Setting of import tolerance for flutriafol in hops

European Food Safety Authority (EFSA),
Alba Brancato, Daniela Brocca, Chloé De Lentdecker, Zoltan Erdos, Lucien Ferreira, Luna Greco, Samira Jarrah, Dimitra Kardassi, Renata Leuschner, Christopher Lythgo, Paula Medina, Ileana Miron, Tunde Molnar, Alexandre Nougadere, Ragnor Pedersen, Hermine Reich, Angela Sacchi, Miguel Santos, Alois Stanek, Juergen Sturma, José Tarazona, Theobald Anne, Benedicte Vagenende, Alessia Verani and Laura Villamar-Bouza

Abstract
In accordance with Article 6 of Regulation (EC) No 396/2005, the applicant Cheminova A/S submitted a request to the competent national authority in Spain to set an import tolerance for the active substance flutriafol in hops. The data submitted in support of the request were found to be sufficient to derive an import tolerance proposal of 20 mg/kg for crops under consideration. Adequate analytical methods for enforcement are available to control the residues of flutriafol in plant matrices under consideration. Based on the risk assessment results, EFSA concluded that the short-term and long-term intake of residues resulting from the use of flutriafol according to the reported agricultural practice is unlikely to present a risk to consumer health. However, as flutriafol belongs to the triazole chemical group, EFSA recommends that a separate risk assessment should be performed for triazole derivative metabolites (TDMs) as soon as the confirmatory data requested for triazole compounds in the framework of Regulation (EC) No 1107/2009 have been evaluated and a general methodology on the risk assessment of triazole compounds and their TDMs is available.

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Keywords: flutriafol, triazole derivative metabolites, hops, pesticide, MRL, consumer risk assessment

Requestor: European Commission
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Correspondence: pesticides.mrl@efsa.europa.eu
Summary

In accordance with Article 6 of Regulation (EC) No 396/2005, Cheminova A/S submitted an application to the competent national authority in Spain [evaluating Member State (EMS)] to set import tolerance for the active substance flutriafol in hops. The EMS drafted an evaluation report in accordance with Article 8 of Regulation (EC) No 396/2005, which was submitted to the European Commission and forwarded to the European Food Safety Authority (EFSA) on 10 November 2016. The EMS proposed to establish maximum residue levels (MRLs) for hops imported from the USA at the level of 20 mg/kg.

EFSA based its assessment on the evaluation report submitted by the EMS, the draft assessment report (DAR) (its additional report and its addendum) prepared under Directive 91/414/EEC, the Commission review report on flutriafol, the conclusion on the peer review of the pesticide risk assessment of the active substance flutriafol, the Joint Meeting on Pesticide Residues (JMPR) evaluation report as well as the conclusions from previous EFSA reasoned opinions on flutriafol including the review of the existing MRLs under Article 12 of Regulation (EC) No 396/2005.

The metabolism of flutriafol in primary crops following foliar application was investigated in crops belonging to the groups of fruit crops, root and tuber vegetables, cereals and pulses/oilseeds. Based on these studies, the residue definitions for plant products were proposed as flutriafol only for enforcement and risk assessment, pending on a harmonised approach on how to consider TDMs in the risk assessment.

Studies investigating the effect of processing on the nature of flutriafol (hydrolysis studies) demonstrated that the active substance is stable. Analytical methods to monitor flutriafol residues in hops at the limit of quantification (LOQ) of 0.01 mg/kg are available.

The available residue trials are sufficient to calculate an MRL proposal of 20 mg/kg for hops.

Since the proposed use of flutriafol is for imported crops and since hops are not fed to livestock, the residues in rotational crops and in commodities of animal origin were not assessed under the current application.

Under the current application, a median processing factor (PF) of 0.006 has been calculated from dried hops to beer from four processing studies.

The toxicological profile of flutriafol was evaluated in the framework of Directive 91/414/EEC and the data were sufficient to derive an acceptable daily intake (ADI) of 0.01 mg/kg body weight (bw) per day and acute reference dose (ARfD) of 0.05 mg/kg bw.

