CONCLUSION ON PESTICIDES PEER REVIEW

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

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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, the Netherlands, and co-rapporteur Member State, the United Kingdom, for the pesticide active substance flutolanil, and the assessment of applications for maximum residue levels (MRLs) are reported. The context of the peer review was that required by Commission Implementing Regulation (EU) No 844/2012, as amended by Commission Implementing Regulation (EU) No 2018/1659. The conclusions were reached on the basis of the evaluation of the representative uses of flutolanil as a fungicide on potatoes, tulips and iris (field uses). MRLs were assessed for a potato in-furrow treatment. The reliable end points, appropriate for use in regulatory risk assessment are presented. Missing information identified as being required by the regulatory framework is listed. Concerns are reported where identified.

Keywords: flutolanil, peer review, risk assessment, pesticide, fungicide, MRL Article 10

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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 as amended by Commission Implementing Regulation (EU) No 2016/183. Flutolanil is one of the active substances listed in that Regulation.

In accordance with Article 1 of the Regulation, the rapporteur Member State (RMS), the Netherlands, and co-rapporteur Member State (co-RMS), the United Kingdom, received an application from Nihon Nohyaku Co., Ltd. for the renewal of approval of the active substance flutolanil. In addition, Nihon Nohyaku Co., Ltd. submitted applications for maximum residue levels (MRLs), as referred to in Article 7 of Regulation (EC) No 396/2005.

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

The uses of flutolanil according to the representative uses as a fungicide on potatoes, tulips and iris (field uses) as proposed at EU level result in sufficient fungicidal efficacy against the target *Rhizoctonia solani*.

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 and chemical properties and analytical methods**.

In the assessment for **mammalian toxicology**, several issues not finalised were identified: the test material used in the 2-year rat study could not be concluded as representative of the technical specification and an immunotoxic potential of flutolanil could not be completely excluded. For the representative use on potato seed, the operator and worker exposures were not demonstrated to be below the (A)AOEL on the basis of a field study.

The data available on **residues** are sufficient to derive residue definitions for enforcement and to derive MRL. However, the consumer risk assessment could not be finalised for the metabolites M-101, M-102, M-02 and TFA, due to lack of conclusion on their (geno)toxicity profile (for M-101, M-102 and M-02) or missing information regarding the potential occurrence of metabolite TFA in rotational crops, and regarding the metabolism of flutolanil in poultry. Consequently, the consumer risk assessment could not be finalised for any of the representative uses.

In addition to the above, data gaps were also identified for the MRL request. Information was missing on the occurrence of residues in rotational crops and on the nature of residues in processed commodities. Therefore, the consumer risk assessment could not be finalised for the **MRL requests**.

The data available on **environmental fate and behaviour** are sufficient to carry out the required environmental exposure assessments at the European Union (EU) level. For the use on tulips and iris, there is the potential for groundwater exposure by flutolanil above the parametric drinking water limit of 0.1 μg/L in geoclimatic situations represented by three out of six FOCUS scenarios. A data gap was identified for information on the effect of water treatment processes on the nature of the residues of flutolanil and metabolite M-11 that might be present in surface water, when surface water is abstracted for the production of drinking water. This gap leads to the fact that the consumer risk assessment from the consumption of drinking water could not be finalised for all the representative uses.

For **ecotoxicology**, a high risk to wild mammals, aquatic organisms, bees and earthworms was concluded for the representative uses on tulips and iris.

According to point 3.6.5 and 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605, based on the available information, it can be concluded that flutolanil is not an endocrine disruptor for humans and non-target organisms.

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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 and maximum 30 months, depending on the type of information requested.

In accordance with Article 1 of the Regulation, the RMS the Netherlands and co-RMS the United Kingdom received an application from Nihon Nohyaku Co., Ltd. for the renewal of approval of the active substance flutolanil. In addition, Nihon Nohyaku Co., Ltd. submitted applications for maximum residue levels (MRLs) as referred to in Article 7 of Regulation (EC) No 396/2005[3]. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicant, the co-RMS (the United Kingdom), the European Commission and EFSA about the admissibility.

The RMS provided its initial evaluation of the dossier on flutolanil in the RAR, which was received by EFSA on 3 July 2018 (the Netherlands, 2018). The RAR included a proposal to set MRLs, submitted under Article 7 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, Nihon Nohyaku Co., Ltd. for consultation and comments on 16 October 2018. EFSA also provided comments. In addition, EFSA conducted a public consultation on the RAR. EFSA collated and forwarded all comments received to the European Commission on 19 December 2018. At the same time, the collated comments were forwarded to the RMS for compilation and evaluation in the format of reporting table. In addition, the applicant was invited to respond to the comments received 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, the RMS on 14 February 2019. 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.

In addition, following a consultation with Member States in the Pesticides Peer Review Expert meeting 06 (12–13 June 2019) in the ecotoxicology area, it was considered necessary to apply an additional clock stop of 30 months in accordance with Commission Implementing Regulation (EU) No 2018/1659, to be able to conclude whether the approval criteria for endocrine disruption in line with

[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] 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.

[3] 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.

the scientific criteria for the determination of endocrine-disrupting properties, as laid down in Commission Regulation (EU) 2018/605[4], are met.

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

The conclusions arising from the consideration by EFSA, and as appropriate by the RMS, of the points identified in the evaluation table, together with the outcome of the expert consultation and the written consultation on the assessment of additional information, where these took place, were reported in the final column of the evaluation table.

A final consultation on the conclusions arising from the peer review of the risk assessment and on the proposed MRLs took place with Member States via a written procedure in December 2023.

This conclusion report summarises the outcome of the peer review of the risk assessment of the active substance and the representative formulation, evaluated on the basis of the representative use of flutolanil as a fungicide on potatoes, tulips and iris, 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. MRLs were assessed in potatoes in-furrow treatment.

A list of the relevant end points for the active substance and the formulation and the proposed MRLs is provided in Appendix B. In addition, the considerations as regards the cut-off criteria for flutolanil 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, 2023), which is a compilation of the documentation developed to evaluate and address all issues raised in the peer review, from the initial commenting phase to the conclusion. The peer review report comprises the following documents, in which all views expressed during the course of the peer review, including minority views, where applicable, can be found:

- the comments received on the RAR;
- the reporting table (14 February 2019 and 29 June 2022[5]);
- the evaluation table (16 January 2023);
- the report(s) of the scientific consultation with Member State experts (where relevant);
- the comments received on the assessment of the additional information (where relevant);
- the comments received on the draft EFSA conclusion.

Given the importance of the RAR, including its revisions (The Netherlands, 2022), and the peer review report, both documents are considered as background documents to this conclusion and thus are made publicly available.

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

The active substance and the formulation for representative uses

Flutolanil[6] is the ISO common name for 3′-isopropoxy-2-(trifluoromethyl)benzanilide (IUPAC).

The formulation for representative uses for the evaluation was 'Moncut 40 SC', a suspension concentrate (SC) containing 460 g/L flutolanil. It should be mentioned that the formulation for representative uses is manufactured with and without a dye.

The representative uses evaluated were applications before planting or at planting on ware, seed and starch potatoes and spray applications followed by incorporation in soil in rows where tulip and iris bulbs are planted, for the control of *Rhizoctonia solani* in the EU. It should be noted that the application rate for potatoes is based on planting up to 4 t/ha which is considered as a realistic GAP

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

[5] Reporting table following consultation on the revised RAR on the assessment of the endocrine-disrupting properties and negligible exposure assessment made available after the 3-month clock stop.

