Evaluation of confirmatory data following the Article 12 MRL review for flutolanil

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Abstract

The applicant Nihon Nohyaku Co. Ltd. submitted a request to the competent national authority in Finland to evaluate the confirmatory data that were identified for flutolanil in the framework of the maximum residue level (MRL) review under Article 12 of Regulation (EC) No 396/2005 as not available. The data gaps related to new residue trials for globe artichokes and beans with pods and for storage stability data in products of animal origin were addressed. Further risk management consideration is required regarding the tentative MRL on peppers and on certain products of animal origin, since the data gaps identified in the MRL review were not addressed or only partially addressed. A new metabolism study on ruminants was provided which will be assessed in the framework of the renewal of the active substance flutolanil; formally, this data gap is considered to be addressed. EFSA updated the most recent consumer risk assessment for flutolanil and concluded that the long-term dietary intake is unlikely to present a risk to consumer health. The conclusion reported in this reasoned opinion may need to be reconsidered in light of the outcome of the EU pesticides peer review.

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**Keywords:** flutolanil, confirmatory data, pesticide, MRL, consumer risk assessment

**Requestor:** European Commission

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Summary

In 2013, when the European Food Safety Authority (EFSA) reviewed the existing Maximum Residue Levels (MRLs) for flutolanil according to Article 12 of Regulation (EC) No 396/2005, EFSA identified some information as unavailable (data gaps) and derived tentative MRLs for those uses which were not fully supported by data but for which no risk to consumers was identified. The following data gaps were noted:

1) Residue studies on globe artichokes, peppers and beans with pods investigating the magnitude of metabolites and their conjugates in compliance with the residue definition for risk assessment;
2) A validated livestock metabolism study on ruminants;
3) A study on storage stability in commodities of animal origin;
4) A validated analytical method for enforcement in commodities of animal origin.

Tentative MRL proposals have been implemented in the MRL legislation by Commission Regulation (EU) No 2015/603, including footnotes related to data gaps numbers 1, 2, 3 and 4, indicating the type of confirmatory data that should be provided by a party having an interest in maintaining the proposed tentative MRL by 17 April 2017. The footnote related to data gaps numbers 2, 3 and 4 for liver and kidney of swine, bovine, sheep and goat origin was deleted by Commission Regulation (EU) No 2016/567, because the Codex MRL of 0.5 mg/kg was implemented in the European Union (EU) legislation.

In accordance with the agreed procedure set out in the working document SANTE/10235/2016, Nihon Nohyaku Co. Ltd. submitted an application to the competent national authority in Finland (rapporteur Member State (RMS)) to evaluate the confirmatory data identified during the MRL review. The RMS assessed the new information in an evaluation report, which was submitted to the European Commission and forwarded to EFSA on 8 March 2018. When assessing the evaluation report, EFSA identified points which needed further clarifications. On 5 October 2018, the RMS submitted a revised evaluation report which replaced the previously submitted evaluation report.

The peer review of the renewal of approval of the active substance in accordance with Regulation (EC) No 1107/2009 is currently ongoing and therefore the conclusions reported in this reasoned opinion may need to be reconsidered in the light of the outcome of the EU pesticides peer review.

The summary table below provides an overview of the assessment of confirmatory data and the recommended MRL modifications to Regulation (EU) No 396/2005.

| Code      | Commodity          | Existing MRL | Proposed MRL | Conclusion/recommendation                                                                 |
|-----------|--------------------|--------------|--------------|--------------------------------------------------------------------------------------------|
| 0231020   | Sweet peppers/bell peppers | 0.01* (ft 1) | 0.01* (further risk management consideration required) | The data gap identified by EFSA has not been addressed. Residue trials analysed in accordance with the residue definition for risk assessment have not been submitted. Instead, the applicant provided a justification for waiving the requested studies, claiming that the occurrence of residues related to flutolanil and its metabolites in peppers being treated in accordance with the GAP reported in the MRL review is unlikely. However, in accordance with the legal provisions, this assumption should be confirmed by data. A risk management decision is required whether the existing authorisations need to be withdrawn, considering that the MRL confirmatory data gap has not been addressed. Regarding the consumers’ dietary exposure, the use of the tentative conversion factor for peppers derived during the MRL review from rotational crop studies leads to additional non-standard uncertainties in the consumer risk assessment. However, the margin of safety of the exposure calculation is sufficiently large, and, consequently, a risk for consumer is unlikely. |
| Code(a) | Commodity | Existing MRL(b) | Proposed MRL | Conclusion/recommendation |
|---------|-----------|----------------|--------------|----------------------------|
| 0260010 | Beans (with pods) | (ft 1) 0.01* | 0.01* | The data gap identified by EFSA has been addressed. Residue trials analysed for residues in accordance with the residue definition for risk assessment have been provided. The previously derived MRL is confirmed. Risk for the consumer is unlikely. |
| 0270050 | Globe artichokes | 0.01* (ft 1) | 0.01* | |
| 1011010 | Swine, muscle | 0.05* (ft 2) | 0.05* (further risk management consideration required) | Storage stability in animal matrices has been sufficiently addressed and supports the acceptability of the livestock feeding studies. Previous consumer risk assessment remains valid. Further validation data were provided to demonstrate that the available analytical method is suitable to enforce flutolanil residues according to the residue definition tentatively proposed during the MRL review and currently implemented in the MRL legislation. However, the documentation is not complete and the data gap identified in the MRL review is considered only partially addressed. Further risk management consideration is therefore required, which shall take into consideration that the need for an analytical method capable to enforce residues in products of animal origin according to the current tentative residue definition may become obsolete if a different residue definition is established in the context of the EU pesticides peer review. |
| 1011020 | Swine, fat | 0.05* (ft 2) | 0.05* (further risk management consideration required) | |
| 1012010 | Bovine, muscle | 0.05* (ft 3) | 0.05* (further risk management consideration required) | Storage stability in animal matrices has been sufficiently addressed and supports the acceptability of the livestock feeding studies. Previous consumer risk assessment remains valid. A new metabolism study on ruminants is available and the data gap is considered to be formally addressed. However, the study and its impact on the residue definition for animal products will be assessed in the framework of the renewal of the active substance flutolanil. Further validation data were provided to demonstrate that the available analytical method is suitable to enforce flutolanil residues according to the residue definition tentatively proposed during the MRL review and currently implemented in the MRL legislation. However, the documentation is not complete and the data gap identified in the MRL review is considered only partially addressed. Further risk management consideration is therefore required, which shall take into consideration that the need for an analytical method capable to enforce residues in products of animal origin according to the current tentative residue definition may become obsolete if a different residue definition is established in the context of the EU pesticides peer review. |
| 1012020 | Bovine, fat | 0.05* (ft 3) | 0.05* (further risk management consideration required) | |
| 1013010 | Sheep, muscle | 0.05* (ft 3) | 0.05* (further risk management consideration required) | |
| 1013020 | Sheep, fat | 0.05* (ft 3) | 0.05* (further risk management consideration required) | |
| 1014010 | Goat, muscle | 0.05* (ft 3) | 0.05* (further risk management consideration required) | See conclusions/recommendations for swine (muscle and fat). |
| 1014020 | Goat, fat | 0.05* (ft 3) | 0.05* (further risk management consideration required) | |
| 1016010 | Poultry, muscle | 0.05* (ft 2) | 0.05* (further risk management consideration required) | See conclusions/recommendations for swine (muscle and fat). |
| 1016020 | Poultry, fat | 0.05* (ft 2) | 0.05* (further risk management consideration required) | |
| 1016030 | Poultry, liver | 0.05* (ft 2) | 0.05* (further risk management consideration required) | |
| 1020010 | Milk, Cattle | 0.05* (ft 3) | 0.05* (further risk management consideration required) | See conclusions/recommendations for bovine, sheep, goat (muscle and fat). |
| 1020020 | Milk, Sheep | 0.05* (ft 3) | 0.05* (further risk management consideration required) | |
| 1020030 | Milk, Goat | 0.05* (ft 3) | 0.05* (further risk management consideration required) | |
| Code\(^a\) | Commodity | Existing MRL\(^b\) | Proposed MRL | Conclusion/recommendation |
|----------|-----------|-------------------|--------------|--------------------------|
| 1030000  | Birds eggs | 0.05* (ft 2)      | 0.05*        | See conclusions/recommendations for swine (muscle and fat) |