The consumer risk assessment was performed with revision 2 of the EFSA Pesticide Residues Intake Model (PRIMo). A long-term consumer intake concern was not identified for any of the European diets incorporated in the EFSA PRIMo. The total chronic intake calculated accounted for up to 34.5% of the ADI (WHO Cluster B). The contribution of residues in hops to the total consumer exposure accounted for less than 1% of the ADI. Additionally, the highest acute consumer exposure was calculated to be 3% of the ARfD for hops, showing no concern in an acute exposure scenario for European consumers related to the import tolerance requested.

It should be highlighted that the above assessment does not consider the possible impact of plant metabolism on the isomer ratio of the active substance and further investigation on this matter would in principle be required. Since guidance is not yet available on the consideration of isomer ratios in the consumer risk assessment, EFSA recommends that this issue is reconsidered when such guidance is available.

EFSA emphasises that the above assessment does not yet take into consideration triazole derivative metabolites (TDMs). As these metabolites may be generated by several pesticides belonging to the group of triazole fungicides, EFSA recommends that a separate risk assessment should be performed for TDMs as soon as the confirmatory data requested for triazole compounds in the framework of Regulation (EC) No 1107/2009 have been evaluated and a general methodology on the risk assessment of triazole compounds and their TDMs is available.

EFSA concluded that the proposed use of flutriafol on hops will not result in a consumer exposure exceeding the toxicological reference values and therefore is unlikely to pose a risk to consumer health.
EFSA proposes to amend the existing MRL as reported in the summary table below.

| Code<sup>(a)</sup> | Commodity | Existing EU MRL (mg/kg) | Proposed EU MRL (mg/kg) | Comment/justification |
|-------------------|-----------|------------------------|-------------------------|------------------------|
| 070000            | Hops      | 0.05*                  | 20                      | Import tolerance (USA)MRL derived from supervised residue trials in hops and for which no concern has been identified to European consumers |

MRL: maximum residue level.

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

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

Regulation (EC) No 396/2005 (hereinafter referred to as ‘the MRL regulation’) establishes the rules governing the setting of pesticide maximum residue levels (MRLs) at European Union (EU) level. Article 6 of the MRL regulation lays down that any party having a legitimate interest or requesting an authorisation for the use of a plant protection product in accordance with Council Directive 91/414/EEC, repealed by Regulation (EC) No 1107/2009, shall submit an application to a Member State to set an import tolerance in accordance with the provisions of Article 7 of the MRL regulation.

The applicant Cheminova A/S submitted an application to the competent national authority in Spain, hereafter referred to as the evaluating Member State (EMS), to set an import tolerance for the active substance flutriafol in hops imported from USA. This application was notified to the European Commission and the European Food Safety Authority (EFSA) and was subsequently evaluated by the EMS in accordance with Article 8 of the MRL regulation.

The EMS summarised the data provided by the applicant in an evaluation report which was submitted to the European Commission and forwarded to EFSA on 10 November 2016. The application was included in the EFSA Register of Questions with the reference number EFSA-Q-2016-00719 and the following subject:

*Flutriafol – IT MRLs in hops.*

Spain proposed to raise the existing MRL of flutriafol in hops from the limit of quantification (LOQ) of 0.05 to 20 mg/kg. EFSA assessed the application and the evaluation report as required by Article 10 of the MRL regulation.

Terms of Reference

In accordance with Article 10 of Regulation (EC) No 396/2005, EFSA shall assess the application and the evaluation report and give a reasoned opinion on the risks to the consumer and where relevant to animals associated with the setting of the requested MRLs. The opinion shall include:

- an assessment of whether the analytical method for routine monitoring proposed in the application is appropriate for the intended control purposes;
- the anticipated LOQ for the pesticide/product combination;
- an assessment of the risks of the acceptable daily intake and acute reference dose being exceeded as a result of the modification of the MRL;
- the contribution to the intake due to the residues in the product for which the MRLs was requested;
- any other element relevant to the risk assessment.

In accordance with Article 11 of the MRL regulation, EFSA shall give its reasoned opinion as soon as possible and at the latest within three months from the date of receipt of the application.

The evaluation report submitted by the EMS (Spain, 2016) and the exposure calculations using the EFSA Pesticide Residues Intake Model (PRIMo) are considered as supporting documents to this reasoned opinion and, thus, are made publicly available as background documents to this reasoned opinion. Furthermore, a screenshot of the Report sheet of the PRIMo is presented in Appendix C.