[6] It should be noted that flutolanil is identified as a pesticide active substance that meets the definition of per- and polyfluoroalkyl substances (PFAS) based on its chemical structure as reported on the ECHA website at the following link: https://echa.europa.eu/hot-topics/perfluoroalkyl-chemicals-pfas.

for ware and starch potatoes, but unrealistic GAP for seed potatoes for some MSs. Full details of the GAPs can be found in the list of end points in Appendix B.

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

Conclusions of the evaluation

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

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

The applicant proposed the minimum purity of the active substance as manufactured as 975 g/kg. Based on batch data from industrial scale production and also on quality control data, the RMS, supported by EFSA, proposed to update the specification to minimum 985 g/kg, considering also the changes in the impurity profile. It should be noted that evaluation of the toxicological relevance of one impurity is open (see Section 2) and consequently, new data such as spectral data, content of the impurities before and after the storage of the formulation and methods for analysis of the relevant impurities in the formulation might be required. The batches used in the toxicological assessment support both original and newly proposed reference specification except for the batch used in one of the toxicological studies (see Sections 2 and 9.1.1). There was insufficient information available to confirm whether the batches used in the ecotoxicology studies are compliant with the reference specification (see Sections 5 and 10). A FAO specification is not available for flutolanil.

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

Adequate methods were available for the generation of data required for the risk assessment except for the toxicological studies for which information on the methods used has not been provided (data gap; see Sections 2 and 9.1.1). Methods of analysis are available for the determination of the active substance in the technical material and in the formulation for representative uses.

The residue definition for monitoring in plant matrices was defined as flutolanil. The DFG S19 multiresidue method with GC–MS can be used for the determination of flutolanil in high water content matrices with a limit of quantification (LOQ) of 0.01 mg/kg flutolanil, while the QuEChERS multiresidue enforcement method with HPLC–MS/MS can be used for the determination of residues of flutolanil in high acid content, high oil content and dry crop matrices with LOQs of 0.01 mg/kg. It is noted that to address extraction efficiency of the DFG S19 method for high water content matrices, the applicant submitted a reasoned statement, which has been considered acceptable by the RMS. However, EFSA and some MSs considered that the extraction efficiency of the method is still not sufficiently addressed (data gap, see Section 10). In addition, for the same method, a formal data gap was identified for the final ILV study report (data gaps; see Section 10). Appropriate LC–MS/MS methods are available for the determination of residues of flutolanil in food of animal origin with a LOQ of 0.01 mg/kg in all animal matrices.

Appropriate LC–MS/MS methods exist for monitoring flutolanil in soil and water with LOQs of 0.01 mg/kg and 0.1 μg/L, respectively. Flutolanil residues in air can be monitored by HPLC-UV with a LOQ of 2.7 $\mu g/m^3$.

Monitoring the residues of flutolanil and M-4 in body tissues can be done using LC–MS/MS method with LOQs of 0.01 mg/kg, for each analyte. It should be noted that the method quantifies M-4 free and conjugated since an enzymatic hydrolysis step is included in the analysis. Residue of flutolanil in body fluids can be monitored by LC–MS/MS with an LOQ of 0.05 mg/L. Data gap for a method for monitoring of M-4 in body fluids was identified.

2. Mammalian toxicity

The toxicological profile of the active substance flutolanil and its metabolites was discussed at the Pesticide Peer Review Meeting 7 in June 2019. The assessment is based on the following guidance documents: European Commission (2003, 2012), EFSA (2014b, 2017), EFSA PPR Panel (2012) and ECHA (2017).

Regarding the proposed reference specification, the toxicological relevance of one impurity cannot be concluded based on the available data (data gap; see Section 10). The composition of the batches used in the toxicity studies can be considered representative of the specification proposed for the

renewal as well as of the original one, except that insufficient information is available to judge if the batch used in the 2-year rat study is sufficiently representative of the reference specification. Furthermore, information on analytical methods used in support of the toxicological studies has not been provided (issue not finalised; see Sections 1 and 9.1.1).

After oral administration, flutolanil is **absorbed** up to 70%, and widely **distributed**, without showing potential for bioaccumulation in any tissue. Flutolanil is rapidly **excreted** in urine and faeces, the primary **metabolite** being M-4. *In vitro* comparative metabolism with liver microsomes from rat, mouse, rabbit, dog and human indicated that the respective metabolic pathways of flutolanil were qualitatively comparable. The residue definition for human biomonitoring (body fluids and tissues) does include flutolanil and the metabolite M-04.

In **acute toxicity** studies, flutolanil was shown to be of low toxicity by the oral, dermal or inhalation routes of exposure. It was not an irritant to eyes or skin, not phototoxic *in vitro* and it did not cause skin sensitisation.

In **short-term toxicity** studies, the main target organs were the liver and the thyroid. The relevant NOAELs identified for the different species were 37 mg/kg body weight (bw) per day for the rat, based on increased thyroid weight in a 90-day study; 80 mg/kg bw per day for the dog, based on increased liver weight with hepatocyte hypertrophy in a 90-day study; and 680 mg/kg bw per day for the mouse (supportive study), based on reduced body weight gain and increased liver weight in a 90-day study. Additionally, in a 2-year dog study, the NOAEL was 50 mg/kg bw per day based on clinical signs (emesis, salivation, excretion, soft faeces).

Regarding **genotoxicity** assessment, *in vitro* studies (Ames test and mouse lymphoma assay) demonstrated that flutolanil is not mutagenic. One *in vitro* chromosome aberration test (with hamster lung cells) was weakly positive but not confirmed in another test with human lymphocytes. Furthermore, the *in vivo* micronucleus tests gave negative results with sufficient evidence of exposure of the bone marrow. Based on the available data, flutolanil is unlikely to be genotoxic.

In the **long-term** rat toxicity study, the systemic NOAEL is 8.7 mg/kg bw per day based on slight anaemia in females and histopathological changes in the spleen in males. Based on increased incidences of rare tumours (liver cholangioma and urinary bladder papilloma), with a carcinogenic NOAEL of 8.7 mg/kg bw per day, the experts agreed that the criteria for classification according to Regulation (EC) No 1272/2008[7] may be met for **category 2 carcinogen**.[8] In the mouse study, the systemic NOAEL is 32 mg/kg bw per day based on periacinar hepatocytic fatty vacuolation (in males), no treatment-related tumours were observed.

In the **multigeneration** rat study, no adverse effect was observed on the reproductive parameters and on the offspring development up to the highest dose tested (1614 mg/kg bw per day). The parental NOAEL was 157 mg/kg bw per day based on increased liver weight. In the **developmental** studies, all maternal NOAELs were the highest dose tested (1,000 mg/kg bw per day). In rats, the developmental effects included increased incidences of skeletal findings (metacarpal/metatarsal) and malformations with a NOAEL of 200 mg/kg bw per day. In rabbits, an increased incidence of resorptions and (early embryo) fetal deaths in two different studies triggered an overall developmental NOAEL of 40 mg/kg bw per day. During the experts' meeting,[9] it was concluded that the criteria for classification according to Regulation (EC) No 1272/2008[6] may be met for **category 2 reproductive** toxicity, considering the findings in the rabbit studies (increased resorptions/embryofetal deaths), and some incidences of fetal malformations in the rat study.

