GD) 20, in dams at lactation day (LD) 21 and in pups at post natal day (PND) 10 and 21.

The postulated **mode of action** (**MoA**) indicated CAR/PXR induction as a plausible molecular initiating event (MIE) and Phase I/II enzymes induction as plausible downstream intermediate key events (KEs), whereas increase Uridine Diphosphate glucuronyltransferase (UDP-GT) activity was observed in male rats. In addition, there is evidence of decreased liver deiodinase activity in male rats.

Moreover, it is noted that flufenacet was discussed as part of the OECD Integrated Approaches to Testing and Assessment (IATA) case study in 2022 (OECD, 2022). In the case of flufenacet, developmental neurotoxicity (DNT) study (OECD TG 426, OECD, 2007) was considered as positive and of concern because flufenacet is negative in the DNT in vitro battery (IVB) and therefore a thyroid mediated MoA (i.e. DNT changes consequent to altered thyroid hormone homeostasis) cannot be excluded. In the DNT study, changes in the linear measurements of the caudate putamen area were observed from the low dose of 1.7 mg/kg bw per day in female rats at PND 72 and considered adverse.

Overall, based on the available and sufficiently investigated dataset and on the MoA analysis, the experts at the peer review meeting,[35] except the RMS, agreed that the ED criteria for the T-modality are met for flufenacet (**Scenario 1b** of the ECHA/EFSA ED Guidance, 2018).

In the studies conducted with flufenacet, the lowest-observed adverse effect level (LOAEL), where T- mediated adversity was observed in males at termination in the form of thyroid histopathological changes (i.e. thyroid follicular cell hyperplasia), is 11.23 mg/kg bw per day in a 70-day mechanistic toxicity study in rats. A no-observed adverse effect level (NOAEL) of 2.19 mg/kg bw per day can be derived for thyroid histopathology in the same study. The lowest effect level (LOEL) for endocrine activity in the most sensitive population (i.e. statistically significant decrease in T4 in dams at GD 20) was observed at 34.6 mg/kg bw per day in the CTA study with a no effect level (NOEL) at 6.6 mg/kg bw per day. The lowest effect level (LOEL) for endocrine activity in the lactating dams (i.e. statistically significant decrease in T3 and T4 at LD 21) and in pups (i.e. statistically significant decrease in T3 at PND 21) was observed at 6.6 mg/kg bw per day in the CTA study with a no effect level (NOEL) at 1.3 mg/kg bw per day.

The **EAS-modalities** were considered sufficiently investigated and EAS-mediated adversity was not identified. It has to be noted that the Hershberger bioassay in rats (OECD TG 441, OECD, 2009b) was positive and flufenacet was considered anti-androgenic in the context of this study. An OECD TG 443 study was not conducted, as recommended by EFSA, and although the conduction of the extended one-generation reproductive toxicity study in rats (OECD TG 443, OECD, 2018) still remains the preferred option (in line with the EFSA/ECHA (2018) ED guidance), A-mediated endpoints i.e. anogenital distance, nipple retention, balanopreputial separation, genital abnormalities, testes, seminal vesicles and epididymes weight and histopathology (including staging) and seminology have been all investigated in the studies submitted during the regulatory clock stop. Therefore, the dataset was considered sufficient to conclude on the A-modality. Overall, based on the available and sufficient dataset, it was concluded that the ED criteria are not met for the EAS-modalities (**Scenario 1a** of the ECHA/EFSA ED Guidance, 2018).

The conclusion drawn for humans for the **T-modality (ED criteria met)**, also applies to **wild mammals** as **non-target organisms**. The experts at the meeting[36] agreed that the population relevance of the observed effects cannot be excluded when considering:

(i) the effects observed in the available DNT study, i.e. changes in the linear measurement of the caudate putamen in females at PND 72. Those effects are linked to learning, emotion, attachment behaviour and motor functions; and,
(ii) the DNT IVB for flufenacet is negative suggesting that DNT changes consequent to altered THs homeostasis cannot be excluded; while it is unlikely that flufenacet would act as a direct developmental neurotoxicant.

For the EAS-modalities for wild mammals, the same conclusion as the one reported above for humans applies.

For **non-mammalian species**, an Extended Amphibian Metamorphosis Assay (EAMA according to Ortego et al., 2021) and a Fish Short-term Reproduction Assay (FSTRA according to OECD TG 229, OECD, 2012) were available to investigate the endocrine activity through the T- and EAS-modalities, respectively. Both studies were discussed at the experts' meeting.[37]

In the available EAMA, the main findings were changes in the thyroid histopathology at the intermediate and highest tested concentrations and delay in reaching metamorphosis at the highest concentration. At the same concentrations, decrease in body weight and growth parameters (i.e. Snout to Vent Length) was also observed. Overall, the experts considered likely that flufenacet interferes with the HPT axis, however it could not be excluded, based on the available evidence, that the T-mediated effects were secondary to systemic toxicity (i.e. decrease in wet weight both at day 7 and study termination and delay in developmental stage already observed in premetamorphsis).[36] Moreover, considering the protocol of the EAMA has not been standardised, a data gap is identified to further confirm the findings of the available EAMA by performing a study according to an internationally agreed protocol (see Section 10).

For the EAS-modalities, decrease in fecundity and changes in female gonads histopathology were observed in the available FSTRA. No changes in the investigated mechanistic parameters were observed.