MRL: maximum residue level; GAP: Good Agricultural Practice.

\(^a\): Commodity code number according to Annex I of Regulation (EC) No 396/2005.

\(^b\): Existing EU MRL and corresponding footnote on confirmatory data.

**Ft 1:** The European Food Safety Authority identified some information on residue trials as unavailable. When reviewing the MRL, the Commission will take into account the information referred to in the first sentence, if it is submitted by 17 April 2017, or, if that information is not submitted by that date, the lack of it (Footnote related to data gap No 1).

**Ft 2:** The European Food Safety Authority identified some information on analytical methods and storage stability as unavailable. When reviewing the MRL, the Commission will take into account the information referred to in the first sentence, if it is submitted by 17 April 2017, or, if that information is not submitted by that date, the lack of it (Footnote related to data gap No 3 and 4).

**Ft 3:** The European Food Safety Authority identified some information on analytical methods, storage stability and metabolism in ruminants as unavailable. When reviewing the MRL, the Commission will take into account the information referred to in the first sentence, if it is submitted by 17 April 2017, or, if that information is not submitted by that date, the lack of it (Footnote related to data gap No 2, 3 and 4).
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Assessment

The review of existing maximum residue levels (MRLs) for the active substance flutolanil according to Article 12 of Regulation (EC) No 396/2005¹ (MRL review) has been performed in 2013 (EFSA, 2013). The European Food Safety Authority (EFSA) identified some information as unavailable (data gaps) and derived tentative MRLs for those uses not fully supported by data but for which no risk to consumers was identified. The Good Agricultural Practices (GAPs) assessed in the framework of the MRL review that were not fully supported by data and for which confirmatory data were requested are listed in Appendix A.

The MRL modifications proposed in the MRL review have been implemented in the MRL legislation by Commission Regulation (EU) No 2015/603², including footnotes that specified for the relevant MRLs the type of information that was identified as missing. Any party having an interest in maintaining the proposed tentative MRL was requested to address the confirmatory data by 17 April 2017. With Regulation (EU) 2016/567³, a number of Codex MRLs have been taken over in the EU MRL legislation, including MRLs for liver and kidney of mammals other than marine mammals. In this regulation, risk managers decided to delete the footnotes requesting further information on analytical methods, storage stability and for a metabolism in ruminants for liver and kidney of swine, bovine, sheep and goat.

In accordance with the specific provision set out in the working document of the European Commission SANTE/10235/2016 (European Commission, 2016), the applicant Nihon Nohyaku Co. Ltd. submitted an application to the competent national authority in Finland (rapporteur Member State (RMS)) to evaluate the confirmatory data identified during the MRL review. To address the data gaps identified by EFSA, the applicant provided the following:

- new residue trials on globe artichokes and beans with pods (see Section 1.2.1), and storage stability data to demonstrate the validity of these trials (see Section 1.1.5);
- a justification to support that residue trials on peppers investigating the magnitude of M-2 and M-4 metabolites and their conjugates in compliance with the residue definition for risk assessment are not required (see Section 1.2.1);
- a new metabolism study in ruminants (see Section 2.1.1);
- storage stability data in animal matrices (see Section 2.1.3);
- additional validation data for the analytical method proposed to enforce MRLs in commodities of animal origin according to the residue definition for enforcement tentatively derived in the MRL review (see Section 2.1.2).

The RMS assessed the new information in an evaluation report, which was submitted to the European Commission and forwarded to EFSA on 20 March 2018 (Finland 2018). EFSA assessed the application as requested by the European Commission in accordance with Article 9 of Regulation (EC) No 396/2005. During the detailed assessment, EFSA identified points which needed further clarifications. On 5 October 2018, the RMS submitted the reply in a revised evaluation report which replaced the previously submitted evaluation report.

EFSA based its assessment on the revised evaluation report submitted by the RMS (Finland, 2018) and the reasoned opinion on the MRL review according to Article 12 of Regulation (EC) No 396/2005 (EFSA, 2013).

