Peer review of the pesticide risk assessment for the active substance flutianil in light of confirmatory data on the endocrine disruption assessment

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Abstract
The conclusions of EFSA following the peer review of the initial risk assessment carried out by the competent authority of the rapporteur Member State Belgium, for the pesticide active substance flutianil, are reported. The context of the peer review was that requested by the European Commission following the submission and evaluation of confirmatory information with regard to the endocrine disruption potential of the substance. The conclusions were reached on the basis of the evaluation of the representative uses of flutianil as a fungicide on grapevine and ornamental crops. Assessments not finalised, together with the missing information identified as being required by the regulatory framework, are listed.

Keywords: flutianil, peer review, confirmatory data, risk assessment, pesticide, fungicide

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Summary

Flutianil was approved on 14 April 2019 by Commission Implementing Regulation (EU) No 2019/481 in accordance with Regulation (EC) No 1107/2009 and amending the Annex to Commission Implementing Regulation (EU) No 540/2011. It was a specific provision of the approval that the applicant was required to submit to the European Commission, the Member States and EFSA confirmatory information as regards:

1) the technical specification of the active substance as manufactured (based on commercial scale production) and the compliance of the batches used in toxicological studies with the confirmed technical specification;
2) the effect of water treatment processes on the nature of residues present in surface and groundwater, when surface water or ground water is abstracted for drinking water;
3) an updated assessment of the information submitted and, where relevant, further information confirming that flutianil is not an endocrine disruptor in accordance with points 3.6.5 and 3.8.2 of Annex II of Regulation (EC) No 1107/2009, applying also the ECHA and EFSA guidance for identification of endocrine disruptors.

The applicant was requested to provide the information (referred to in point 1) by 14 April 2020; (referred to in point 2) within 2 years from the date of publication, by the Commission, of a guidance document on the evaluation of the effect of water treatment processes on the nature of residues present in surface and groundwater; and (referred to in point 3) by 14 April 2021.

The requirement for confirmatory data regarding point 1 has already been addressed previously (refer to the EFSA Technical Report issued on 1 June 2021, EFSA Supporting publication 2022:EN-6823).

As regards point 3, in accordance with the specific provision, the applicant, OAT Agrio Co., Ltd., submitted confirmatory information which was evaluated by the designated rapporteur Member State (RMS), Belgium, in the form of a revised draft assessment report. In compliance with the guidance document SANCO 5634/2009-rev.6.1, the RMS distributed the revised volumes of the draft assessment report to the Member States, the applicant and EFSA for comments on 15 November 2021. The RMS collated all comments in the form of a reporting table, which was submitted to EFSA on 11 February 2022. EFSA added its scientific views on the specific points raised during the commenting phase in column 4 of the reporting table, leading to the Technical Report finalised on 7 March 2022 (EFSA Supporting publication 2022:EN-7217).

In the Technical Report, EFSA concluded that overall, based on the available data and weight of evidence, flutianil does not meet the criteria for endocrine disruption (ED) for humans for the estrogen, androgen, thyroid, steroidogenesis (EATS)-modalities according to point 3.6.5 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) No 2018/605. As part of the confirmatory information on the potential ED properties of flutianil, for non-mammalian species, an Amphibian Metamorphosis Assay (AMA) and a Fish Short-Term Reproduction Assay (FSTRA) were submitted. In the Technical Report, EFSA indicated the need for expert discussion on the appropriateness of the study design for both studies and to confirm if the information is sufficient to conclude whether or not the ED criteria for non-target organisms other than mammals are met.

For this purpose, in April 2022, the European Commission requested EFSA to arrange the necessary expert discussion to answer these questions. In case the information is considered not sufficient to conclude on whether the ED criteria for non-target organisms other than mammals are met or not, the experts should identify in their discussion which additional studies would be needed for reaching this conclusion.

Overall, for non-target organisms, the design of the tests did not allow for a consistent interpretation of the results, therefore a conclusion on the ED criteria according to point 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605, could not be drawn.
Table of contents

Abstract ...................................................................................................................................................... 1
Summary ..................................................................................................................................................... 3
Background ............................................................................................................................................... 5
The active substance and the formulated product ..................................................................................... 6
1. Conclusions of the evaluation ............................................................................................................. 6
2. Concerns and related data gaps ........................................................................................................ 7
2.1. Issues that could not be finalised ................................................................................................ 7
2.2. Critical areas of concern ................................................................................................................. 7
3. List of other outstanding issues ......................................................................................................... 8
References ................................................................................................................................................ 8
Abbreviations .......................................................................................................................................... 8
Appendix A – Consideration of cut-off criteria for flutianil according to Annex II of Regulation (EC) No 1107/2009 of the European Parliament and of the Council ......................................................... 9
Appendix B – Used compound codes ................................................................................................ 10
Background

Flutianil was approved on 14 April 2019 by Commission Implementing Regulation (EU) No 2019/481, in accordance with Regulation (EC) No 1107/2009 and amending the Annex to Commission Implementing Regulation (EU) No 540/2011. The European Food Safety Authority (EFSA) previously finalised a Conclusion on this active substance on 28 July 2014 (EFSA, 2014) and a Statement on the impact of the harmonised classification on the conclusion on the peer review of the pesticide risk assessment of the active substance flutianil (EFSA, 2018).