Regarding its **neurotoxic** potential, in the absence of alerting chemical structure or indications in the available studies (including specific 4-week rat neurotoxicity study), flutolanil can be concluded as unlikely to be neurotoxic to humans. With regard to the **immunotoxic** potential, the agreed NOAEL in a T-cell-dependent antibody assay is 61.1 mg/kg bw per day based on the dose-related reduction in overall spleen cell count and viable cells/ spleen consistent with the histopathological changes observed in the spleen in the 2-year rat study. Therefore, the experts agreed that a weak immunotoxic potential cannot be excluded[10] (issue not finalised; see Section 9.1.1).

Regarding the toxicological reference values, the **acceptable daily intake** (ADI) is 0.09 mg/kg bw per day based on the 2-year rat study; the **acute reference dose** (ARfD) is 0.4 mg/kg bw based on

[7] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. OJ L 353, 31.12.2008, p. 1–1355.
[8] Refer to experts' consultation 2.2 in the Report of Pesticides Peer Review Experts' Meeting 07 (EFSA, 2023).
[9] Refer to experts' consultation 2.3 in the Report of Pesticides Peer Review Experts' Meeting 07 (EFSA, 2023).
[10] Refer to experts' consultation 2.4 in the Report of Pesticides Peer Review Experts' Meeting 07 (EFSA, 2023).

the developmental rabbit study. The **acceptable operator exposure level** (AOEL) is 0.26 mg/kg bw per day based on the 90-day rat study, with a correction for an oral absorption value of 70%. The **acute acceptable operator exposure level** (AAOEL) is 0.28 mg/kg bw based on the developmental rabbit study, correcting for the oral absorption of 70%. The standard uncertainty factor (UF) of 100 was applied to the derivation of all values. Default dermal absorption values of 10% for the concentrate and 50% for the in-use dilution were applied in the absence of study with the representative formulation Moncut 40 SC. It is noted that during the previous peer review of flutolanil (EFSA, 2008), the same ADI was derived, the AOEL was 0.56 mg/kg bw per day based on 90-day dog study (applying a correction for 70% oral absorption), and the derivation of an ARfD was considered as not necessary.

Non-dietary exposure estimates were discussed for both representative uses[11]: soil treatment before planting flower bulbs (tulips/iris) and potato seed tuber treatment. For the operator exposure during application to and planting of **seed potatoes**, the results of a field study were considered, including five sites with one operator investigated per site, scaled up for an 8 h working day, with use of the maximum measured value for the short-term exposure and of the parametric 95th percentile for acute exposure. The short-term exposure at one site was higher than in the other sites (due to one operator at site 5), i.e. amounting up to 108% of AOEL with use of normal workwear and gloves versus 16–77% of AOEL for the others. The experts concurred that this should be considered as part of a realistic scenario. The RMS is of the opinion that this exceedance of the AOEL is an overestimated value. The acute exposure for operators is estimated at 94% of the AAOEL with the use of normal workwear and gloves. For the worker exposure, the results of the same field study were considered applicable since some of the operators were handling treated potatoes. Exposure of bystanders and residents is expected to be not significant for this representative use on potato seed tuber before and during planting.

For the operator during use on fields where **flower bulbs** (tulips/iris) are planted, the predicted systemic exposure estimates with the EFSA calculator (EFSA, 2014b) are below the (A)AOEL when using work wear and gloves during mixing/loading and application. The predicted systemic exposure of residents and bystanders is below the (A)AOEL when drift reduction is applied as well as a 5 m buffer zone (excluding the exposure pathway of 'entry into treated crops' since it is not relevant for the representative use). The exposure of workers is not expected as the application is to bare soil followed by incorporation (mechanical planting) to a depth of at least 10 cm.

Regarding the assessment of **metabolites,** the experts discussed M-101, M-102, M-03, M-06, M-11, M-02, M-05 and M-07.[12] It is noted that the metabolite **M-04**, being a major rat metabolite, is considered as covered by the toxicological reference values of flutolanil. For **M-101**, the majority of the experts agreed that its aneugenic potential was sufficiently tested with fluopyram (for which M-101 is a major metabolite) (EFSA, 2013a). Based on a 28-day rat study, **M-101** seems to be more toxic than flutolanil with additional target organ toxicity (kidney). The agreed ADI is 0.004 mg/kg bw per day, based on the 28-day rat study and applying an overall UF of 1,000. For **M-102**, in the absence of a conclusion on the aneugenic potential (no data available), the experts agreed that toxicological reference values could not be set (data gap; see Sections 3 and 9.1.1). Notwithstanding that conclusion, EFSA notes that based on the EFSA guidance on aneugenicity assessment (EFSA, 2021), in principle, it is possible to establish health-based guidance values for substances that are aneugenic but not clastogenic nor causing gene mutations. Consequently, the ADI of 0.25 mg/kg bw per day agreed during the expert meeting (applying an UF of 1,000 to the 28-day rat NOAEL of 252 mg/kg bw per day) may be applicable to the metabolite M-102. For both M-101 and M-102, an additional UF of 10 was applied to take into account the extrapolation from subacute to long-term toxicity and the lack of investigation of some key toxicological endpoints. Similarly, for these two metabolites, an ARfD could not be derived on the basis of the limited data package (data gap; see Sections 3 and 9.1.1). The metabolites **M-03**, **M-06** and **M-11** are considered structurally similar to flutolanil and, based on QSAR and read-across analysis, these metabolites do not raise a concern for genotoxicity. The metabolites **M-02**, **M-05** and **M-07** have an additional organic functional group on the benzene group, i.e. OH group. Based on read-across and Q-SAR analysis, the genotoxic potential of metabolites M-02, M-05 and M-07 cannot be excluded based on alerts, and the general toxicity profile cannot be concluded (data gap for M-02; see Sections 3 and 9.1.1). For the metabolite trifluoroacetic acid (**TFA**), the toxicological reference values agreed during the peer review of flurtamone (EFSA, 2016) are applicable: an ADI of 0.05 mg/kg bw per day based on a 90-

[11] Refer to experts' consultation 2.9 in the Report of Pesticides Peer Review Experts' Meeting 07 (EFSA, 2023).
[12] Refer to experts' consultation 2.6 and 2.7 in the Report of Pesticides Peer Review Experts' Meeting 07 (EFSA, 2023).

day rat study, applying an increased UF of 200 for the extrapolation from subchronic to chronic toxicity; and an ARfD of 0.05 mg/kg bw based on a 14-day rat study, applying an UF of 200 for the incomplete data package.[13,14]

3. Residues

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

3.1. Representative uses

Flutolanil was discussed at the Pesticides Peer Review Experts' Meeting 9 in June 2019.

Primary metabolism studies of flutolanil were investigated in root crops (potatoes), leafy crops (cabbage), cereals/(rice) and pulses/oilseeds (peanuts) following foliar, soil and seed treatment. For potatoes, the treatments were by seed and in-furrow with both aniline and phenyl-labelled flutolanil covering all uses under assessment (representative uses and MRL application). Based on these studies, a general residue definition for enforcement could be proposed as flutolanil only. For the risk assessment, two separate residue definitions were proposed: (1) sum of flutolanil and metabolite M-04 (free and conjugated), expressed as flutolanil; (2) **Metabolite M-101**. In the absence of acute toxicological data for M-101 (see Section 2), the proposed residue definitions for risk assessment are provisional (issue not finalised; see Section 9.1.1). In addition, the metabolites **M-02** found in potatoes foliage for 44% of total radioactive residue (TRR), and **M-102** found in potatoes tuber 38% of TRR, should require further investigations on genotoxicity and general toxicity (M-102 and M-02) (see Section 2) considering their occurrence in the metabolism studies.