Although some concerns were raised considering the outcome of the Hershberger Assay in rodents suggesting flufenacet to be an anti-androgenic (AA) compound, and the evidence in the FSTRA which were in line with the findings from other known anti-androgens, the experts overall concluded that flufenacet is unlikely to be an endocrine disruptor for EAS-modalities.[38] The conclusion was reached considering that (i) no AA-mediated findings were observed in the available higher tier in-vivo mammalian studies and (ii) mammalian and non-mammalian species have similar metabolism based on the available metabolism data.

Overall, it was concluded that, for humans and wild mammals, flufenacet meets the criteria for the T-modality 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, leading to a **critical area of concern** (**see Section 9.1.2**). Flufenacet was not considered to meet the ED criteria for EAS-modalities for humans and non-target organisms.

[35]See expert consultation point 2.17 of the Pesticide Peer Review Experts' meeting TC 99 (EFSA, 2024).
[36]See expert consultation point 5.5 of the Pesticides Peer Review Experts' meeting TC 99 (EFSA, 2024).
[37]See expert consultation points 5.5 and 5.6 of the Pesticides Peer Review Experts' meeting TC 99 (EFSA, 2024).
[38]See expert consultation point 5.6 of the Pesticides Peer Review Experts' meeting TC 99 (EFSA, 2024).

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
Flufenacet	High risk to soil organisms for the representative uses on wheat and barley at 160 g a.s./ha and on winter cereals (wheat, barley and rye) at 120 g a.s./ha. Low risk for the representative uses on winter wheat, barley and rye at 240 g a.s./ha (autumn application only)
FOE oxalate	Low risk to soil organisms
FOE sulfonic acid	Low risk to soil organisms
FOE methylsulfone	Low risk to soil organisms
FOE thiadone	Low risk to soil organisms
FOE trifluoroethanesulfonic acid	Low risk to soil organisms
Trifluoroacetic acid	Low risk to soil organisms

TABLE 2 Groundwater.[a]

Compound (name and/or code)	>0.1 μg/L at 1 m depth for the representative uses[b] Step 2	Biological (pesticidal) activity/ relevance Step 3a	Hazard identified Steps 3b and 3c	Consumer RA triggered Steps 4 and 5	Human health relevance
Flufenacet	No	Yes	–	–	Yes
FOE oxalate	A po 240 g/ha 4/9 scenarios 0.007–0.344 A po 160 g/ha 4/9 scenarios 0.004–0.213 A pr 120 g/ha 2/9 scenarios 0.004–0.18 S po 160 g/ha No S pr 120 g/ha No	No	No	Open ADI for parent flufenacet might be used as it is considered unlikely to be of higher toxicity than flufenacet. Though water concentrations are <0.75 μg/L there are crop residues and the consumer risk assessment could not be finalised whilst the assessment of residue levels in following crops and animal products have not been finalised	Assessment not finalised
FOE sulfonic acid	A po 240 g/ha all 9 scenarios 0.446–8.211 A po 160 g/ha all 9 scenarios 0.297–5.447 A pr 120 g/ha all 9 scenarios 0.64–4.226 S po 160 g/ha all 9 scenarios 0.203–4.175 S pr 120 g/ha all 9 scenarios 0.152–3.127	No	No	Yes ADI for parent flufenacet might be used as it is expected to be of lower toxicity than flufenacet Water concentrations are >0.75 μg/L. Consumer risk assessment could not be finalised whilst the assessment of residue levels in following crops and animal products have not been finalised	Assessment not finalised

(Continues)

TABLE 2 (Continued)

Compound (name and/or code)	>0.1 μg/L at 1 m depth for the representative uses[b] Step 2	Biological (pesticidal) activity/ relevance Step 3a	Hazard identified Steps 3b and 3c	Consumer RA triggered Steps 4 and 5	Human health relevance
FOE methylsulfone	A po 240 g/ha 6/9 scenarios 0.002–0.268 A po 160 g/ha 5/9 scenarios 0.001–0.161 A pr 120 g/ha 2/9 scenarios 0.001–0.119 S po 160 g/ha 3/9 scenarios 0.001–0.126 S pr 120 g/ha No	data gap	No	No as it is <0.75 μg/L and not a significant residue in plant or animal products ADI for parent flufenacet might be used as it is expected to be of lower toxicity than flufenacet	Not relevant
FOE thiadone	No	Assessment not triggered	Assessment not triggered	No	Assessment not triggered
FOE trifluoroethanesulfonic acid	A po 240 g/ha 7/9 scenarios 0.061–2.432 A po 160g/ha 6/9 scenarios 0.04–1.609 A pr 120 g/ha 6/9 scenarios 0.051–1.268 S po 160 g/ha 2/9 scenarios <0.001–0.223 S pr 120 g/ha 1/9 scenarios <0.001–0.167	No	No	Yes Reference values for consumer risk assessment are necessary and could not be proposed with the available data. Water concentrations are >0.75μg/L	Assessment not finalised
Trifluoroacetic acid	A po 240 g/ha all 9 scenarios 16.05–96.6 A po 160 g/ha all 9 scenarios 10.68–64.4 A pr 120 g/ha all 9 scenarios 8.2–49 S po 160 g/ha all 9 scenarios 11.7–65.28 S pr 120 g/ha 7/9 scenarios 8.78–48.97	No	Neither mutagenic nor clastogenic; aneugenicity was not investigated.[39] A CLH proposal for reproductive toxicity category 1B has been sent to ECHA	Yes Toxicity studies performed with sodium trifluoroacetate ADI of 0.05 mg/kg bw per day is set. Water concentrations are >0.75 μg/L. Consumer risk assessment could not be finalised whilst residue levels in primary and following crops and animal products have not been finalised	Assessment not finalised

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

[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, 2014b) guidance. A: Autumn, S: spring, po: post emergence, pr: pre emergence.