For this application, the data requirements established in Regulation (EU) No 544/2011⁴ and the relevant guidance documents at the date of implementation of the confirmatory data requirements by

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¹ Regulation (EC) No 396/2005 of the 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.
² Commission Regulation (EU) 2015/603 of 13 April 2015 amending Annexes II, III and V to Regulation (EC) No 396/2005 of the European Parliament and of the Council as regards maximum residue levels for 2-naphthoxyacetic acid, acetochlor, chloropicrin, diflubenzuran, dithiocarbamates, fenamidone, flutolanil and spinosad in or on certain products. OJ L 100, 17.4.2015, p. 10–59.
³ Commission Regulation (EU) 2016/567 of 6 April 2016 amending Annexes II and III to Regulation (EC) No 396/2005 of the European Parliament and of the Council as regards maximum residue levels for chlorantraniliprole, cyflumetofen, cyprodinil, dimethomorph, dithiocarbamates, fenamidone, fluopyram, flutolanil, imazamox, metrafenone, myclobutanil, propiconazole, sedaxane and spirodiclofen in or on certain products. C/2016/1879, OJ L 100, 15.4.2016, p. 1–60.
⁴ Commission Regulation (EU) No 544/2011 of 10 June 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards the data requirements for active substances. OJ L 155, 11.6.2011, p. 1–66.
Regulation (EU) No 2015/603 are applicable. The assessment is performed in accordance with the legal provisions of the Uniform Principles for the Evaluation and the Authorisation of Plant Protection Products adopted by Commission Regulation (EU) No 546/2011.

An updated list of end points, including the end points of relevant studies evaluated in this application, is presented in Appendix B.

The peer review of the renewal of approval of the active substance in accordance with Regulation (EC) No 1107/2009 is currently ongoing. The conclusions derived in this reasoned opinion might need to be reconsidered in the light of the outcome of the EU pesticides peer review.

The evaluation report submitted by the RMS (Finland, 2018) and the exposure calculations using the EFSA Pesticide Residues Intake Model (PRIMo) are considered a supporting document to this reasoned opinion and, thus, are made publicly available as a background document to this reasoned opinion.

1. Residues in plants

1.1. Nature of residues and methods of analysis in plants

1.1.1. Nature of residues in primary crops

Not relevant for the current assessment.

1.1.2. Nature of residues in rotational crops

Not relevant for the current assessment.

1.1.3. Nature of residues in processed commodities

Not relevant for the current assessment.

1.1.4. Methods of analysis in plants

Not relevant for the current assessment.

1.1.5. Stability of residues in plants

A new frozen storage stability study was submitted in the framework of this application (Finland, 2018). Samples of spinach leaves and potato tubers where homogenised, fortified with aliquots of flutolanil and a mix of M-2 and M-4 and stored under deep frozen conditions (−18°C) for up to 24 months. Flutolanil and its metabolites M-2 and M-4 remained stable in plant matrices representing the high water content group for the whole storage period tested (i.e. 24 months). Although samples for storage were fortified with free (unconjugated) metabolites, this study is considered adequate to address the storage stability of the conjugated form of the metabolites, because the conjugates are only expected to release free M-2 and M-4.

1.1.6. Proposed residue definitions

Previously derived residue definitions are applicable (EFSA, 2013).

1.2. Magnitude of residues in plants

1.2.1. Magnitude of residues in primary crops

All samples from the new residue trials submitted were analysed for the parent compound and the metabolites M-2 and M-4. According to the RMS, the samples were analysed with methods appropriately validated and capable to release conjugates of M-2 and M-4. Samples of these trials were stored under conditions for which their integrity was demonstrated (Finland, 2018).

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

In order to address the data gap number 1, the applicant provided the results of four new residue trials conducted according to the GAP assessed in the MRL review. At harvest, residues of flutolanil, M-2 (free and conjugated) and M-4 (free and conjugated) were below the limit of quantification (LOQ) of 0.01 mg/kg. EFSA concluded that the data gap identified in the MRL review has been addressed.

• **Beans with pods**

In order to address the data gap number 1, the applicant provided the results of 12 new residue trials conducted indoor according with the GAP (± 25% tolerance in application rate) assessed in the MRL review. None of these trials investigated residues beyond the preharvest interval (PHI) of 3 days. However, in samples collected just after the second application (zero day) and 1, 2 and 3 days (PHI) after last application, flutolanil and M-2 were never quantifiable and a decline for M-4 was observed (except one sample). EFSA concluded that the data gap identified in the MRL review has been addressed.

• **Pepper (sweet and bell)**

Nine trials with samples analysed for parent compound have been assessed in the framework of the MRL review. Since data on the residue concentrations in accordance with the residue definition for risk assessment (i.e. ‘sum of flutolanil, metabolites M-2 and M-4 and their conjugates, expressed as flutolanil’) were missing, confirmatory data was requested (data gap number 1). No new residue trials were submitted. Instead, the applicant provided the following argumentation to waive the submission of new data:

- the critical use pattern in pepper is a soil application after transplanting, hence well before the edible part of the crop is formed,
- the normal vegetation period covers any possible residue and at harvest (PHI 47 days) no quantifiable residues are expected,
- this assumption is confirmed by the nine residue trials assessed in the MRL review (EFSA, 2013) where residues of flutolanil were below the LOQ of 0.01 mg/kg at PHI 47 days, and
- the dietary intake of the metabolites M-2 and M-4 and their conjugates through consumption of pepper was considered negligible.

The RMS concluded that the dietary potential exposure to these metabolites and their conjugated forms for risk assessment purpose was not necessary to be taken into account for the use pattern authorised on peppers.

EFSA acknowledged that a significant uptake of M-2 and M-4 and their conjugates to the edible part of the crop is unlikely, but without appropriate data it cannot be fully excluded. At least two residue trials reflecting the GAP and confirming that residues are not present in the edible part of the crop are usually necessary (European Commission, 2017).

1.2.2. **Magnitude of residues in rotational crops**

Not relevant for the current assessment.

1.2.3. **Magnitude of residues in processed commodities**

Not relevant for the current assessment.

1.2.4. **Proposed MRLs**

The available data were considered sufficient to confirm the existing MRLs for beans with pods and globe artichokes and to derive risk assessment values.

For peppers, the applicant provided a justification for waiving the submission of new residue trials (see Section 1.2.1). However, according to EFSA, the assumption made has not been confirmed by empirical data; consequently, the MRL confirmatory data gap has not been addressed. In Section 3, EFSA assessed whether the expected residues on these crops are likely to pose a consumer health risk.

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6 Data gap number 1: Residue studies on globe artichokes, peppers and beans with pods investigating the magnitude of metabolites and their conjugates in compliance with the residue definition for risk assessment.