The active substance and its use pattern

The detailed description of the intended use of flutriafol in the USA in hops, which is the basis for the current MRL application, is reported in Appendix A.

Flutriafol is the ISO common name for (RS)-2,4'-difluoro-α-(1H-1,2,4-triazol-1-ylmethyl)benzhydryl alcohol (IUPAC). The chemical structures of the active substance and its main metabolites are reported in Appendix E. Flutriafol is a racemic mixture of two enantiomers.

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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 Council Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products on the market. OJ L 230, 19.8.1991, p. 1–32.
3 Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. OJ L 309, 24.11.2009, p. 1–50.
4 Cheminova A/S, PO Box 9, 7620 Lemvig, Denmark.
Flutriafol was evaluated in the framework of Directive 91/414/EEC with the United Kingdom designated as rapporteur Member State (RMS) for the representative use as foliar applications on wheat. In 2006, the applicant voluntarily withdrew, in accordance with Article 11e of Regulation (EC) No 1490/2002, the support for the inclusion of this substance in Annex I of Directive 91/414/EEC. Consequently, a first decision on non-inclusion of the active substance flutriafol was published by means of Commission Decision 2008/934/EC, which entered into force on 31 December 2008. In accordance with the provisions laid down in Chapter III of Regulation (EC) No 33/2008, flutriafol was subject to a resubmission procedure. It was included in Annex I of Directive 91/414/EEC by Directive 2011/42/EU which entered into force on 1 June 2011 for use as a fungicide only. In accordance with Commission Implementing Regulation (EU) No 540/2011, flutriafol is approved under Regulation (EC) No 1107/2009, repealing Council Directive 91/414/EEC.

The EU MRLs for flutriafol are established in Annexes II of Regulation (EC) No 396/2005. The review of existing MRLs according to Article 12 of Regulation (EC) No 396/2005 (MRL review) has been performed (EFSA, 2014) and the proposed modifications have been implemented in the MRL legislation. After completion of the MRL review, EFSA has issued several reasoned opinions on the modification of MRLs for flutriafol. The proposals from one of these reasoned opinions have been considered in recent regulation for EU MRL legislation.

| Procedure(a) | Considered by Regulation | Remarks |
|--------------|--------------------------|---------|
| Art. 12 (EFSA, 2014) | (EU) 2016/71 | Review of existing MRLs |
| Art. 10 (EFSA, 2016a) | (EU) 2016/1902 | Strawberries (import tolerance USA) |
| Art. 10 (EFSA, 2016b) | (EU) 2017/626 | Cucumbers, gherkins, courgettes and other cucurbits with edible peel (import tolerance USA/Canada) |

MRL: maximum residue level.
(a): Art. 10: Assessment of MRL application according to Article 6 to 10 of Regulation (EC) No 396/2005
Art. 12: Review of the existing MRLs according to Article 12 of Regulation (EC) No 396/2005.

Assessment

EFSA has based its assessment on the evaluation report submitted by the EMS (Spain, 2016), the draft assessment report (DAR), the additional report and its addendum prepared under Council Directive 91/414/EEC (United Kingdom, 2006, 2010a,b), the Commission review report on flutriafol (European Commission, 2011), the conclusion on the peer review of the pesticide risk assessment of the active substance flutriafol (EFSA, 2010a), the Joint Meeting on Pesticide Residues (JMPR) evaluation reports (FAO, 2011, 2015) as well as the conclusions from previous EFSA opinions on flutriafol (EFSA, 2010b, 2013, 2016a,b) including the review of the existing MRLs according to Article 12 of Regulation (EC) No 396/2005 (EFSA, 2014). Information on the MRLs set in the country of origin.
for the requested import tolerance was provided and the tolerance for residues established in USA for flutriafol in hops is 20 mg/kg. For this application, the data requirements established in Regulation (EU) No 283/2013 and the guidance documents applicable at the date of submission of the application to the EMS are applicable (European Commission, 1997a–g, 2000, 2010a,b, 2016; OECD, 2008, 2011, 2013). 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. A selected list of end points of the studies assessed by EFSA in the framework of the MRL review relevant for the current application, including relevant information provided with the current application, is presented in Appendix B.