TABLE 3 Surface water and sediment.

Compound (name and/or code)	Ecotoxicology
Flufenacet	High risk in eight out of nine FOCUS scenarios for all the representative uses[40]
FOE oxalate	Low risk to aquatic organisms
FOE sulfonic acid	High risk to aquatic plants not excluded (data gap)
FOE methylsulfide	Low risk to aquatic organisms
FOE methylsulfone	Low risk to aquatic organisms
FOE thiadone	High risk to algae not excluded (data gap)
FOE trifluoroethanesulfonic acid	Low risk to aquatic organisms
Trifluoroacetic acid	High risk to fish not excluded for the representative uses on winter wheat, barley and rye at 240 g a.s./ha (data gap)

[39]Version 11 of the European Commission guidance on the relevance of groundwater metabolites (2021), introduced the need to include an in vitro micro nucleus test (and then assessment of aneugenicity). This is applicable to dossiers submitted from 1 May 2022 but can be applied earlier by applicants.

[40]For the representative use on wheat and barley, spring application, at 160 g a.s./ha and 120 g a.s/ha low risk was identified for five out of nine relevant FOCUS scenarios with the implementation of up to 20 m n-spray buffer zone. However, since the GAP includes cereals, i.e. both autumn application and spring application, the overall outcome (worst case) is summarised in the tables and main text.

TABLE 4 Air.

Compound (name and/or code)	Toxicology
Flufenacet	Low acute toxicity by inhalation (rats), 28-day, rat: 20 mg/m^3 [ca 7 mg/kg bw per day]
FOE thiadone	Toxicity by inhalation considered covered by flufenacet.
trifluoroacetic acid	Sodium trifluoroacetate was non-toxic after acute inhalation exposure (LC_{50} > 2350 mg/m^3)

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).

8.1 | Particular conditions proposed for the representative uses evaluated

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

Representative use	w. wheat w. barley w. rye 0.24 kg/ha BBCH 10–13 (only autumn application) Foliar spray	w. wheat w. barley 0.24 kg/ha BBCH 11–13 (only autumn application) Foliar spray	Wheat barley 0.16 kg/ha BBCH 11–13 Foliar spray	w. wheat w. barley w. rye 0.12 kg/ha BBCH 0–22 Foliar spray
Risk to aquatic organisms	For the scenario D3, low risk to algae was concluded with the implementation of mitigation measures up to 20 m buffer zone. Mitigation measures up to 20 m buffer zone were needed to conclude a low risk for aquatic plants for the relevant FOCUS scenarios D3 and R1	For the scenario D3, low risk to algae was concluded with the implementation of mitigation measures up to 20 m buffer zone. Mitigation measures up to 20 m buffer zone were needed to conclude a low risk for aquatic plants for the relevant FOCUS scenarios D3 and R1	For the scenario D3, low risk to algae was concluded with the implementation of mitigation measures up to 20 m buffer zone. Mitigation measures up to 20 m buffer zone were needed to conclude a low risk for aquatic plants for the relevant FOCUS scenarios, R1, R3 and R4	For the scenario D3, low risk to algae was concluded with the implementation of mitigation measures up to 20 m buffer zone. RMM were needed to conclude low risk to aquatic plants for the FOCUS scenarios R1 and R3
Risk to non-target terrestrial plants	5 m buffer zone or 50% drift reduction for the representative uses on winter cereals (wheat, barley and rye) are needed to conclude low risk	5 m buffer zone or 50% drift reduction for the representative uses on winter cereals (wheat, barley and rye) are needed to conclude low risk	5 m buffer zone or 50% drift reduction for the representative uses on winter cereals (wheat, barley and rye) are needed to conclude low risk	–

8.2 | Particular conditions proposed for the confirmatory data following Article 12 MRL review

None.

9 | CONCERNS AND RELATED DATA GAPS

9.1 | Concerns for the representative uses evaluated

9.1.1 | 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[41] 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 non-relevance assessment of groundwater metabolites: FOE oxalate, FOE sulfonic acid, FOE trifluoroethanesulfonic acid and trifluoroacetic acid could not be finalised:

   a. the available data (general toxicity data) were insufficient to propose reference values for consumer risk assessment for FOE trifluoroethanesulfonic acid (see Section 2).
   b. as total consumer intakes could not be finalised due to missing exposure levels in human food commodities to compare to the ADI for flufenacet (relates to FOE oxalate and FOE sulfonic acid, i.e. data gap 2.b. below) or the ADI for trifluoroacetic acid, i.e. data gaps 2.a. and 2.c. below (see Sections 2, 3 and 4).