7 At growth stage of leaf development, BBCH 13–15, 3rd to 5th leaf on main shoot unfolded.
2. **Residues in livestock**

2.1. **Nature of residues and methods of analysis in livestock**

2.1.1. **Nature of residues in livestock**

In order to address the data gap number 2, a new metabolism study in a lactating goat performed with flutolanil radiolabelled in the aniline ring was provided. The RMS proposed to refer the assessment of this study to the EU pesticides peer review (renewal process for the active substance), as suggested in the Commission Working Document SANTE/10235/2016.

EFSA concluded that the metabolism study identified in the MRL review as missing is available. However, the results of its assessment will be reported in the EFSA conclusion on the renewal of the active substance.

2.1.2. **Method of analysis in products of animal origin**

The applicant did not provide a new analytical enforcement method for commodities of animal origin (data gap number 4). Instead, the applicant provided additional information on the validation of the common moiety analytical method that was originally assessed in the framework of the MRL review (EFSA, 2013).

The method involves the extraction of flutolanil and its metabolites using acetonitrile/hexane; in a second step the residues are converted to 2-trifluoromethylbenzoic acid moiety (TFBA) using base hydrolysis. After solvent partition clean-up, the residue is methylated and determined with gas chromatography with mass spectrometry (GC-MS). Although further details on the individual validation for the parent compound and the selected metabolites (M-2, M-4 and M-7) were provided, several deficiencies and deviation to the currently applicable guidance document (European Commission, 2010) were noted, e.g.:

- validation data were not provided for each matrix, spiking level and analyte combinations, except for milk;
- linearity of the method was determined for the TFBA moiety; linearity of calibration curves for the single analytes were not provided;
- only one or two replicates per spiking level/matrix were analysed instead of the number of 5;
- matrices of tissues and eggs were spiked at the LOQ and additionally at 4 to 200 \( \times \) LOQ levels; only milk was spiked at LOQ and 10 \( \times \) LOQ;
- accuracy and precision were not fully demonstrated;
- matrix effect response was not reported;
- evidence of confirmation of the identification of each single analyte was not provided.

In the independent laboratory validation (ILV), recovery and relative mean standard deviation from two replicates per each spiking level (LOQ and 5 \( \times \) LOQ) showed to be within acceptable limits for all the four analytes and matrices (milk, fat, muscle, egg). Anyway the linearity of the method and the absence of matrix effect were not reported.

Since the validation of the analytical method proposed for the enforcement and of its ILV had some deficiencies, EFSA concluded that the data gap was only partially addressed.

2.1.3. **Stability of residues in products of animal origin**

In order to address the data gap number 3, the applicant provided the results of the investigations on storage stability conducted to support the results of the livestock feeding studies assessed in the MRL review (EFSA, 2013).

Samples of whole milk, bovine muscle, bovine fat, chicken liver and eggs were fortified with aliquots of flutolanil, M-2, M-4 and M-7 and, then, stored under deep frozen conditions (\(-20°C\)) for about 4 months, except fat samples that were stored for up to about 3 months. Tissue and egg samples were analysed at three time points (including time zero), whereas milk samples only at 0 and 115 days storage. The samples were analysed with the same common moiety method employed to quantify residues in the feeding studies.

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8 Data gap number 2: A validated livestock metabolism study on ruminants.
9 Data gap number 4: A validated analytical method for enforcement in commodities of animal origin.
10 Data gap number 3: A study on storage stability in commodities of animal origin.
Stability of flutolanil, M-2, M-4 and M-7 in muscle, liver and egg matrices was demonstrated during the whole storage period. In fat matrix, flutolanil showed to be stable for up to 90 days, but M-2, M-4, M-7 were not stable during the investigated period (already at the first time point of 88 days). In the new metabolism study in goats with flutolanil radiolabelled in the aniline ring reported in the evaluation report (Finland, 2018), flutolanil was the main component of the total residues and these three metabolites were not observed in significant amounts (< 10% total radioactive residue (TRR) and < 0.001 mg/kg). Based on the data available, it can be assumed that the lack of demonstrated storage stability of these metabolites in fat matrix has a limited relevance.

Overall, EFSA concluded that the data gap identified in the MRL review is considered as sufficiently addressed.

2.1.4. Proposed residue definition

In the framework of the MRL review, the enforcement residue definition in products of animal origin was proposed on a tentative basis (i.e. 'sum of flutolanil and all metabolites containing the 2-trifluoromethylbenzoic acid moiety, expressed as flutolanil'), pending the assessment of a new metabolism study on ruminants (EFSA, 2013). A new metabolism study on goats has been reported in the framework of the confirmatory data application. According to the RMS, the results of the study trigger a revision of the residue definition for enforcement in animal products. Since the study is currently under assessment in the framework of the renewal of the active substance, the RMS proposed to have the decision on the residue definition for products of animal origin taken in the context of EU pesticides peer review (Finland, 2018). EFSA and Commission agreed with this proposal, which is in line with the provisions of the working document SANTE/10235/2016.

2.2. Magnitude of residues in livestock

Not relevant for the current assessment.

2.2.1. Proposed MRLs

The tentative MRLs for mammalian muscle, mammalian fat, poultry liver, milks and eggs proposed in the framework of the MRL review have been sufficiently supported by storage stability. The data gap related to the analytical method to enforce flutolanil residues in commodities of animal origin according to the residue definition tentatively proposed during the MRL review and currently in place in the MRL legislation has been partially addressed.

3. Consumer risk assessment

EFSA updated the chronic dietary risk assessment performed in the framework of the MRL review for flutolanil (EFSA, 2013), including the relevant median residue (STMR) values for beans with pods and globe artichokes derived in this confirmatory data assessment and for the Codex MRLs that have been taken over in the EU MRL legislation after the MRL review (EFSA, 2013, 2014, FAO, 2013). For peppers, residue field data were not analysed for the full residue definition for risk assessment. Lacking empirical information, the exposure was calculated using the conversion factor\(^\text{11}\) of 2 tentatively derived from rotational crops studies during the MRL review. A short-term consumer risk assessment was not performed as an acute reference dose (ARfD) was not deemed necessary for flutolanil (European Commission, 2008).

The estimated long-term dietary intake of flutolanil was in the range of 0.1–3% of the acceptable daily intake (ADI). The contribution of residues in beans with pods and in globe artichokes accounted for a maximum 0.04% and 0.01% of the ADI, respectively.