Confined rotational crops studies conducted with spinach, barley and radish covering all plant back intervals allowed to depict the nature of residues in rotational crops to be characterised. Flutolanil is extensively metabolised in rotational crops. Apart from metabolite trifluoroacetic acid (TFA) significantly formed in rotational crops, the metabolic pattern was similar to primary crops. Therefore, the residue definitions proposed for primary crops also apply to rotational crops. Nonetheless, **trifluoroacetic acid (TFA**) is also considered for inclusion in the risk assessment residue definition, noting that it may be also released by other active substances; for the toxicological assessment of TFA see Section 2.

In a phenyl ring-labelled hydrolysis study simulating the conditions of pasteurisation, boiling/ brewing/baking and sterilisation flutolanil were shown to be stable. Thus, an additional study investigating aniline-labelled flutolanil was not needed. The stability of residues in plant matrices during storage was properly addressed for all compounds included in the residue definitions for enforcement and risk assessment.

The available residue trials for the magnitude of residues in primary crops were sufficient to support the representative uses. Concerning the magnitude of residues in rotational crops, only two trials, conducted on spinach, radish and barley which analysed for parent, M-04 (including conjugates), M-02 (including conjugates), M-101 and M-102 were available and they were not sufficient (data gap, see Section 10). However, field rotational crops trials for TFA were not available although they are needed (data gap; see Section 9.1.1).

The stability of residues in animal matrices during storage was properly addressed for all compounds included in the residue definitions.

The metabolism of flutolanil in ruminants was sufficiently addressed. For poultry however, only one metabolism study performed with the phenyl labelling of flutolanil provided reliable information. This study indicates that the parent compound is extensively degraded into several metabolites in eggs, liver and muscle, with metabolite M-101 being the predominant one. Since the potential cleavage of the molecule was noted, the majority of the experts[15] (RMS excluded) were in favour of asking for a new guideline-compliant metabolism study on poultry conducted with the aniline labelling of flutolanil (data gap; see Section 9.1.1). The available old aniline-labelled study did not allow a conclusion on the

[13] Note: Adverse developmental effects in rabbits after exposure to TFA were observed in a development toxicity study (2021) conducted by the applicant Bayer and the REACH lead registrant producer of TFA under Regulation (EC) No 1907/2006 (REACH); as investigations on TFA revealed potential adverse effects, a notification under Article 56 of regulation (EC) 1107/2009 was submitted on 7 January 2021. Further follow-up investigations are currently underway.

[14] It should be noted that trifluoroacetic acid is identified as a metabolite that meets the definition of per- and polyfluoroalkyl substances (PFAS) based on its chemical structure as reported on the ECHA website at the following link: https://echa.europa.eu/hot-topics/perfluoroalkyl-chemicals-pfas.

[15] Refer to the Report of Pesticides Peer Review Meeting 09 (EFSA, 2023).

nature of residues in poultry to be drawn due to several shortcomings (i.e. low TRR levels and no metabolites identification). Based on the available metabolism studies, the residue definition for enforcement was proposed as flutolanil for both ruminants and poultry, while for the risk assessment, separate proposals were made provisionally also considering the toxicological evaluation. Therefore, for ruminants: (1) sum of flutolanil and metabolite M-04 (free and conjugated), expressed as flutolanil; (2) metabolite M-02 (free and conjugated) noting that the expression of the residue definition (separately or combined) is pending the outcome of toxicological evaluation of M-02 free and conjugates (see Section 2). For poultry, (1) flutolanil (2) Metabolite M-101. The inclusion of metabolites M-02 (free and conjugated) and M-102 may need to be considered, pending on the outcome of requested data to address their toxicological profile (see Section 2).

Livestock feeding studies investigating residue levels for all compounds proposed for inclusion in the residue definitions were available.

Metabolism studies for fish were not submitted since the calculated dietary burden was below 0.1 mg/kg.

Regarding the magnitude of residues in pollen and bee products for human consumption, these would not be triggered in the primary crops due to the application timing (BBCH 00), but they are triggered due to the occurrence of residues in the rotational crops (data gap; see Section 10).

Two provisional consumer risk assessment calculations only for residues defined as flutolanil were made by using EFSA PRIMo rev.2 and EFSA PRIMo rev 3.1. The chronic (TMDI) was calculated for maximum 1.8% of ADI (FR toddler) by using PRIMo rev.2 and 2% of ADI (NL toddlers) by using PRIMo 3.1. For the acute intake (IESTI), the max 9.2% of ARfD resulted for both PRIMo. However, considering the data gaps related to the other residue definitions proposed in this conclusion (see data gaps for M-101, M-102 and M-02 in Section 2; residue levels of TFA in rotational crops; metabolism of flutolanil in poultry), the overall consumer risk assessment for flutolanil residues could not be finalised (issue not finalised; see Section 9.1.1).

It is noted that, in the framework of the current peer review for the renewal of the approval of flutolanil, the derivation of an ARfD was considered necessary (see Section 2). Thus, acute consumer intake calculations associated with the MRLs derived during the Article 12 review under Regulation (EC) No 396/2005 (EFSA, 2013b) were performed; the IESTI accounted for 9.2% of the ARfD for potatoes UK diet. However, this exposure calculation is indicative since it covers only residues of flutolanil.

The consumer risk assessment from the consumption of drinking water is also not finalised considering the lack of appropriate information to address the effect of water treatment processes on the nature of residues of the flutolanil and metabolite M-11, that might be present in surface water, when surface water is abstracted for drinking water (issue not finalised; see Sections 4 and 9.1.1).

3.2. Maximum residue levels

The number of valid residue trials supporting the GAP proposed for the MRL application (in-furrow treatment on potatoes) was sufficient to derive MRL and risk assessment values. A conversion factor of 1.33 was derived.

Concerning the magnitude of residues in rotational crops, the available trials were appropriately dosed compared to the maximum seasonal rate of GAPs (in-furrow treatment on potatoes) and showed relevant residue levels occur following the proposed uses.

Since only two trials (1 NEU and 1 SEU) for each investigated crop (see Section 3.1) were not sufficient to conclude, residue levels need to be determined in at least four rotational field trials (2NEU/2SEU) on each crop representative of the relevant crop groups is needed (issue not finalised for the representative use and the MRL application; see Section 9.2.1); furthermore, trials on pulses and oilseeds crops were missing. The trials should be performed in the main production area representative for the crops and should cover the maximum seasonal rate of application of the intended use in the MRL application. As regards TFA occurrence, no data was submitted under the current application (see Section 3.1).

Regarding the nature of M-04 and M-101 residues in processed commodities, standard hydrolysis studies were not provided although they are needed since these compounds were found at relevant level in both primary and rotational crops (issue not finalised for the MRL application; see Section 9.2.1).

The dietary burden intake was triggered for ruminants and poultry considering the available rotational field trials. The available feeding studies performed on lactating cattle and laying hens analysing for flutolanil and all metabolites relevant for the proposed residue definitions were used to derive MRL and risk assessment values in livestock commodities (see Appendix B).

The overall consumer risk assessment for flutolanil residues could not be finalised due to the reasons mentioned above, as well as the lack of data on the residues in rotational crops and on the nature of residues in processed commodities.

4. Environmental fate and behaviour

Flutolanil was discussed at the Pesticides Peer Review Meeting 5 in June 2019.