2. The consumer risk assessment could not be finalised due to the lack of (see Section 3):

   a. residue field trials analysing for trifluoroacetic acid in primary crops.
   b. a sufficient number of field rotational crop trials analysing for compounds containing the *N*-fluorophenyl-*N*-isopropyl moiety (e.g. FOE oxalate, FOE sulfonic acid and flufenacet).
   c. clarification whether the limited field rotational crops trials cover the maximum PECsoil calculated for TFA. If this is not the case limited field rotational crops trials would be needed.

3. The consumer risk assessment was not finalised with regard to the unknown nature of residues that might be present in drinking water, consequent to the water treatment process of chlorination following abstraction of groundwater or surface water that might contain residues from flufenacet (see Sections 3 and 4).

   a. satisfactory information to address the effect of water treatment processes using chlorination (other than the non formation of haloacetonitriles and halonitromethanes) on the nature of residues (active substance and transformation products) in surface and groundwater, when surface water or groundwater are abstracted for drinking water was not available. Should a future consideration of this 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 would be needed (relevant for all representative uses evaluated; see Section 4).

4. The exposure and risk assessments for the diflufenican active substance in the product for representative uses have not been included in the RAR and list of agreed endpoints and have not been peer reviewed[42] (see Sections 4 and 5).

   a. Predicted environmental concentrations (PEC) in soil, groundwater, surface water and sediment for diflufenican and its transformation products were not available (see Section 4).
   b. A risk assessment for the formulation for representative uses which includes the second active diflufenican and its transformation products was not available for non-target organisms (see Section 5).

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

[42]With the exception that the human non dietary exposure assessment was concluded on by EFSA, see Section 2, so this aspect was peer reviewed.

9.1.2 | 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. High risk to algae was concluded for the majority of the relevant FOCUS scenarios (8 out of 9) for all the representative uses of flufenacet (see Section 5).[43]
6. The assessment of the endocrine disrupting properties for humans and non-target organisms: the criteria 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 are met for the T-modality.

9.1.3 | 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		w. wheat w. barley w. rye 0.24 kg/ha BBCH 10–13 (only autumn application)	w. wheat w. barley 0.24 kg/ha BBCH 11–13 (only autumn application)	Wheat barley 0.16 kg/ha BBCH 11–13	w. wheat w. barley w. rye 0.12 kg/ha BBCH 0–22
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]
Risk to wild non-target terrestrial vertebrates	Risk identified	X	X		
	Assessment not finalised	X[4]	X[4]	X[4]	X[4]
Risk to wild non-target terrestrial organisms other than vertebrates	Risk identified	X[a]	X[a]	X	X[b]
	Assessment not finalised	X[4]	X[4]	X[4]	X[4]

(Continues)

[43]For the representative use on wheat and barley, spring application, at 160 g a.s./ha and 120 g a.s/ha low risk was identified for five out of nine relevant FOCUS scenarios with the implementation of up to 20 m n-spray buffer zone. However, since the GAP includes both autumn application and spring application, the overall outcome (worst case) is summarised in the tables and main text.

TABLE 6 (Continued)

Representative use		w. wheat w. barley w. rye 0.24 kg/ha BBCH 10–13 (only autumn application)	w. wheat w. barley 0.24 kg/ha BBCH 11–13 (only autumn application)	Wheat barley 0.16 kg/ha BBCH 11–13	w. wheat w. barley w. rye 0.12 kg/ha BBCH 0–22
Risk to aquatic organisms[44]	Risk identified	X[5]	X[5]	X[5]	X[5]
	Assessment not finalised	X[4]	X[4]	X[4]	X[4]
Groundwater exposure to active substance	Legal parametric value breached				
	Assessment not finalised				
Groundwater exposure to metabolites	Legal parametric value breached				
	Parametric value of 10 µg/L[c] breached				
	Assessment not finalised	X[1,4]	X[1,4]	X[1,4]	X[1,4]

Notes: The superscript numbers relate to the numbered points indicated in Sections 9.1.1 and 9.1.2. Where there is no superscript associated with an X, see Section 5.

[a]High risk was concluded on bees for the treated crop for the representative use on cereals at 240 g a.s./ha. However, based on the new knowledge (EFSA, 2023), cereals are not considered attractive to bees.

[b]According to new knowledge (EFSA, 2023) the weed scenarios are considered relevant for application to cereals at BBCH ≥20.

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

9.2 | Issues related to the confirmatory data following Article 12 MRL review

None.

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:

- For one of the components of the formulation for representative uses 'DFF+FFA SC 600', in order to allow a final conclusion on the safety assessment of 'DFF + FFA SC 600', further information on this component in relation to genotoxicity and repeated-dose toxicity information over short- and long-term may 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').
- RMS's assessment of the relevance and reliability of the search of the scientific peer-reviewed open literature on the active substance and its relevant metabolites, dealing with side effects on health and published within 10 years before the date of submission of the dossier, to be conducted and reported in accordance with EFSA guidance on the submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (EFSA, 2011) (relevant for all representative uses evaluated; submission date proposed by the applicant: already submitted; see the Section on the active substance and the formulated product).
- Content of the relevant impurity (toluene) before and after the storage of the plant protection product is missing and should be provided (relevant for all representative uses evaluated; see Section 1).
- Method for determination of the relevant impurity (toluene) in the formulation is missing and should be provided (relevant for all representative uses evaluated; see Section 1).
- A method for monitoring residues in air that covers the proposed residue definition is required (relevant for all representative uses evaluated; see Section 1).
- A method for monitoring residues in body tissues that covers the proposed residue definition is required (relevant for all representative uses evaluated; see Section 1).
- Data on screening for biological activity (European Commission, 2003a - stage 1 of step 3) of metabolite FOE methylsulfone should be submitted (relevant for all representative uses evaluated; see Table 2 in Section 7).