The contribution of peppers to the total long-term exposure was low (maximum 0.01% of the ADI). The use of the tentative conversion factor for peppers derived from rotational crop studies leads to additional non-standard uncertainties. The margin of safety of the exposure calculation is sufficiently large and, consequently, a risk for consumer is unlikely.

For further details on the exposure calculations, a screenshot of the Report sheet of the PRIMo is presented in Appendix C.

\(^{11}\) The RMS performed the consumer risk assessment without using any CF for pepper, assuming that no residues are expected in the edible commodity when flutolanil is used according to the authorised GAP (Finland, 2018).
4. Conclusion and Recommendations

To data gap related to new residue trials for globe artichokes and beans with pods were satisfactorily addressed and the use of flutolanil according to the good agricultural practices assessed in the MRL review is unlikely to present a risk to consumer health.

The data gap identified for peppers has not been addressed by providing new field residue trials analysed for the full residue definition for risk assessment. Instead, the applicant provided a justification for waiving the request. Although the occurrence of residues in peppers being treated in accordance with the GAP reported in the framework of the MRL review is unlikely, the assumption has not been confirmed by data. A risk management decision is required weather the existing authorisations on peppers need to be withdrawn, considering that the MRL confirmatory data gap has not been addressed. The use of the tentative conversion factor for peppers derived from rotational crop studies leads to additional non-standard uncertainties in the consumer risk assessment performed. The margin of safety of the exposure calculation is sufficiently large, and, consequently, a risk for consumer is unlikely.

A new metabolism study on ruminants is available. The RMS proposed to perform the detailed assessment of the study in the framework of the renewal process of the active substance, which is in line with the provisions of the working document SANTE/10235/2016. Thus, the data gap is considered to be formally addressed.

Storage stability in products of animal origin has been sufficiently addressed. The data gap related to a validated analytical method to enforce flutolanil residues in commodities of animal origin according to the residue definition tentatively proposed during the MRL review and currently in place in the MRL legislation has been partially addressed. Further risk management consideration is therefore required.

The peer review of the renewal of approval of the active substance in accordance with Regulation (EC) No 1107/2009 is not yet finalised and therefore the conclusions reported in this reasoned opinion may need to be reconsidered in light of the outcome of the EU pesticides peer review.

The MRL recommendations are summarised in Appendix B.4.

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Abbreviations

a.s. active substance
ADI acceptable daily intake
ARfD acute reference dose
BBCH growth stages of mono- and dicotyledonous plants
bw body weight
CCPR Codex Committee on Pesticide Residues
CF conversion factor for enforcement to risk assessment residue definition
CXL Codex maximum residue limit
DAT days after treatment
FAO Food and Agriculture Organization of the United Nations
GAP Good Agricultural Practice
GC–MS gas chromatography with mass spectrometry
HR highest residue
IEDI international estimated daily intake
ILV independent laboratory validation
InChIKey International Chemical Identifier Key
IUPAC International Union of Pure and Applied Chemistry
LOQ limit of quantification
Mo monitoring
MRL maximum residue level
MS Member States
NEU northern Europe
OECD Organisation for Economic Co-operation and Development
PHI preharvest interval
PRIMo (EFSA) Pesticide Residues Intake Model
RA risk assessment
RD residue definition
RMS rapporteur Member State
SANCO Directorate-General for Health and Consumers
SC suspension concentrate
SEU southern Europe
STMR supervised trials median residue
TFBA 2-trifluoromethylbenzoic acid
TRR total radioactive residue
WHO World Health Organization
### Appendix A – Summary GAPs assessed in the evaluation of confirmatory data

| Crop and/or situation | NEU, SEU, MS or country | F | G | Pests or group of pests controlled | Preparation | Application | Application rate per treatment | PHI (days) | Remarks |
|-----------------------|-------------------------|---|---|-----------------------------------|-------------|-------------|---------------------------------|------------|---------|
| Peppers               | NEU                     | G |    | Rhizoctonia solani                | SC 460 g/L | BBCH 13–15 | 575–862.5 g/ha 47 Drip irrigation |
| Beans, with pods      | SEU                     | G |    | Rhizoctonia solani                | SC 460 g/L | BBCH 71–89 | 575–862.5 g/ha 3 Drip irrigation |
| Globe artichokes      | SEU                     | F |    | Rhizoctonia solani                | SC 460 g/L | BBCH 0–1  | 57.5–69 g/hL NA Dipping of a cutting or spraying of a cutting prior to planting |

**GAP:** Good Agricultural Practice; **NEU:** northern European Union; **SEU:** southern European Union; **MS:** Member State; **a.s.:** active substance; **SC:** suspension concentrate.

(a): Outdoor or field use (F), greenhouse application (G) or indoor application (I).

(b): CropLife International Technical Monograph no 2, 6th Edition. Revised May 2008. Catalogue of pesticide formulation types and international coding system.

(c): Growth stage range from first to last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including, where relevant, information on season at time of application.

(d): PHI: minimum preharvest interval.
Appendix B – List of end points

B.1. Residues in plants

B.1.1. Nature of residues and methods of analysis in plants

B.1.1.1. Metabolism studies, methods of analysis and residue definitions in plants

No additional studies were provided under the MRL confirmatory data application, except additional storage stability data in high water content matrices (see Section B.1.1.2). For available metabolism in primary and rotational crops and methods of analysis for monitoring of residues in plants, see previous assessment (EFSA, 2013).

| Plant residue definition for monitoring (RD-Mo) | Flutolanil (EFSA, 2008) |
| Plant residue definition for risk assessment (RD-RA) | Sum of flutolanil, metabolites M-2 and M-4 and their conjugates, expressed as flutolanil (EFSA, 2008) |

B.1.1.2. Stability of residues in plants

| Plant products (available studies) | Category | Commodity | T (°C) | Stability period | Compounds covered | Comment/Source |
|----------------------------------|----------|-----------|--------|-----------------|-------------------|----------------|
|                                  | High water content | Potato, Spinach | –18 | 24 Months | Flutolanil | Finland (2018) |
|                                  |           | Potato, Spinach | –18 | 24 Months | M-2<sup>(a)</sup> | Finland (2018) |
|                                  |           | Potato, Spinach | –18 | 24 Months | M-4 | Finland (2018) |
|                                  | High oil content | Rape seed | –18 | 18 Months | Flutolanil | EFSA (2008) |
|                                  | Dry | Wheat grain | –18 | 18 Months | Flutolanil | EFSA (2008) |
|                                  | Others | Wheat straw | –18 | 18 Months | Flutolanil | EFSA (2008) |