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, flutolanil exhibited high to very high persistence. No major metabolites (> 10% applied radioactivity (AR)) or minor metabolites in soil at > 5% AR at two or more consecutive time points or > 5% AR and increasing at the final time point in soil were formed. Mineralisation of the aniline and phenyl ring ^{14}C radiolabel to carbon dioxide accounted for 0.4–27.5% AR after 105–365 days and 0.8–1.6% AR after 120 days, respectively. The formation of unextractable residues for these radiolabels accounted for 3.0–27.9% AR after 105–365 days and 3.2–4.1% AR after 120 days, respectively. In anaerobic soil incubations, flutolanil was essentially stable. Photodegradation does not play a role in the degradation of flutolanil in soil. Flutolanil exhibited medium to low mobility in soil. Because less than four adsorption constant values were available for flutolanil according to OECD 106 test guideline (data gap; see Section 10), the exposure assessment was carried out using the lowest value of the remaining three experiments.[16] It was concluded that there was no indication that adsorption of flutolanil was pH dependent based on the limited number of endpoints available. In satisfactory field dissipation studies carried out at three sites in the Netherlands and one site in the UK (spray application to the soil surface on bare soil plots in two trials and spray application to the soil surface on bare soil followed by immediate incorporation in other two trials) flutolanil exhibited medium to high persistence. Sample analyses were only carried out for the parent flutolanil. Field study DT50 values were accepted as being reasonable estimates of degradation and were normalised to FOCUS reference conditions (20°C and pF2 soil moisture) using the time step normalisation procedure in accordance with FOCUS (FOCUS, 2006) kinetics guidance. The experts of the Pesticides Peer Review Meeting 05 identified some uncertainties over the study design of the spray field study results (Manningtree and Ottersum trials), and therefore, a data gap was identified for two additional soil DegT50s for flutolanil from field trials in line with the current guidelines, but it was agreed that the endpoints could be used for triggering and modelling to complete the exposure assessment (data gap; see Section 10).[17] The possible accumulation of flutolanil under field conditions was determined in a soil trial site in the USA. However, as the representativeness of this USA study for the EU agroclimatic conditions has not been demonstrated (data gap; see Section 10), the results were not used in the exposure assessment. The field data endpoints were not combined with laboratory values to derive modelling endpoints.

In laboratory incubations in dark aerobic natural sediment water systems, flutolanil partitioned from the water phase into the sediment. No transformation products ≥ 10% AR were observed in the water or sediment layer. Metabolite M-11 was found > 5% AR at two consecutive time points (5.4% at day 61 and 6.9% AR at day 105) in the water compartment. No significant quantities of bound residues (< 26.3% AR) or volatiles (< 5.2% AR) were observed throughout the duration of the study. The rate of decline of flutolanil in a laboratory sterile aqueous photolysis experiment was slow relative to that occurred in the aerobic sediment water incubations. No chromatographically resolved component (excluding flutolanil) accounted for > 3% AR. The necessary surface water and sediment exposure assessments (predicted environmental concentrations (PEC) calculations) were carried out for flutolanil and its metabolite M-11 using the appropriate step 3 (FOCUS, 2001) and step 4 calculations.[18] The step 4 calculations 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 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%) combined with 90% drift nozzle reduction 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 while run-off mitigation is included in the step 4 calculations available, the FOCUS (FOCUS, 2007) report acknowledges that for substances with K_{Foc} < 2,000 mL/g (i.e. flutolanil), the

[16] Refer to experts' consultation 4.2 of the Report of Pesticides Peer Review Meeting 05 (EFSA, 2023).
[17] Refer to experts' consultation 4.1 of the Report of Pesticides Peer Review Meeting 05 (EFSA, 2023).
[18] Simulations utilised the agreed Q10 of 2.58 (following FOCUS, 2008) and Walker equation coefficient of 0.7.

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, PELMO 5.5.3 and MACRO 5.5.4. The potential for groundwater exposure from the representative uses by flutolanil above the parametric drinking water limit of 0.1 μg/L was concluded to be low in geoclimatic situations that are represented by all nine FOCUS groundwater scenarios for the representative uses on potatoes (both incorporation and injection applications). For the representative use on flower bulbs (onion used as a surrogate crop), three of six FOCUS scenarios exceeded the limit of 0.1 μg/L when FOCUS PELMO is used for PECgw calculations.

The applicant did not provide appropriate information to address the effect of water treatment processes on the nature of the residues of flutolanil, and metabolite M-11 that might be present in surface water, when surface water is abstracted for drinking water. This has led to the identification of a data gap and results in the consumer risk assessment not being finalised (issue not finalised; see Sections 3 and 9.1.1).

The PEC in soil, surface water, sediment and groundwater covering the representative uses assessed can be found in Appendix B of this conclusion.

5. Ecotoxicology

The risk assessment was based on the following documents: European Commission (2002), SETAC (2001), EFSA (2009), EFSA PPR Panel (2013), EFSA (2013c) and ECHA/EFSA (2018).

Some aspects of the risk assessment for non-target organisms (NTOs) for flutolanil were discussed at the Pesticides Peer Review Meeting 6 in June 2019.

The information available to assess the compliance of the batches used in the ecotoxicological studies with the technical specifications (both original and proposed) was considered insufficient (data gap; see Section 10).

A low risk to **birds** via dietary exposure was concluded for all the representative uses both for flutolanil and the pertinent plant metabolites. Since the representative uses include potato seed tubers, biological characteristics of the common crane were selected as generic focal species for representing potato-eating birds. Uncertainties have been raised about the relevance of this species for that scenario, e.g. it is not clear whether common cranes feed on potatoes. This scenario is not covered in the guidance currently available (EFSA, 2009).[19] Therefore, it was agreed to use the common crane as a focal species until more guidance is available.

For the representative uses on potatoes, a low dietary risk to **mammals** was concluded. For the representative use on tulips and iris, a low acute risk was identified, while a high reproductive risk to mammals was concluded.

A low acute and chronic risk was concluded for mammals when exposed to plant metabolites except for the metabolite M-4 and exposure through treated weeds in the field. This scenario is not covered in the current guidance but was considered relevant by the RMS. Overall, however, considering that: (i) the risk assessment is a screening assessment i.e. the metabolite is assumed as 10 times more toxic than the parent, (ii) the toxicity exposure ratio (TER) is very close to the trigger (4.7), (iii) the risk assessment for weeds is done under conservative assumptions (mammals feeding completely on the treated weeds) and (iv) and it is not known whether weeds are a relevant route of exposure as the representative uses result in incorporation in soil, the risk was considered as low.

Toxicity data with the active substance were available for fish, aquatic invertebrates and algae. The formulation was only tested with algae. However, since algae were not the most sensitive aquatic taxon for flutolanil, it is uncertain whether the toxicity data of the active substance correctly predict the toxicity of the formulation for representative uses. Therefore, this issue has to be further considered at MS level.

Based on the available data and risk assessment, a low risk to **aquatic organisms** is concluded for the representative uses on potatoes by using FOCUS Step 1–3. For the representative use on tulip and iris, a low risk was concluded for fish (acute and chronic) and algae by using FOCUS step 1–3. A high acute risk to aquatic invertebrates was concluded for three of seven FOCUS scenarios. A high chronic risk to aquatic invertebrates was concluded for all the relevant FOCUS scenarios even with the implementation of mitigation measures in FOCUS Step 4.

[19] See reporting table 5(21).

For the pertinent aquatic metabolite M-11, a high risk could not be excluded based on a screening assessment (metabolite considered 10 times more toxic than the parent) for all the assessed representative uses[20] (data gap; see Section 10).