1. Residues in plants

1.1. Nature of residues and methods of analysis in plants

1.1.1. Nature of residues in primary crops

In the framework of the peer review, the metabolism of flutriafol in primary crops was investigated in the root, cereal/grass and pulses/oilseed crop groups (EFSA, 2010a). An additional study was submitted and evaluated in the framework of a previous MRL application (EFSA, 2010b). The metabolism studies showed that flutriafol is the predominant compound of the total radioactive residues (TRRs) in all the crop groups investigated. In cereal grain crop group, where the cleavage of the parent molecule at the triazole bound occurred, triazole alanine and the triazole acetic acid were found to be the predominant compounds of the total residues (EFSA, 2014). The summary of the available metabolism studies that were used to set the current residue definitions are summarised in Appendix B.

1.1.2. Nature of residues in rotational crops

Investigations of residues in rotational crops are not required for imported crops.

1.1.3. Nature of residues in processed commodities

The effect of processing on the nature of flutriafol residues has been evaluated by EFSA in a previous reasoned opinion (EFSA, 2016a) and it was concluded that the residues of flutriafol are stable under standard hydrolysis studies simulating representative conditions of pasteurisation, boiling and sterilisation.

1.1.4. Methods of analysis in plants

Analytical methods for the determination of flutriafol residues in plant matrices using high-performance liquid chromatography-tandem mass spectrometry detector (HPLC-MS/MS) were assessed during the peer review under Directive 91/414/EEC (EFSA, 2010a) and it was concluded that validated methods are available to analyse flutriafol residues in high water (wheat whole plant, sugar beet root and foliage), dry/starch (wheat grain), dry/protein matrices (pea) and wheat straw at the LOQ of 0.01 mg/kg. The multiresidue Quick, Easy, Cheap, Effective, Rugged, and Safe (QuEChERS) method in combination with HPLC-MS/MS, as described by the European Committee for Standardisation (CEN, 2008), was also reported for analysis of flutriafol in high oil and acidic content commodities at a LOQ of 0.01 mg/kg (EFSA, 2010a).

12 US Code of Federal Regulations 40 CFR §180.629 Flutriafol: tolerances for residues. http://www.ecfr.gov/cgi-bin/retrieveECFR?gp=&SID=75c174e654c5f3833418b5d7b1cf06mc=true&n=PARTn=pt40.24.180#se40.26.180_1629
13 Commission Regulation (EU) No 283/2013 of 1 March 2013 setting out the data requirements for active substances, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market. OJ L 93, 3.4.2013, p. 1–84.
14 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.
15 The updated list of endpoints reflects the decisions on implementing MRL recommendations taken in Commission Regulation (EU) 2016/53.

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In the framework of the current application, the HPLC-MS/MS method used in the analysis of the samples from the residue trials has been described by the EMS (Spain, 2016). However, this method was not peer reviewed by EFSA in the previous assessments and full validation data were not reported in the evaluation report. Nevertheless, considering that the method evaluated in the previous assessments was fully validated in straw which represents another complex matrix, it can be concluded that an analytical method for the enforcement of flutriafol in complex matrices as hops at the LOQ of 0.01 mg/kg is available. The full validation data of the method described by the EMS for hops are still desirable.

1.1.5. Stability of residues in plants

In the framework of the peer review as well as previous MRL assessments, residues of flutriafol were demonstrated to be stable in frozen conditions for a period of 12 months in high water content (apple, wheat whole plant), dry commodities (wheat grain) and high oil content commodities (oilseed rape), and for a period of 23 months in commodities with high acid content (grapes) (EFSA, 2014).

1.1.6. Proposed residue definitions

Based on the metabolic pattern identified in metabolism studies, the residue definition for enforcement and risk assessment has been set as flutriafol only, pending on a harmonised approach on how to consider triazole derivative metabolites (TDMs) in the risk assessment.

In addition, EFSA notes that the above studies do not investigate the possible impact of plant metabolism on the isomer ratio of flutriafol and in principle, further investigation would be required on this matter. Since guidance on the consideration of isomer ratios in the consumer risk assessment is not yet available, EFSA recommends that this issue is reconsidered when such guidance will be available.

1.2. Magnitude of residues in plants

1.2.1. Magnitude of residues in primary crops

In support of the import tolerance request, four residue trials on hops performed in USA in 2013 according to the USA good agricultural practices (GAP) [4 × 128 g/ha preharvest interval (PHI) 7 days] were submitted. The samples of the supervised field trials were collected at PHI 7 days; in one residue trial, samples were also taken at 0, 7, 14, 21 and 28 days after the last application. As the trial samples were stored for a maximum period of 7 months under conditions for which integrity of the samples was demonstrated, it is concluded that the residue data are valid with regard to storage stability. The samples were analysed for parent flutriafol and the TDMs.