(a): Slightly decreased mean recoveries (exceeding 30%) were observed at intermediate testing points of 9 and 12 months in both spinach and potato matrices and at the end of the study for two individual values in potato matrix.
### B.1.2. Magnitude of residues in plants

#### B.1.2.1. Summary of residues data from the supervised residue trials

| Commodity          | Region/ Indoor\(^{(a)}\) | Residue levels observed in the supervised residue trials (mg/kg) | Comments/Source\(^{(b)}\) | Calculated MRL (mg/kg) | HR\(^{(c)}\) (mg/kg) | STMR\(^{(d)}\) (mg/kg) | CF\(^{(e)}\) |
|--------------------|---------------------------|-----------------------------------------------------------------|-----------------------------|------------------------|----------------------|------------------------|------------|
| Peppers Indoor     | Mo: 9 × < 0.01 (EFSA, 2013) RA: – | Residue trials compliant with GAP assessed in the MRL review. No information is available on residues according to the residue definition for risk assessment | 0.01* Mo: 0.01 RA: – | Data gap |
| Beans (fresh with pods) Indoor | Mo: EFSA, 2013: 8 × < 0.01 Finland, 2018: 12 × < 0.01 RA: 11 × < 0.03; 0.07 | Residue trials compliant with GAP analysed for flutolanil, M-2 and M-4. M-2 (free and conj.): 12 × < 0.01 M-4 (free and conj.): 10 × < 0.01; 0.01; 0.04 | 0.01* Mo: 0.01 RA: 0.07 Mo: 0.01 RA: 0.03 3.7 (4 trials) |
| Globe artichokes SEU | Mo: EFSA, 2013: 4 × < 0.01 Finland, 2018: 4 × < 0.01 RA: 4 × < 0.03 | Residue trials compliant with GAP analysed for flutolanil, M-2 and M-4. Samples harvested 199–251 DAT. M-2 (free and conj.): 4 × < 0.01 M-4 (free and conj.): 4 × < 0.01 | 0.01* Mo: 0.01 RA: 0.03 Mo: 0.01 RA: 0.03 NA |

MRL: maximum residue level; GAP: Good Agricultural Practice; Mo: monitoring; RA: risk assessment.

*: Indicates that the MRL is proposed at the limit of quantification.

(a): NEU: Outdoor trials conducted in northern Europe, SEU: Outdoor trials conducted in southern Europe, Indoor: indoor EU trials or Country code: if non-EU trials. DAT, days after treatment.

(b): Residues of M-4 ≥ 0.01 mg/kg were corrected by a factor of 1.15 based on molecular weight ratio (flutolanil: M-4 = 323.3:281.2) to express the amounts as flutolanil equivalents prior to be summed up.

(c): Highest residue. The highest residue for risk assessment refers to the whole commodity and not to the edible portion.

(d): Supervised trials median residue. The median residue for risk assessment refers to the whole commodity and not to the edible portion.

(e): Conversion factor to recalculate residues according to the residue definition for risk assessment. When residues were below the LOQ according to both residue definition for enforcement and risk assessment, the CF was not calculated (NA, not applicable). Considering the very short PHI of 3 days, the median conversion factor for risk assessment for beans with pods was calculated from the individual trials with residues of M-4 at or above the LOQ observed after the last application (1 trial), after PHI 2 days (2 trials) and at PHI 3 days (one trial).
B.1.2.2. Residues in rotational crops

Not relevant.

B.1.2.3. Processing factors

Processing studies were not requested in the framework of the MRL confirmatory data.

B.2. Residues in livestock

B.2.1. Nature of residues and methods of analysis in livestock

B.2.1.1. Metabolism studies, methods of analysis and residue definitions in livestock

| Livestock (available studies) | Animal | Dose (mg/kg bw per day) | Duration (days) | Comment/Source |
|-------------------------------|--------|-------------------------|-----------------|----------------|
| Laying hen                    | 0.035  | 4                       | Hens, label position U-14C-aniline ring (EFSA, 2008) |
|                               | 1      | 4                       |                 |                |
| Lactating ruminants           | 0.27   | 5                       | Goat, label position U-14C-aniline ring (Finland, 2018) |
|                               |        |                         | Not assessed in this reasoned opinion (a) |
| Pig                           | Not required | –                     | EFSA (2008)    |
| Fish                          | NA     |                         |                 |                |

(a): A new metabolism study on ruminants was provided under the current application. The study and its impact on the residue definition for animal products will be assessed in the framework of EFSA conclusion on the renewal of the active substance flutolanil.

Animal residue definition for monitoring (RD-Mo)

Sum of flutolanil and all metabolites containing the 2-trifluoromethylbenzoic acid moiety, expressed as flutolanil (tentative) (EFSA, 2013)

Animal residue definition for risk assessment (RD-RA)

Sum of flutolanil and all metabolites containing the 2-trifluoromethylbenzoic acid moiety, expressed as flutolanil (EFSA, 2013)

Fat soluble residues

No

Methods of analysis for monitoring of residues (analytical technique, matrix, LOQs)

Common moiety method not fully validated. Confirmatory method missing. ILV not fully validated. Milk, Eggs, Muscle, Fat, Liver: GC–MS, LOQ 0.05 mg/kg. (Finland, 2018)

B.2.1.2. Stability of residues in livestock

| Animal products (available studies) | Animal | Commodity | T (°C) | Stability period Value | Compounds covered | Comment/Source |
|------------------------------------|--------|-----------|--------|------------------------|-------------------|----------------|
|                                    |        |           |        | Days                   | Parent, M-2, M-4, M-7 | Finland (2018) |
| Bovine                             | Muscle | –20       | 127    | Days                   | Parent            | Finland (2018) |
| Bovine                             | Fat    | –20       | 88     | Days                   | Parent            | Finland (2018) |
| Bovine                             | Fat    | –20       | < 88 (a) | Days                   | M-2, M-4, M-7     | Finland (2018) |
| Chicken                            | Liver  | –20       | 122    | Days                   | Parent, M-2, M-4, M-7 | Finland (2018) |
| Bovine                             | Milk   | –20       | 115    | Days                   | Parent, M-2, M-4, M-7 | Finland (2018) |
| Chicken                            | Eggs   | –20       | 125    | Days                   | Parent, M-2, M-4, M-7 | Finland (2018) |

(a): A significant decline was observed for M-2, M-4 and M-7 in fat matrix already at the first time point of 88 days.
B.2.2. Magnitude of residues in livestock

No additional studies provided under the MRL confirmatory data application. See previous assessment (EFSA, 2013).