Based on the available data, a low acute risk to **honeybees** was concluded by using the SANCO (European Commission, 2002) and EFSA (2013c) guidance for all the representative uses. A low chronic risk to adult bees and low risk to larvae were demonstrated for the representative uses on potatoes. The chronic risk assessment for adult bees resulted in the exposure toxicity ratio (ETR) (0.031) slightly above the trigger (0.03) for the treated crop and for succeeding crops according to EFSA (2013c) for the representative use on tulips and iris. A semifield study was available. Although slight transient effects on flight intensity were observed in the absence of any other effect, that study presented some deficiencies such as only two replicates were available in the control, the exposure lasted only 8 days and a different formulation than the representative one was used. Based on those drawbacks, the study could not be considered further in the assessment. Overall although the TER is only slightly breached in Tier 1 risk assessment, low chronic risk could not be fully demonstrated. It has to be noted that the RMS concluded low risk with the following reasons: (i) ETR is only slightly above the trigger and (ii) only marginal effects were observed in the semi-field study.

Similar to the parent, high risk could not be excluded for the pertinent metabolite M-4 occurring in pollen and nectar, based on a screening risk assessment for the representative use on tulips and iris (data gap; see Section 10).

Low risk to **larvae** was concluded as well as low risk to honeybees from exposure to contaminated water. Data were not available to assess sublethal effects, for accumulative effects and for wild bees (data gap to assess sublethal effects; see Section 10).

Tier 1 and 2 toxicity data were available for **non-target arthropods**. Based on those data, it was concluded that flutolanil posed low risk to non-target arthropods.

Toxicity data with the formulation for representative uses were available for **earthworms**, other soil macro-organisms and soil microorganisms. Low risk to soil organisms was concluded for all the representative uses based on Tier 1 data.

A low risk was concluded for organisms involved in **biological methods for sewage treatment**.

6. Endocrine disruption properties

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

With regard to T modality, the data set was considered complete and a pattern of T-mediated adversity was not identified. With regard to EAS modality, the data set was considered complete based on the available information on endocrine activity and a pattern of EAS-mediated adversity was not observed.

Therefore, based on the available and sufficient data set, it was concluded that the ED criteria are not met for the EAST modalities (Scenario 1a of the EFSA/ECHA (2018) ED Guidance).

The outcome of the assessment reported above for humans also applies to wild mammals as non-target organisms.

For non-target organisms other than mammals, the endocrine activity was sufficiently investigated for EATS modalities, in line with the testing strategy recommended in the ECHA/EFSA guidance (2018). No evidence suggesting T-mediated endocrine activity was observed in the available amphibian metamorphosis assay (AMA). The available fish short-term reproduction assay showed treatment-related effects in a number of parameters both in males and females.[21] These findings were, however, not confirmed in the available level 5 study (Fish Full Life Cycle Test) with the same

[20] For three of six FOCUS scenarios for the representative uses on potatoes for fish, invertebrates including sediment dwellers and for two out of six for algae by using FOCUS step 3 PECsw. For the representative use on tulip, iris, high risk could not be excluded for fish, algae and sediment-dwelling organisms (three of seven FOCUS scenarios) and for all the FOCUS scenarios for aquatic invertebrates.

[21] Refer to experts' consultation 5.3 in Report of the Pesticides Peer Review experts' meeting 06 (EFSA, 2023).

species which did not show any significant effect in any of the measured parameters. Therefore, no adversity was identified for EAS-modalities based on a complete data set.

According to point 3.6.5 and 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605, based on the available information, it can be concluded that flutolanil is not an endocrine disruptor for humans and non-target organisms.

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
Flutolanil	Low risk to soil organisms for the representative uses in potatoes;
	High risk to earthworms for the use in tulips and iris.

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
Flutolanil	No for the representative uses on potatoes; 3 out of 6 FOCUS GW scenarios > 0.1 μg/L for the representative use on tulips and iris (FOCUS PELMO max 0.235 μg/L)	Yes	–	–	Yes

(a): Assessment according to European Commission guidance of the relevance of groundwater metabolites (2003).
(b): FOCUS scenarios or relevant lysimeter. Ranges indicated for FOCUS scenarios include the result from the model giving the highest concentration at each scenario, as needed to comply with European Commission (2014a,b) guidance.

Table 3: Surface water and sediment

Compound (name and/or code)	Ecotoxicology
Flutolanil	High risk to aquatic organisms for the representative use on tulips and iris. Low risk for the representative use on potatoes.
M-11	High risk to aquatic organisms could not be excluded.[a]

(a): Metabolite assumed 10 times more toxic than the parent.

Table 4: Air

Compound (name and/or code)	Toxicology
Flutolanil	Low acute toxicity in rats: LC50 > 5.98 mg/L/4 h (body); LC50 > 2 mg/L/4 h (snout)

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. 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	Potato seed	Tulips, iris
Operator risk		Gloves during MLA[(a)]
Worker exposure		
Bystander/resident exposure		Drift reduction technique and buffer zone of 5 m

(a): MLA: mixing, loading and application tasks.

9. Concerns and related data gaps

9.1. Concerns and related data gaps 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 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 test material used in the toxicological studies has not been demonstrated as fully representative of the reference specification (see Section 2).
    a) No information on the detailed composition of the batches used in the 2-year rat study has been provided (relevant for all representative uses, see Sections 1 and 2);
    b) Validated analytical methods were not provided in support of the toxicological studies (relevant for all representative uses, see Sections 1 and 2).
2) The absence of immunotoxic potential for flutolanil cannot be concluded on the basis of the available data (see Section 2).
    a) Potential for immunotoxicity of flutolanil should be further investigated (relevant for all representative uses, see Section 2).
3) The consumer risk assessment could not be finalised due to the lack of data on the metabolites relevant for the risk assessment residue definitions in plants and animals:
    a) Additional investigations of the acute toxicity of the metabolite M-101 (see Section 2);
    b) Additional investigations of the acute toxicity and aneugenic potential of the metabolite M-102 (see Section 2);
    c) Additional investigations of the genotoxicity and general toxicity profile of the metabolite M-02 (see Section 2);

d) Data on the metabolism of flutolanil in poultry to elucidate the metabolic pattern (see Section 3);
e) Rotational crops field trials analysing TFA residues and covering the maximum PEC soil of flutolanil resulting from the uses of flutolanil (relevant for all representative uses evaluated; see Section 3).

4) The consumer risk assessment from the consumption of drinking water could not be finalised, while satisfactory information was missing on the effect of water treatment processes on the nature of the residues of flutolanil and metabolite **M-11** that might be present in surface water when surface water is abstracted for the production of drinking water (see Sections 3 and 4).

a) An assessment of the effect of water treatment processes on the nature of residues of flutolanil, and its metabolite M-11 present in surface water, when surface water is abstracted for drinking water is not available. In the first instance, a consideration of the processes of ozonation and chlorination appear appropriate. If an argumentation is made that concentrations at the point of abstraction for drinking water purposes will be low, this argumentation should cover metabolites predicted to be in surface water as well as the active substance. Should this consideration indicate novel compounds might be expected to be formed from water treatment, the risk to human or animal health through the consumption of drinking water containing them should be addressed (relevant for all representative uses evaluated; see Section 4).

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:

No critical areas of concern have been identified.

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.)