At intended PHI of 7 days, the residues of flutriafol were found in the range of 4.14–7.96 mg/kg and the metabolite 1,2,4-triazole was found to be below the LOQ. Triazole alanine metabolites were detected in a range of 0.09–0.16 mg/kg and triazole acetic values ranged from the LOQ to 0.05 mg/kg. One residue decline study has been submitted with detections until PHI 28 days and it has not been observed any pattern of concern for increasing metabolites over time.

1.2.2. Magnitude of residues in processed commodities

Four studies conducted in Germany in 2014 where dried hops were processed to beer were submitted under the current application (Spain, 2016) and a median processing factor of 0.006 was derived for beer (Table B.1.2.2).

1.2.3. Proposed MRLs

The available data are considered sufficient to derive MRL proposal as well as risk assessment values for hops imported from USA (see Appendix B.1.2.1). In Section 3, EFSA assessed whether residues on this crop resulting from the intended use are likely to pose a consumer health risk.

2. Residues in livestock

Hops are not used to feed livestock; therefore the impact of residues of flutriafol from the intended use in hops does not need to be assessed in this application.
3. **Consumer risk assessment**

EFSA performed a dietary risk assessment using revision 2 of the EFSA PRIMo (EFSA, 2007). This exposure assessment model contains food consumption data for different subgroups of the EU population and allows the acute and chronic exposure assessment to be performed in accordance with the internationally agreed methodology for pesticide residues (FAO, 2016).

The toxicological reference values for flutriafol used in the risk assessment [i.e. acceptable daily intake (ADI) and acute reference dose (ARfD) values] were derived in the framework of the EU pesticides peer review (EFSA, 2010a). The input values used in the exposure calculations are summarised in Appendix C.

3.1. **Short-term (acute) dietary risk assessment**

The short-term exposure assessment was performed only with regard to the commodity assessed in this application in accordance with the internationally agreed methodology (FAO, 2016). The acute exposure assessment has been performed assuming the consumption of a large portion of the food item as reported in the national food surveys (EFSA, 2007) and that hops contained residues at the highest residue (HR) level as observed in supervised field trials (see Appendix D).

The short-term exposure did not exceed the ARfD for the crop assessed in this application. It was calculated to account for a maximum of 3% of the ARfD (see Appendix C).

3.2. **Long-term (chronic) dietary risk assessment**

In the framework of the MRL review a comprehensive long-term exposure assessment was performed, taking into account the existing uses at EU level and the acceptable Codex maximum residue limits (CXLs) (EFSA, 2014). EFSA updated the calculation performed under the MRL review including the STMRs derived in the previous EFSA opinions published after the MRL review (EFSA, 2016a,b) and the supervised trials median residue (STMR) derived from the residue trials submitted in support of this MRL application for hops. The food commodities, for which MRLs were set at the LOQ in the Commission Regulation 2017/626, have been excluded from the exposure calculation, assuming that there is no use of flutriafol on these crops (see Appendix D).

The estimated long-term dietary intake accounted for up to 34.5% of the ADI (WHO Cluster B). The contribution of residues due to the intended use in hops to the overall long-term exposure accounted for less than 1% of the ADI (United Kingdom, adult) (see Appendix C).

**Conclusions and recommendations**

The data submitted in support of this assessment were found to be sufficient to derive an import tolerance proposal for hops.

Analytical methods to monitor flutriafol residues in hops at the LOQ of 0.01 mg/kg are available.

Based on the risk assessment results, EFSA concludes that residues of flutriafol on hops expected after treatment according to the USA GAP will not result in a consumer exposure exceeding the toxicological reference values and therefore is unlikely to pose a concern for public health in Europe.

However, it should be highlighted that the above assessment does not consider the possible impact of plant metabolism on the isomer ratio of the active substance and further investigation on this matter would in principle be required. Since guidance is not yet available on the consideration of isomer ratios in the consumer risk assessment, EFSA recommends that this issue is reconsidered when such guidance is available.