B.3. Consumer risk assessment

| ARfD                      | Unnecessary (European Commission, 2008) |
|---------------------------|----------------------------------------|
| ADI                       | 0.09 mg/kg bw per day (European Commission, 2008) |
| Highest IEDI, according to EFSA PRImo | 2.6% ADI (NL child diet)           |
|                          | Contribution of crops assessed:       |
|                          | Peppers: 0.01% of ADI                |
|                          | Beans, with pods: 0.04% of ADI       |
|                          | Globe artichokes: 0.01% of ADI       |

Assumptions made for the calculations

The calculation is based on the median residue levels derived for raw agricultural commodities assessed in the MRL review confirmatory data and in previous assessments (EFSA, 2013, 2014). The median residue derived according to the residue definition for enforcement was multiplied for potatoes by the conversion factor (CF) for risk assessment of 3; for peppers, lacking empirical data, the tentative CF of 2 has been used (EFSA, 2013). The contributions of commodities where no GAP or safe Codex MRL (CXL) was reported to EFSA were not included in the calculation.

ADI: acceptable daily intake; bw: body weight; IEDI: international estimated daily intake; PRImo: (EFSA) Pesticide Residues Intake Model; MRL: maximum residue level; GAP: Good Agricultural Practice.

B.4. Recommended MRLs

| Code(a) | Commodity                                      | Existing MRL(b) | Proposed MRL | Conclusion/recommendation                                                                                                                                 |
|---------|------------------------------------------------|-----------------|--------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| 0231020 | Sweet peppers/bell peppers                    | 0.01* (ft 1)    | 0.01*        | The data gap identified by EFSA has not been addressed. Residue trials analysed in accordance with the residue definition for risk assessment have not been submitted. Instead, the applicant provided a justification for waiving the requested studies, claiming that the occurrence of residues related to flutolanil and its metabolites in peppers being treated in accordance with the GAP reported in the MRL review is unlikely. However, in accordance with the legal provisions, this assumption should be confirmed by data. A risk management decision is requiredweather the existing authorisations need to be withdrawn, considering that the MRL confirmatory data gap has not been addressed. Regarding the consumers’ dietary exposure, the use of the tentative conversion factor for peppers derived during the MRL review from rotational crop studies leads to additional non-standard uncertainties in the consumer risk assessment. However, the margin of safety of the exposure calculation is sufficiently large, and, consequently, a risk for consumer is unlikely. |

Enforcement residue definition for plant products and honey and other apiculture products: Flutolanil

Enforcement residue definition for animal products (except honey and other apiculture products): Flutolanil and metabolites containing the 2-trifluoromethylbenzoic acid moiety, expressed as flutolanil.

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| Code | Commodity | Existing MRL (b) | Proposed MRL | Conclusion/recommendation |
|------|-----------|-----------------|--------------|---------------------------|
| 0260010 | Beans (with pods) | 0.01* (ft 1) | 0.01* | The data gap identified by EFSA has been addressed. Residue trials analysed for residues in accordance with the residue definition for risk assessment have been provided. The previously derived MRL is confirmed. Risk for the consumer is unlikely. |
| 0270050 | Globe artichokes | 0.01* (ft 1) | 0.01* | |
| 1011010, 1011020 | Swine, muscle | 0.05* (ft 2) | 0.05* (further risk management consideration required) | Storage stability in animal matrices has been sufficiently addressed and supports the acceptability of the livestock feeding studies. Previous consumer risk assessment remains valid. Further validation data were provided to demonstrate that the available analytical method is suitable to enforce flutolanil residues according to the residue definition tentatively proposed during the MRL review and currently implemented in the MRL legislation. However, the documentation is not complete and the data gap identified in the MRL review is considered only partially addressed. Further risk management consideration is therefore required, which shall take into consideration that the need for an analytical method capable to enforce residues in products of animal origin according to the current tentative residue definition may become obsolete if a different residue definition is established in the context of the EU pesticides peer review. |
| 1012010, 1012020 | Bovine, muscle | 0.05* (ft 3) | 0.05* (further risk management consideration required) | Storage stability in animal matrices has been sufficiently addressed and supports the acceptability of the livestock feeding studies. Previous consumer risk assessment remains valid. |
| 1013010, 1013020 | Sheep, muscle | 0.05* (ft 3) | 0.05* (further risk management consideration required) | A new metabolism study on ruminants is available and the data gap is considered to be formally addressed. However, the study and its impact on the residue definition for animal products will be assessed in the framework of the renewal of the active substance flutolanil. Further validation data were provided to demonstrate that the available analytical method is suitable to enforce flutolanil residues according to the residue definition tentatively proposed during the MRL review and currently implemented in the MRL legislation. However, the documentation is not complete and the data gap identified in the MRL review is considered only partially addressed. Further risk management consideration is therefore required, which shall take into consideration that the need for an analytical method capable to enforce residues in products of animal origin according to the current tentative residue definition may become obsolete if a different residue definition is established in the context of the EU pesticides peer review. |
| 1014010, 1014020 | Goat, muscle | 0.05* (ft 3) | 0.05* (further risk management consideration required) | |
| 1016010, 1016020, 1016030 | Poultry, muscle | 0.05* (ft 2) | 0.05* (further risk management consideration required) | See conclusions/recommendations for swine (muscle and fat). |
| 1020010, 1020020, 1020030 | Milk, Cattle | 0.05* (ft 3) | 0.05* (further risk management consideration required) | See conclusions/recommendations for bovine, sheep, goat (muscle and fat). |
| Code<sup>a</sup> | Commodity      | Existing MRL<sup>b</sup> | Proposed MRL                                           | Conclusion/recommendation                                                        |
|----------------|----------------|--------------------------|--------------------------------------------------------|----------------------------------------------------------------------------------|
| 1030000        | Birds eggs     | 0.05* (ft 2)            | 0.05* (further risk management consideration required) | See conclusions/recommendations for swine (muscle and fat)                        |

MRL: maximum residue level; GAP: Good Agricultural Practice.

*: Indicates that the MRL is set at the limit of analytical quantification (LOQ).

<sup>a</sup>: Commodity code number according to Annex I of Regulation (EC) No 396/2005.