It was a specific provision of the approval that the applicant was required to submit to the European Commission, the Member States and EFSA confirmatory information as regards:

1) the technical specification of the active substance as manufactured (based on commercial scale production) and the compliance of the batches used in toxicological studies with the confirmed technical specification;
2) the effect of water treatment processes on the nature of residues present in surface and groundwater, when surface water or ground water is abstracted for drinking water;
3) an updated assessment of the information submitted and, where relevant, further information confirming that flutianil is not an endocrine disruptor in accordance with points 3.6.5 and 3.8.2 of Annex II of Regulation (EC) No 1107/2009, applying also the ECHA and EFSA guidance for identification of endocrine disruptors.

The applicant was requested to provide the information (referred to point 1) by 14 April 2020; (referred to in point 2) within 2 years from the date of publication, by the Commission, of a guidance document on the evaluation of the effect of water treatment processes on the nature of residues present in surface and groundwater; and (referred to in point 3) by 14 April 2021.

The requirement for confirmatory data regarding point 1 has already been addressed previously (refer to the EFSA Technical Report issued on 1 June 2021; EFSA, 2022a).

As regards point 3, in accordance with the specific provision, the applicant, OAT Agrio Co., Ltd., submitted confirmatory information, which was evaluated by the designated rapporteur Member State (RMS), Belgium, in the form of a revised draft assessment report (Belgium, 2021). In compliance with the guidance document SANCO 5634/2009-rev.6.1 (European Commission, 2013), the RMS distributed the revised volumes of the draft assessment report to the Member States, the applicant and EFSA for comments on 15 November 2021. The RMS collated all comments in the format of a reporting table, which was submitted to EFSA on 11 February 2022, together with a revised confirmatory data assessment (Belgium, 2022). EFSA added its scientific views on the specific points raised during the commenting phase in column 4 of the reporting table, leading to the Technical Report finalised on 7 March 2022 (EFSA, 2022b).

Overall, based on the available data and weight of evidence, the Technical Report from EFSA concluded that flutianil does not meet the criteria for endocrine disruption (ED) for humans. As part of the confirmatory information on the potential ED properties of flutianil, for non-mammalian species, an Amphibian Metamorphosis Assay (AMA) and a Fish Short-Term Reproduction Assay (FSTRA) were submitted. In the Technical Report, EFSA indicated the need for expert discussion on the appropriateness of the study design for both studies and to confirm if the information is sufficient to conclude whether or not the ED criteria for non-target organisms other than wild mammals are met.

For this purpose, on 7 April 2022 the European Commission requested EFSA to arrange the necessary expert discussion to answer these questions. In case the information is considered not...
sufficient to conclude on whether the ED criteria for non-target organisms other than mammals are met or not, the experts should identify in their discussion which additional studies would be needed for reaching this conclusion.

To address the request of the mandate, flutianil was discussed at the Pesticides Peer Review Experts’ Teleconference TC 73 on Mammalian Toxicology and Ecotoxicology joint session on ED on 29 April 2022. Details of the issues discussed, together with the outcome of these discussions were presented in the report of the scientific consultation with Member State experts (EFSA, 2022c).

A final consultation on the conclusions arising from the peer review took place with Member States via a written procedure in June 2022.

The conclusions laid down in this report were reached on the basis of the peer review of the RMS’s evaluation of the confirmatory data submitted in relation to the ED properties of flutianil. A key supporting document to this conclusion is the peer review report (EFSA, 2022c), comprising of the following documents, in which all views expressed during the course of the confirmatory data peer review, including minority views, if applicable, can be found:

- the report of the scientific consultation with Member State experts;
- the comments received on the draft EFSA conclusion.

Given the importance of the RMS assessment (revised version of May–June 2022; Belgium, 2022) and the peer review report, these documents are considered as background documents to this conclusion.

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

The active substance and the formulated product

Flutianil is the ISO common name for \((2Z)-[2\text{-fluoro}-5-(\text{trifluoromethyl})\text{phenyl}]\text{thio})[3-(2\text{-methoxyphenyl})\text{thiazolidin}-2\text{-ylidene}]\text{acetonitrile} (IUPAC).

The representative formulated product for the evaluation for the approval was ‘Flutianil 5% EC’ an emulsifiable concentrate. The representative uses evaluated comprised indoor foliar spraying against fungi on ornamental crops and outdoor foliar spraying against fungi on grapevine (see Appendix A in EFSA, 2014).