[44]For the representative use on wheat and barley, spring application, at 160 g a.s./ha and 120 g a.s/ha low risk was identified for five out of nine relevant FOCUS scenarios with the implementation of up to 20 m n-spray buffer zone. However, since the GAP for those uses includes both autumn application and spring application, the overall outcome (worst case) is summarised in the tables and main text.

- RMS's assessment of the relevance and reliability of quantitative structure–activity relationship (QSAR) analysis of impurities presenting robust summary reports in the RAR should be provided to allow conclusion on their relevance (relevant for all representative uses evaluated; submission date proposed by the applicant: already submitted but not assessed by the RMS; see Section 2).
- The phototoxic potential of flufenacet at UVB ranges should be addressed once an appropriate OECD test for UVB absorbers is available (relevant for all representative uses evaluated; see Section 2).
- RMS's assessment of supplementary studies on flufenacet presenting robust summary reports in the RAR should be provided (relevant for all representative uses evaluated; submission date proposed by the applicant: already submitted; see Evaluation Table Section 2, data requirement 2.10).
- Aneugenicity of TFA was not investigated and should be assessed (relevant for all representative uses evaluated; see Section 2).
- A study addressing the fate of the *N*-fluorophenyl-*N*-isopropyl moiety metabolites under the standard hydrolysis conditions at processing with focus on the predominant compound recovered in wheat grain (FOE oxalate) is missing (relevant for all representative uses evaluated, see Section 3).
- Storage stability data for trifluoroacetic acid in plant matrices and covering the maximum storage time period of the residue samples from residue trials in primary and rotational crops is missing (relevant for all representative uses evaluated, see Section 3).
- Information on the storage duration of the samples in the ruminant feeding study conducted with FOE oxalate is missing. If the storage period until analysis exceeds 30 days stability data N-fluorophenyl-N-isopropyl moiety metabolites in animal matrices would be needed (relevant for all representative uses evaluated, see Section 3).
- A study addressing the residue levels in pollen and in bee products for human consumption resulting from residues taken up by honeybees from rotated crops at blossom is missing (relevant for all representative uses evaluated, see Section 3).
- Satisfactory information from field soil dissipation investigations for the soil metabolite FOE methylsulfone was not available. Field investigation was triggered based on FOE methylsulfone DT_{90} in laboratory incubations. The exposure assessments for the EU representative uses have been completed without this information using laboratory endpoints (relevant for all representative uses evaluated; see Section 4).
- The RMS did not provide a final FOCUS surface water exposure assessment for flufenacet, that included the additional flufenacet soil incubation and adsorption endpoints and incorporated mitigation at Step 4 (though the RMS confirmed that this had been included in the applicant's modelling report). Consequently, the aquatic exposure and risk assessments in this conclusion have been completed using more conservative degradation and adsorption values than needed (relevant for all representative uses evaluated; submission date for an updated modelling report using final peer reviewed substance properties: unknown; see Section 4).
- The information to support the compliance of the batches used in ecotoxicological studies with the proposed renewal specification and the original reference specification was considered insufficient (relevant for all representative use evaluated; see Section 5).
- Further data on algae, aquatic plants and fish would be needed for the pertinent surface water metabolites FOE thiadone, FOE sulfonic acid and TFA (relevant for all representative use evaluated; see Section 5).
- Further data are needed to assess potential sub-lethal effects of flufenacet on honey bees and for performing the risk assessment of relevant metabolites other than TFA that have the potential to be present in pollen and nectar (relevant for all representative use evaluated; see Section 5).
- Chronic data with the formulation for representative uses was not available for bees, and is required according to Regulation 284/2013 in case of PPP with more than one active substance (relevant for all representative use evaluated; see Section 5).
- A new study conducted according to internationally agreed protocols is needed to further confirm the findings in the available extended amphibian metamorphosis assay (relevant for all representative uses, see Section 6).

ABBREVIATIONS

AMA	Amphibian Metamorphosis Assay
a.s.	active substance
AChE	acetylcholinesterase
ADE	actual dermal exposure
ADI	acceptable daily intake
AF	assessment factor
AAOEL	acute acceptable operator exposure level
AhR	aryl hydrocarbon receptor
AOEL	acceptable operator exposure level
AOP	adverse outcome pathway
AP	alkaline phosphatase
AR	applied radioactivity
AR	androgen receptor