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		Potato seed	Tulips and iris
Operator risk	Risk identified	X[(b)]	
	Assessment not finalised		
Worker risk	Risk identified	X	
	Assessment not finalised		
Resident/bystander risk	Risk identified		
	Assessment not finalised		
Consumer risk	Risk identified		
	Assessment not finalised	X[3,4]	X[3,4]
Risk to wild non-target terrestrial vertebrates	Risk identified		X
	Assessment not finalised		
Risk to wild non-target terrestrial organisms other than vertebrates	Risk identified		X
	Assessment not finalised		
Risk to aquatic organisms	Risk identified		X
	Assessment not finalised		
Groundwater exposure to active substance	Legal parametric value breached		3/6 FOCUS scenarios
	Assessment not finalised		
Groundwater exposure to metabolites	Legal parametric value breached		
	Parametric value of 10 µg/L[(a)] breached		
	Assessment not finalised		

The superscript numbers relate to the numbered points indicated in Sections 9.1.1 and 9.1.2. Where there is no superscript number, see Sections 2–7 for further information.
(a): Value for non-relevant metabolites prescribed in SANCO/221/2000-rev. 10 final, European Commission (2003)).
(b): Based on a field study with a limited number of operators (and scaling data to a 8-h working day), the maximum exposure estimate for short-term exposure is above the AOEL for one upon five operators.

9.2. Issues related to the maximum residue level applications

9.2.1. Issues not finalised under the maximum residue level applications

1) Besides consumer risk assessment not finalised triggered by the representative uses, additionally for MRL the consumer risk assessment was not finalised due to the missing standard hydrolysis study for M-04 and M-101 and additional field rotational trials (see Section 3).

   a) Standard hydrolysis study for M-04 and M-101 are missing (see Section 3).
   b) At least four rotational field trials (2NEU/2SEU) on each crop representative of the relevant crop groups are needed (see Section 3).

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:

- Final report on the ILV study by J. Torn (2016) (relevant for all representative uses evaluated, see Section 1).

- Data/information on the extraction efficiency for flutolanil in matrices with high water content for the extraction procedure followed by DFG-S19 (relevant for all representative uses evaluated; see Section 1).
- Analytical method for monitoring of M-4 in body fluids (relevant for all representative uses evaluated; see Section 1).
- Further assessment of the compounds (including metabolites) to be included in the residue definition for human biomonitoring (body fluids and tissues) and validated analytical methods (relevant for all representative uses evaluated; see Sections 1 and 2).
- Further assessment of the toxicological relevance of one impurity (relevant for all representative uses evaluated; see Section 2).
- Further rotational crop field trials analysing metabolites M-04, M-02, M-101 and M-102. Concerning the magnitude of residues in rotational crops, only two trials, conducted on spinach, radish and barley which analysed for parent, M-04 (including conjugates), M-02 (including conjugates), M-101 and M-102 were available and they were not sufficient (relevant for all representative uses evaluated, see Section 3).
- Residue trials for the magnitude of residues in bee products for human consumptions and analysed according to the risk assessment residue definitions (relevant for potato use; see Section 3).
- Two additional soil DegT50s for flutolanil from field trials in line with the OECD guidance document ENV/JM/MONO(2016)6 (DegT50 module) and EFSA Guidance Document on soil DegT50(EFSA, 2014a) (relevant for all representative uses evaluated; see Section 4).
- An evaluation of the representativeness of the field dissipation study sites in Castro 1993 and 1994 for the EU agroclimatic conditions to conclusively include or exclude these studies in the environmental exposure assessment (relevant for all representative uses evaluated; see Section 4).
- OECD 106 guideline-compliant soil adsorption measurements in four soils (relevant for all representative uses evaluated; see Section 4).
- Further information on the compliance of the batches used in ecotoxicological studies with the technical specification (both original and proposed) (relevant for all representative uses evaluated; see Sections 1 and 5).
- Further information to address the risk of the metabolite M-11 on aquatic organisms (relevant for all representative uses evaluated; see Section 5).
- Further information to address the risk to bees for the metabolite M-4 (relevant for the representative use on tulip, iris; see Section 5).
- Data to assess sublethal effects on bees (relevant for all representative uses evaluated; see Section 5).

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Abbreviations

AMA	Amphibian Metamorphosis Assay
ADI	acceptable daily intake
AAOEL	acute acceptable operator exposure level
AOEL	acceptable operator exposure level
ARfD	acute reference dose
bw	body weight
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
ECHA	European Chemicals Agency
EEC	European Economic Community
ETR	exposure toxicity ratio
FAO	Food and Agriculture Organization of the United Nations
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)
GGT	gamma glutamyl transferase
GM	geometric mean
GS	growth stage
GSH	glutathione
Hb	haemoglobin
Hct	haematocrit
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

HQ	hazard quotient
$HQ_{contact}$	hazard quotient for contact exposure
HR	hazard rate
IEDI	international estimated daily intake
IESTI	international estimated short-term intake
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
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
LC–MS	liquid chromatography–mass spectrometry
LC–MS-MS	liquid chromatography with tandem mass spectrometry
LD_{50}	lethal dose, median; dosis letalis media
LDD_{50}	lethal dietary dose; median
LDH	lactate dehydrogenase
LH	luteinising 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
MEOGRT	Medaka Extended One-Generation Reproduction Test
M&K	Maximisation test of Magnusson & Kligman
MLA	mixing, loading and application.
mm	millimetre (also used for mean measured concentrations)
mN	milli-Newton
MOA	mode of action
MRL	maximum residue level
MS	mass spectrometry
MSDS	material safety data sheet
MTD	maximum tolerated dose
MWHC	maximum water-holding capacity
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
Pa	pascal
PD	proportion of different food types
PEC	predicted environmental concentration
pF2	pF value of 2 (suction pressure that defines field capacity soil moisture)
ppm	parts per million (10^{-6})
QSAR	quantitative structure–activity relationship
r^2	coefficient of determination
RAC	regulatory acceptable concentration

RAR	Renewal Assessment Report
RMS	Rapporteur Member State
SC	suspension concentrate
SMILES	simplified molecular-input line-entry system
TER	toxicity exposure ratio
TMDI	theoretical maximum daily intake
TRR	total radioactive residue
UF	uncertainty factor
UV	ultraviolet
WHO	World Health Organization

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

Properties		Conclusion[(a)]
CMR	Carcinogenicity (C)	Flutolanil is considered to meet the criteria for classification as category 2 carcinogen (as agreed by the peer review in the absence of harmonised classification in ECHA) according to point 3.6.2 of Annex II of Regulation (EC) No 1107/2009.
	Mutagenicity (M)	Flutolanil is not considered to be a mutagen according to point 3.6.2 of Annex II of Regulation (EC) No 1107/2009.
	Toxic for Reproduction (R)	Flutolanil is considered to meet the criteria for classification as category 2 reproductive toxicant (as agreed by the peer review in the absence of harmonised classification in ECHA) according to point 3.6.4 of Annex II of Regulation (EC) No1107/2009.
Endocrine-disrupting properties		Flutolanil is not considered to meet the criteria for endocrine disruption for human health and non-target organisms according to points 3.6.5 and 3.8.2 of Annex II of Regulation No 1107/2009, as amended by Commission Regulation (EU) 2018/605.
POP	**Persistence**	Flutolanil is not considered to be a persistent organic pollutant (POP) according to point 3.7.1 of Annex II of Regulation (EC) 1107/2009.
	Bioaccumulation	
	Long-range transport	
PBT	**Persistence**	Flutolanil 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.
	Bioaccumulation	
	Toxicity	
vPvB	**Persistence**	Flutolanil 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.
	Bioaccumulation	