1. Conclusions of the evaluation

In April 2021 the applicant submitted confirmatory information as regards the potential for ED properties of flutianil. The initial assessment of the information was presented by the RMS in the form of a revised draft assessment report (Belgium, 2021, 2022).

In the EFSA Technical Report (EFSA, 2022b), it was concluded that overall, based on the available data and weight of evidence, flutianil does not meet the ED criteria for humans for the estrogen, androgen, thyroid, steroidogenesis (EATS)-modalities according to point 3.6.5 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) No 2018/605 of 19 April 2018 amending Annex II to Regulation (EC) No 1107/2009 by setting out scientific criteria for the determination of endocrine disrupting properties. OJ L 101, 20.4.2018, pp. 33–36.

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

The assessment of the ED properties of flutianil for non-target organisms other than wild mammals was discussed at the Pesticides Peer Review Experts’ Teleconference 73 on Mammalian Toxicology and Ecotoxicology joint session on ED on 29 April 2022. For non-mammalian species, an AMA and a FSTRA were available. The experimental design, in particular, the selection of the concentrations tested in the available tests with non-mammalian species was not considered fully appropriate for the investigation of the potential ED properties of flutianil. Specifically, the experts noted that the highest tested concentration was set at the limit of solubility in water without any indication on whether the maximum tolerated concentration (MTC) could be reached. In addition, based on the available information, it is unclear whether the limit of solubility could be increased by the addition of a suitable organic solvent.

Therefore, considering all available data and in the absence of further information, a conclusion on the ED properties of flutianil for non-target organisms according to point 3.8.2 of Annex II to
2. Concerns and related data gaps

2.1. 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 assessment of the potential endocrine disrupting properties of flutianil for non-target organisms other than wild mammals according to point 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605, could not be finalised. To this regard, the following information would be needed:

   a) It should be demonstrated that it is not possible to test higher concentrations than the ones assessed in the already available tests according to OECD Test Guideline (TG) 229 (FSTRA) and OECD TG 231 (AMA), even when using organic solvents, OR

   b) Suitable tests in line with the previously mentioned OECD TGs where appropriate solvent should be used to test higher concentrations than the limit of solubility in water. Ideally, a range-finder test could be performed for the definite concentrations setting and to provide a clear understanding of the maximum tolerated concentration (MTC).

In the case that a new study(ies) is(are) submitted (because it was possible to test higher concentrations by using a pertinent solvent) and it(they) show(s) positive findings, further testing would be required in line with the ECHA/EFSA (2018) ED guidance (i.e. a Larval Amphibian Growth and Development Assay (LADGA) in line with OECD TG 241 for the T-modality and a Medaka Extended One-Generation Reproduction Test (MEOGRT) in line with OECD TG 240 for the EAS-modalities).

2.2. 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:

Critical areas of concern were not identified.
3. 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:

Other outstanding issues were not identified.

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European Commission, 2013. Guidance document on the procedures for submission and assessment of confirmatory information following approval of an active substance in accordance with Regulation (EC) No 1107/2009. SANCO 5634/2009-rev. 6.1.

Abbreviations

AMA Amphibian Metamorphosis Assay
EATS estrogen, androgen, thyroid, steroidogenic
ECHA European Chemicals Agency
ED endocrine disruption
EEC European Economic Community
FSTRA Fish Short-Term Reproduction Assay
InChiKey International Chemical Identifier Key
ISO International Organization for Standardization
IUPAC International Union of Pure and Applied Chemistry
LAGDA Larval Amphibian Growth and Development Assay
MEOGRT Medaka Extended One-Generation Reproduction Test
SMILES simplified molecular-input line-entry system
Appendix A – Consideration of cut-off criteria for flutianil according to Annex II of Regulation (EC) No 1107/2009 of the European Parliament and of the Council

| Properties                      | Conclusion                                                                                                                                                                                                 |
|---------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Endocrine disrupting properties | Flutianil is not considered to meet the criteria for endocrine disruption for humans for the EATS-modalities according to point 3.6.5 of Annex II of Regulation No 1107/2009, as amended by Commission Regulation (EU) 2018/605. |
|                                 | A conclusion on the endocrine disrupting properties of flutianil for non-target organisms according to point 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605, could not be reached. |
## Appendix B – Used compound codes

| Code/trivial name | IUPAC name/SMILES notation/InChiKey\(^{(a)}\) | Structural formula\(^{(b)}\) |
|-------------------|---------------------------------------------|-----------------------------|
| Flutianil         | (2Z)-([2-fluoro-5-(trifluoromethyl)phenyl]thio)[3-[(2-methoxyphenyl)thiazolidin-2-ylidene]acetonitrile | ![Structural formula](image) |

\(^{(a)}\): ACD/Name 2021.1.3 ACD/Labs 2021 Release (File version N15E41, Build 123,232, 8 July 2021).

\(^{(b)}\): ACD/ChemSketch 2021.1.3 ACD/Labs 2021 Release (File version C25H41, Build 123,835, 29 August 2021).