ARfD	acute reference dose
AST	aspartate aminotransferase (SGOT)
AUC	area under the blood concentration/time curve
AV	avoidance factor
BCF	bioconcentration factor
BUN	blood urea nitrogen
bw	body weight
CAS	Chemical Abstracts Service
CFU	colony forming units
ChE	cholinesterase
CHO	Chinese hamster ovary cells
CI	confidence interval
CIPAC	Collaborative International Pesticides Analytical Council Limited
C&L	classification and labelling
CL	confidence limits
Cmax	concentration achieved at peak blood level
DAA	days after application
DAR	draft assessment report
DAT	days after treatment
DDD	daily dietary dose
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_{50}	emergence rate/effective rate, median
ErC_{50}	effective concentration (growth rate)
ERO	ecological recovery option
ERSTTA	Stably Transfected Human Oestrogen Receptor-alpha Transcriptional Activation Assay
ETO	ecological threshold option
ETR	exposure toxicity ratio
ETR_{acute}	exposure toxicity ratio for acute exposure
ETR_{larvae}	exposure toxicity ratio for chronic exposure
ETR_{larvae}	exposure toxicity ratio for larvae
ETR_{HPG}	exposure toxicity ratio for effects on honeybee hypopharygeal glands
EUROPOEM	European Predictive Operator Exposure Model
f(twa)	time-weighted average factor
FAO	Food and Agriculture Organization of the United Nations
FID	flame ionisation detector
FIR	food intake rate
FOB	functional observation battery
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
FSTRA	Fish Short-Term Reproduction Assay
GAP	Good Agricultural Practice
GC	gas chromatography
GCPF	Global Crop Protection Federation (formerly known as International Group of National Associations of Manufacturers of Agrochemical Products; GIFAP)
GM	geometric mean
GS	growth stage
HGPRT	hypoxanthine-guanine phosphoribosyl transferase
HPLC	high-pressure liquid chromatography or high-performance liquid chromatography
HPLC-MS	high-pressure liquid chromatography–mass spectrometry
HPG	hypopharygeal glands
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_{doc}	organic carbon linear adsorption coefficient
K_{Foc}	Freundlich organic carbon adsorption coefficient
LAGDA	Larval Amphibian Growth and Development Test
LC	liquid chromatography
LC_{50}	lethal concentration, median
LD_{50}	lethal dose, median; dosis letalis media
LDD_{50}	lethal dietary dose; median
LDH	lactate dehydrogenase
LH	luteinizing hormone
LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOQ	limit of quantification
M/L	mixing and loading
MAF	multiple application factor
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
MOA	mode of action
MRL	maximum residue level
MS	mass spectrometry
MSDS	material safety data sheet
MTD	maximum tolerated dose
NESTI	national estimated short-term intake
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NPD	nitrogen–phosphorus detector
OECD	Organisation for Economic Co-operation and Development
OM	organic matter content
PD	proportion of different food types
PEC	predicted environmental concentration
pF2	pF value of 2 (suction pressure that defines field capacity soil moisture)
PHED	pesticide handler's exposure data
PHI	pre-harvest interval
PIE	potential inhalation exposure
pK_a	negative logarithm (to the base 10) of the dissociation constant
P_{ow}	partition coefficient between *n*-octanol and water
PPE	personal protective equipment
PT	proportion of diet obtained in the treated area
PTT	partial thromboplastin time
QSAR	quantitative structure–activity relationship
r^2	coefficient of determination
RAC	regulatory acceptable concentration
RAR	Renewal Assessment Report
REACH	Registration, Evaluation, Authorisation of Chemicals Regulation
RPE	respiratory protective equipment
RUD	residue per unit dose
SC	suspension concentrate
SD	standard deviation
SFO	single first-order
SMILES	simplified molecular-input line-entry system
SPG	specific protection goal
SSD	species sensitivity distribution
STMR	supervised trials median residue
$t_{1/2}$	half-life (define method of estimation)
TER	toxicity exposure ratio

TER_A	toxicity exposure ratio for acute exposure
TER_{LT}	toxicity exposure ratio following chronic exposure
TER_{ST}	toxicity exposure ratio following repeated exposure
TK	technical concentrate
TLV	threshold limit value
Tmax	time until peak blood levels achieved
TMDI	theoretical maximum daily intake
ToxCAST	(US EPA) Toxicity Forecaster
TRR	total radioactive residue
THs	thyroid hormones
TSH	thyroid-stimulating hormone (thyrotropin)
TWA	time-weighted average
UDS	unscheduled DNA synthesis
UF	uncertainty factor
UV	ultraviolet
WG	water-dispersible granule
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.

REQUESTOR
European Commission

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APPENDIX A

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

Properties		Conclusion[a]
CMR	Carcinogenicity (C)	Harmonised classification -Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation: no.)
	Mutagenicity (M)	Harmonised classification -Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation: no.)
	Toxic for Reproduction (R)	Harmonised classification -Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation: no.)
Endocrine disrupting properties		Overall, it was concluded that, for humans and wild mammals, flufenacet meets the criteria for the T-modality 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. Flufenacet was not considered to meet the ED criteria for EAS-modalities for humans and non-target organisms
POP	**Persistence** **Bioaccumulation** **Long-range transport**	Flufenacet 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**	Flufenacet 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**	Flufenacet 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 formulation 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.2024.8997

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[45] or not normalised DT_{50} for field studies (SFO equivalent, when biphasic, the DT_{90} was divided by 3.32 to estimate the DT_{50} 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.