<sup>b</sup>: Existing EU MRL and corresponding footnote on confirmatory data.

Ft 1: The European Food Safety Authority identified some information on residue trials as unavailable. When reviewing the MRL, the Commission will take into account the information referred to in the first sentence, if it is submitted by 17 April 2017, or, if that information is not submitted by that date, the lack of it (Footnote related to data gap No 1).

Ft 2: The European Food Safety Authority identified some information on analytical methods and storage stability as unavailable. When reviewing the MRL, the Commission will take into account the information referred to in the first sentence, if it is submitted by 17 April 2017, or, if that information is not submitted by that date, the lack of it (Footnote related to data gap Nos 3 and 4).

Ft 3: The European Food Safety Authority identified some information on analytical methods, storage stability and metabolism in ruminants as unavailable. When reviewing the MRL, the Commission will take into account the information referred to in the first sentence, if it is submitted by 17 April 2017, or, if that information is not submitted by that date, the lack of it. (Footnote related to data gap Nos 2, 3 and 4).
# Appendix C – Pesticide Residue Intake Model (PRIMo)

## Flutolanil

Status of the active substance: Approved

| LOQ (mg/kg bw) | Proposed LOQ |
|---------------|--------------|
|               |              |

| Toxicological end points |
|--------------------------|
| ADI (mg/kg bw per day):   | 0.09          |
| Proposed ADI:             | n.n.          |
| Source of ADI:            | COM           |
| Year of evaluation:       | 2008          |

| ARfD (mg/kg bw):          | n.n.          |
| Source of ARfD:           | COM           |
| Year of evaluation:       | 2008          |

No of diets exceeding ADI: ---

## Chronic risk assessment – refined calculations

| Commodity/group of commodities | TMDI (range) in % of ADI | No of diets exceeding ADI |
|--------------------------------|--------------------------|---------------------------|
|                                | Minimum – Maximum        |                           |

| Commodity/group of commodities | TMDI (range) in % of ADI | No of diets exceeding ADI |
|--------------------------------|--------------------------|---------------------------|
|                                | Minimum – Maximum        |                           |

**Conclusion:**

The estimated Theoretical Maximum Daily Intakes (TMDI), based on pTMRLs were below the ADI. A long-term intake of residues of Flutolanil is unlikely to present a public health concern.

MRRLs according to regulation (EU) 2016/567 - Assessment of MRL review confirmatory data application.
Appendix D – Input values for the exposure calculations

D.1. Livestock dietary burden calculations

The submitted data do not have an impact on the input values used in the livestock dietary burden calculations based on the EU use on potatoes (EFSA, 2013).

D.2. Consumer risk assessment

| Commodity              | Chronic risk assessment                                                                 |
|------------------------|-----------------------------------------------------------------------------------------|
|                        | Input value (mg/kg) | Comment                                   |
| **Risk assessment residue definition for commodities of plant origin:** Sum of flutolanil, metabolites M-2 and M-4 and their conjugates, expressed as flutolanil | |
| Potatoes               | 0.06 (0.02 × 3)     | STMR × CF (EFSA, 2013)                    |
| Peppers                | 0.02 (0.01 × 2)     | STMR × CF (EFSA, 2013)                    |
| Flowering brassica     | 0.10 (0.05 × 2)     | MRL (FAO, 2013) × CF (EFSA, 2014)         |
| Head brassica          | 0.10 (0.05 × 2)     | MRL (FAO, 2013) × CF (EFSA, 2014)         |
| Beans with pods        | 0.03                | STMR                                       |
| Globe artichokes       | 0.03                | STMR                                       |
| Rice                   | 0.39                | STMR (a) (EFSA, 2013)                     |
| **Risk assessment residue definition for commodities of animal origin:** Sum of flutolanil and all metabolites containing the 2-trifluoromethylbenzoic acid moiety, expressed as flutolanil | |
| Kidney (b)             | 0.04                | STMR (FOA, 2013)                          |
| Liver (b)              | 0.15                | STMR (FOA, 2013)                          |
| Edible offal (b)       | 0.15                | STMR (FOA, 2013)                          |
| Meat (b)               | 0.05                | Existing MRL (LOQ) (EFSA, 2013)            |
| Fat (b)                | 0.05                | Existing MRL (LOQ) (EFSA, 2013)            |
| Poultry tissues        | 0.05                | Existing MRL (LOQ) (EFSA, 2013)            |
| Ruminant milks, birds eggs | 0.05              | Existing MRL (LOQ) (EFSA, 2013)            |

STMR: supervised trials median residue; CF: conversion factor for enforcement to risk assessment residue definition; HR: highest residue; MRL: maximum residue level; LOQ: limit of quantification.
(a): Based on the metabolism study in rice conducted at comparable GAP, the MRL review concluded not to applying any conversion factor for risk assessment (EFSA, 2013).
(b): Swine, bovine, sheep, goats, equine and other farm animals.
## Appendix E – Used compound codes

| Code/trivial name(a) | IUPAC name/SMILES notation/InChiKey(b) | Structural formula(c) |
|---------------------|----------------------------------------|-----------------------|
| flutolanil          | \(\alpha,\alpha,\alpha\)-trifluoro-3'-isopropoxy-o-toluanilide | ![Flutolanil Structural Formula](image) |
| M-2                 | \(\alpha,\alpha,\alpha\)-trifluoro-4'-hydroxy-3'-isopropoxy-o-toluanilide | ![M-2 Structural Formula](image) |
| M-4                 | \(\alpha,\alpha,\alpha\)-trifluoro-3'-hydroxy-o-toluanilide | ![M-4 Structural Formula](image) |
| M-7                 | \(\alpha,\alpha,\alpha\)-trifluoro-4'-hydroxy-3'-methoxy-o-toluanilide | ![M-7 Structural Formula](image) |
| 2-trifluoromethylbenzoic acid (TFBA) | 2-(trifluoromethyl)benzoic acid | ![2-trifluoromethylbenzoic acid Structural Formula](image) |

IUPAC: International Union of Pure and Applied Chemistry; SMILES: simplified molecular-input line-entry system; InChiKey: International Chemical Identifier Key.

(a): The metabolite name in bold is the name used in the conclusion.
(b): ACD/Name 2015 ACD/Labs 2015 Release (File version N20E41, Build 75170, 19 December 2014).
(c): ACD/ChemSketch 2015 ACD/Labs 2015 Release (File version C10H41, Build 75059, 17 December 2014).