(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 representative formulation

Appendix B can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2023.7997

Appendix C – Wording EFSA used in section 4 of this conclusion, in relation to DT and K_{oc} 'classes' exhibited by each compound assessed

Wording	DT_{50} normalised to 20°C for laboratory incubations[22] 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

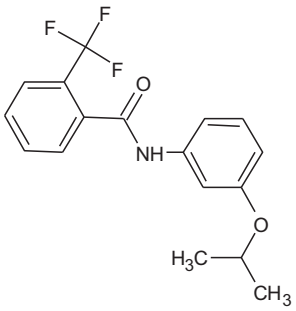
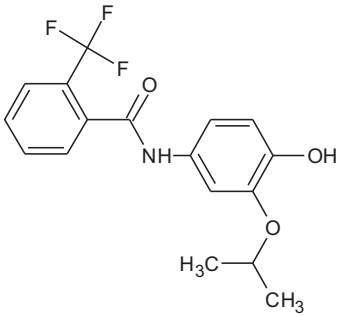
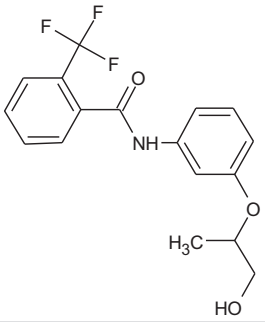
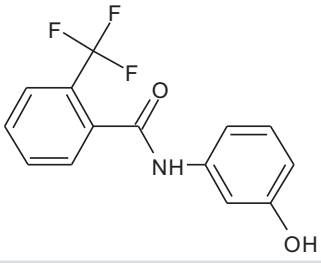
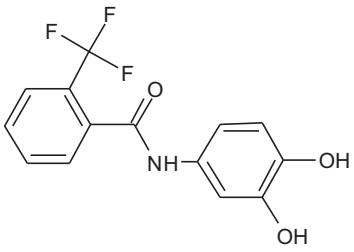
Note these classes and descriptions are unrelated to any persistence class associated with the active substance cut-off criteria in Annex II of Regulation (EC) No 1107/2009. For consideration made in relation to Annex II, see Appendix A.

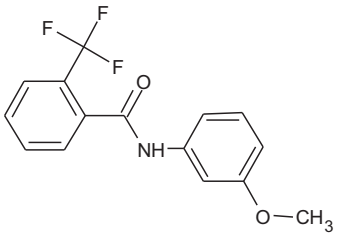
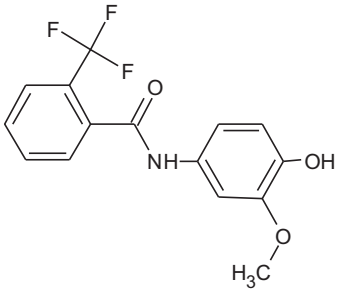
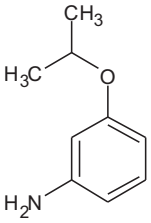
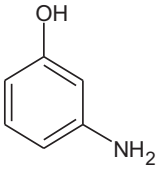
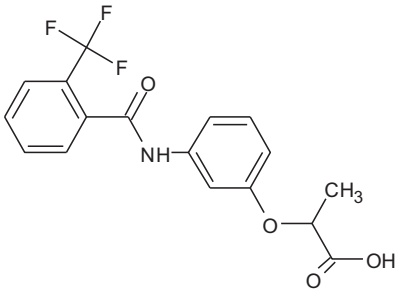
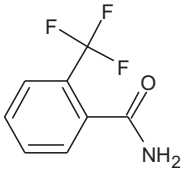
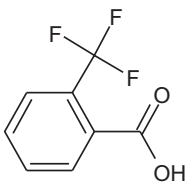
Wording	K_{oc} (either K_{Foc} or K_{doc}) mL/g
Very high mobility	0–50
High mobility	51–150
Medium mobility	151–500
Low mobility	501–2,000
Slight mobility	2,001–5,000
Immobile	> 5,000

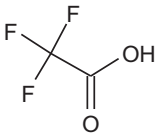
Based on McCall et al. (1980).

[22] 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]
flutolanil	3′-isopropoxy-2-(trifluoromethyl)benzanilide CC(C)Oc1cccc(c1)NC(=O)c1ccccc1C(F)(F)F PTCGDEVVHUXTMP-UHFFFAOYSA-N	
M-2	*N*-{4-hydroxy-3-[(propan-2-yl)oxy]phenyl}-2-(trifluoromethyl)benzamide CC(C)Oc1cc(ccc1O)NC(=O)c1ccccc1C(F)(F)F MZWZZJVZOQEANE-UHFFFAOYSA-N	
M-3	*N*-{3-[(1-hydroxypropan-2-yl)oxy]phenyl}-2-(trifluoromethyl)benzamide FC(F)(F)c1ccccc1C(=O)Nc1cccc(OC(C)CO)c1 KOCLZKSIDCIFDY-UHFFFAOYSA-N	
M-4	*N*-(3-hydroxyphenyl)-2-(trifluoromethyl)benzamide Oc1cccc(NC(=O)c2ccccc2C(F)(F)F)c1 YUWVGNPIDBYWEW-UHFFFAOYSA-N	
M-5	*N*-(3,4-dihydroxyphenyl)-2-(trifluoromethyl)benzamide Oc1ccc(NC(=O)c2ccccc2C(F)(F)F)cc1O YTWSYFMRWSRSNT-UHFFFAOYSA-N	

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
M-6	*N*-(3-methoxyphenyl)-2-(trifluoromethyl)benzamide COc1cccc(NC(=O)c2ccccc2C(F)(F)F)c1 GHNDCJFNRIXYPW-UHFFFAOYSA-N	
M-7	*N*-(4-hydroxy-3-methoxyphenyl)-2-(trifluoromethyl) benzamide Oc1ccc(cc1OC)NC(=O)c1ccccc1C(F)(F)F ITNBPXXRADXDBD-UHFFFAOYSA-N	
M-8	3-[(propan-2-yl)oxy]aniline CC(C)Oc1cccc(N)c1 QMGBIPKOKCSUCL-UHFFFAOYSA-N	
M-9	3-aminophenol Nc1cccc(O)c1 CWLKGDAVCFYWJK-UHFFFAOYSA-N	
M-11	2-{3-[2-(trifluoromethyl)benzamido]phenoxy}propanoic acid CC(Oc1cccc(c1)NC(=O)c1ccccc1C(F)(F)F)C(=O)O NQLVQBQVABMALQ-UHFFFAOYSA-N	
M-101	2-(trifluoromethyl)benzamide FC(F)(F)c1ccccc1C(N) = O QBAYIBZITZBSFO-UHFFFAOYSA-N	
M-102	2-(trifluoromethyl)benzoic acid FC(F)(F)c1ccccc1C(=O)O FBRJYBGLCHWYOE-UHFFFAOYSA-N	

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
TFA	trifluoroacetic acid FC(F)(F)C(=O)O DTQVDTLACAAQTR-UHFFFAOYSA-N	

(a): The name in bold is the name used in the conclusion.
(b): ACD/Name 2021.1.3 ACD/Labs 2021.1.3 (File Version N15E41, Build 123232, 7 July 2021).
(c): ACD/ChemSketch 2021.1.3 ACD/Labs 2021.1.3 (File Version C25H41, Build 123835, 28 August 2021).