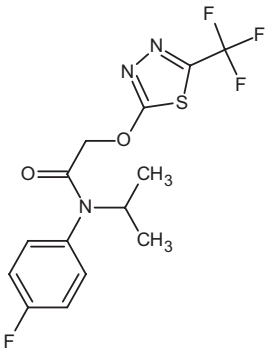
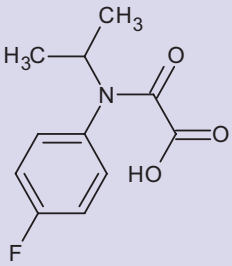
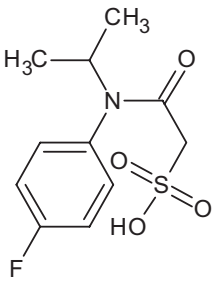
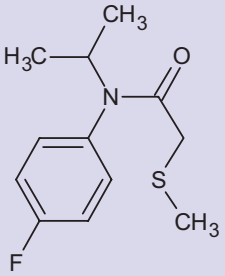
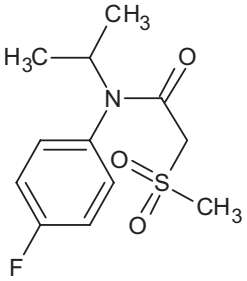
Wording	K_{oc} (either K_{Foc} or K_{doc}) mL/g
Very high mobility	0–50
High mobility	51–150
Medium mobility	151–500
Low mobility	501–2000
Slight mobility	2001–5000
Immobile	> 5000

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

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

APPENDIX D

Used compound codes

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
* **flufenacet,** active substance, a.s. FOE 5043	4′-fluoro-N-isopropyl-2-{[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]oxy}acetanilide O=C(COc1nnc(s1)C(F)(F)F)N(c1ccc(F)cc1)C(C)C IANUJLZYFUDJIH-UHFFFAOYSA-N	
FOE oxalate, M01	[(4-fluorophenyl)(propan-2-yl)amino](oxo)acetic acid CC(C)N(C(=O)C(=O)O)c1ccc(F)cc1 FFKNXXCOXIZLJD-UHFFFAOYSA-N	
FOE sulfonic acid, M02	2-[(4-fluorophenyl)(propan-2-yl)amino]-2-oxoethane-1-sulfonic acid CC(C)N(C(=O)CS(=O)(=O)O)c1ccc(F)cc1 SZCMHDLOUVZYST-UHFFFAOYSA-N	
FOE methylsulfide	*N*-(4-fluorophenyl)-2-(methylsulfanyl)-*N*-(propan-2-yl) acetamide CC(C)N(C(=O)CSC)c1ccc(F)cc1 IOHKBSWDOCUUKO-UHFFFAOYSA-N	
FOE methylsulfone, M07	*N*-(4-fluorophenyl)-2-(methanesulfonyl)-*N*-(propan-2-yl) acetamide CC(C)N(C(=O)CS(C)(=O)=O)c1ccc(F)cc1 QLEUWYMFZWRAGA-UHFFFAOYSA-N	

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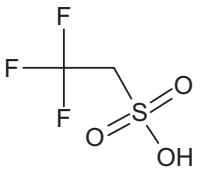
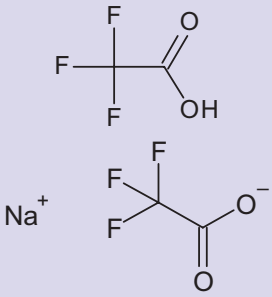
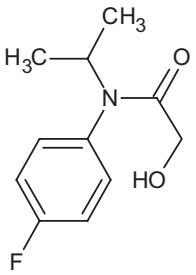
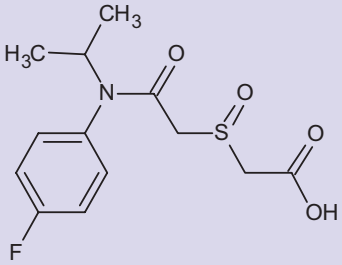
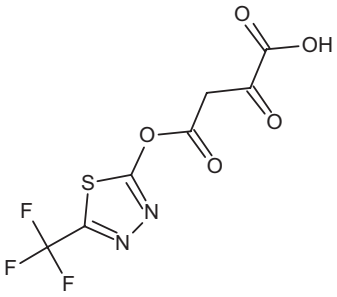
Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
* **FOE thiadone**, M09	5-(trifluoromethyl)-1,3,4-thiadiazol-2(3*H*)-one FC(F)(F)C1 = NNC(=O)S1 JFZSAWUKZISBJM-UHFFFAOYSA-N	 Other tautomeric forms are possible (condition dependent)
* **FOE trifluoroethanesulfonic acid,** M44 (FOE-TFESA)	2,2,2-trifluoroethane-1-sulfonic acid FC(F)(F)CS(=O)(=O)O XGMDYIYCKWMWLY-UHFFFAOYSA-N	
* **trifluoroacetic acid, TFA,** M45	trifluoroacetic acid FC(F)(F)C(=O)O DTQVDTLACAAQTR-UHFFFAOYSA-N sodium trifluoroacetate [Na+].FC(F)(F)C([O-]) = O UYCAUPASBSROMS-UHFFFAOYSA-M	
FOE alcohol	*N*-(4-fluorophenyl)-2-hydroxy-*N*-(propan-2-yl)acetamide CC(C)N(C(=O)CO)c1ccc(F)cc1 RISGISSUGUGJMO-UHFFFAOYSA-N	
FOE thioglycolate sulfoxide, M04	{2-[(4-fluorophenyl)(propan-2-yl)amino]-2-oxoethanesulfinyl} acetic acid CC(C)N(C(=O)CS(=O)CC(=O)O)c1ccc(F)cc1 JCMMUCVPUOXQDO-UHFFFAOYSA-N	
* **FOE thiadone oxalylacetic acid conjugate,** M26	2,4-dioxo-4-{[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]oxy} butanoic acid O=C(Oc1nnc(s1)C(F)(F)F)CC(=O)C(=O)O AOXQTQSEOQZJRR-UHFFFAOYSA-N	

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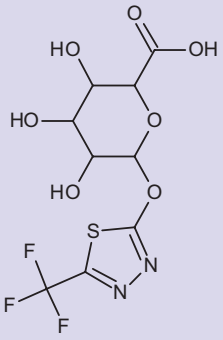
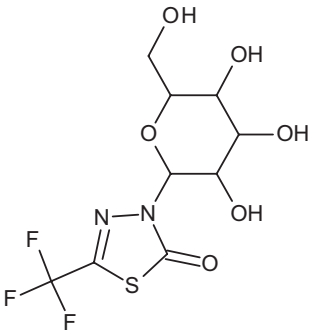
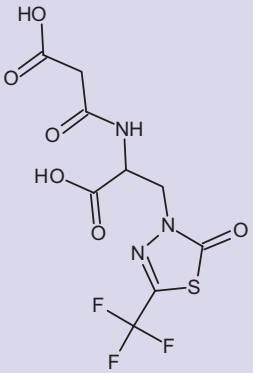
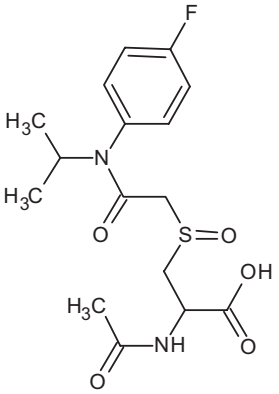
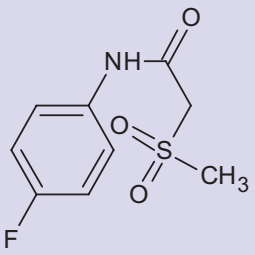
(Continued)

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
* **FOE thiadone glucuronic acid conjugate,** M24	5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl hexopyranosiduronic acid O=C(O)C1OC(Oc2nnc(s2)C(F)(F)F)C(O)C(O)C1O DWAHUTGYKMPLIN-UHFFFAOYSA-N	
* **FOE thiadone N-glucoside conjugate,** thiadone N-glucoside, M25	3-hexopyranosyl-5-(trifluoromethyl)-1,3,4-thiadiazol-2(3*H*)-one O=C1SC(=NN1C1OC(CO)C(O)C(O)C1O)C(F)(F)F UIONEJPRSGOXGT-UHFFFAOYSA-N	
* **FOE thiadone malonylalanyl conjugate,** M34	*N*-(carboxyacetyl)-3-[2-oxo-5-(trifluoromethyl)-1,3,4-thiadiazol-3(2*H*)-yl]alanine O=C1SC(=NN1CC(NC(=O)CC(=O)O)C(=O)O)C(F)(F)F YWCIDCREKIYQNL-UHFFFAOYSA-N	
FOE S-oxo cysteine, M12	*N*-acetyl-3-{2-[(4-fluorophenyl)(propan-2-yl)amino]-2-oxoethanesulfinyl}alanine CC(C)N(C(=O)CS(=O)CC(NC(C)=O)C(=O)O)c1ccc(F)cc1 SHTNJEQOOFRUBG-UHFFFAOYSA-N	
FOE des-i-propyl methylsulfone, M15	*N*-(4-fluorophenyl)-2-(methanesulfonyl)acetamide O=C(Nc1ccc(F)cc1)CS(C)(=O)=O QAEBCZYSBGURHY-UHFFFAOYSA-N	

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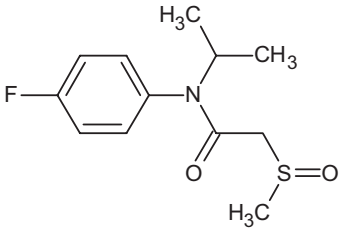
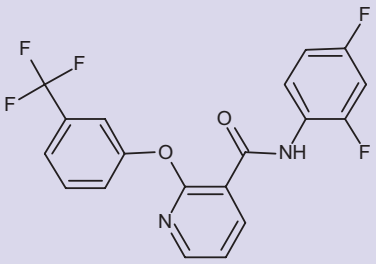
Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
FOE-methylsulfoxide, M06	*N*-(4-fluorophenyl)-2-(methanesulfinyl)-*N*-(propan-2-yl) acetamide CC(C)N(C(=O)CS(C)=O)c1ccc(F)cc1 IBDJPNSYJVOPJL-UHFFFAOYSA-N	
* **diflufenican**	2′,4′-difluoro-2-[3-(trifluoromethyl)phenoxy] pyridine-3-carboxanilide Fc1ccc(NC(=O)c2cccnc2Oc2cccc(c2)C(F)(F)F)c(F)c1 WYEHFWKAOXOVJD-UHFFFAOYSA-N	

*Compounds are identified as meeting the definition of per- and polyfluoroalkyl substances (PFAS) based on their chemical structures (https://echa.europa.eu/hot-topics/perfluoroalkyl-chemicals-pfas).

[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, 7 July 2021).

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