EFSA emphasises that the above assessment does not yet take into consideration TDMs. Since these metabolites may be generated by several pesticides belonging to the group of triazole fungicides, EFSA recommends that a separate risk assessment should be performed for TDMs as soon as the confirmatory data requested for triazole compounds in the framework of Directive 91/414/EEC have been evaluated and a general methodology on the risk assessment of triazole compounds and their TDMs is available.

The MRL recommendations are summarised in Appendix B.4.
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Abbreviations

a.s. active substance  
ADI acceptable daily intake  
AR applied radioactivity  
ARfD acute reference dose  
BBCH growth stages of mono- and dicotyledonous plants  
bw body weight  
CAS Chemical Abstracts Service  
CEN European Committee for Standardisation (Comité Européen de Normalisation)  
CXL Codex maximum residue limit  
DAR draft assessment report  
DAT days after treatment  
EMS evaluating Member State  
FAO Food and Agriculture Organization of the United Nations  
GAP Good Agricultural Practice  
HPLC high-performance liquid chromatography  
HR highest residue  
IEDI international estimated daily intake  
IESTI international estimated short-term intake  
ISO International Organisation for Standardisation  
IUPAC International Union of Pure and Applied Chemistry  
JMPR Joint FAO/WHO Meeting on Pesticide Residues  
LOQ limit of quantification  
MRL maximum residue level  
MS Member States  
MS/MS tandem mass spectrometry detector  
MW molecular weight  
NEU northern Europe  
OECD Organisation for Economic Co-operation and Development  
PF processing factor  
PHI preharvest interval  
PRIMo (EFSA) Pesticide Residues Intake Model  
QuEChERS Quick, Easy, Cheap, Effective, Rugged, and Safe (analytical method)  
RA risk assessment  
RD residue definition  
RMS rapporteur Member State  
SANCO Directorate-General for Health and Consumers  
SC suspension concentrate  
SEU southern Europe  
SMILES simplified molecular-input line-entry system  
STMR supervised trials median residue  
TDMs Triazole derivate metabolites  
TMDI theoretical maximum daily intake  
TRR total radioactive residue  
WHO World Health Organization
| Crop          | Region/MS | F | G | Pests or Group of pests controlled | Preparation | Method | Range of growth stages & season | Number of applications | Interval between application | g a.s./hL | Water L/ha | kg a.s./ha | PHI (days) | Remarks                        |
|--------------|-----------|---|---|-----------------------------------|-------------|--------|-------------------------------|------------------------|-----------------------------|----------|-----------|-----------|------------|--------------------------------|
| Hops         | USA       | F |   | Powdery Mildew, Podosphaera macularis, Sphaerotheca macularis | SC          | Foliar | spray                         | 1-4                    | 14                          | 336       | 112       | 336       | Max. 0.128 | Max. 10–14 fl.oz./A per application, Max. 56 fl.oz./A per year |

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

### Primary crops (available studies)

| Crop groups | Crop(s)     | Application(s) | Sampling (DAT) |
|-------------|-------------|----------------|----------------|
| Fruit crops | Apple       | Foliar, 1 × 0.118 kg/ha | 64             |
| Root crops  | Sugar beet  | Foliar, 1 × 0.125 kg/ha  | 0, 16, 21     |
| Cereals     | Barley, Wheat | Foliar, 1 × 0.081–0.105 kg/ha | 44 to 94 |
| Pulses and oilseeds | Rape seed | Foliar, 1 × 0.125 kg/ha | 0, 14, 42     |

Studies performed with triazolyl- and carbinol-labelled flutriafol
Sources: EFSA, 2010a,b, 2014; FAO, 2011; United Kingdom, 2006, 2010b

### Rotational crops (available studies)

| Crop groups | Crop(s)     | Application(s) | PBI (DAT) |
|-------------|-------------|----------------|-----------|
| Root crops  | Sugar beet  | Spray (bare soil), 1 × 0.25 kg/ha | 30, 120, 365 |
|             | Radish      | Spray (bare soil), 1 × 0.26 kg/ha | 30, 120, 365 |
| Leafy crops | Lettuce     | Spray (bare soil), 1 × 0.26 kg/ha | 30, 120, 365 |
| Cereals     | Wheat       | Spray (bare soil), 1 × 0.25 kg/ha | 30, 120, 365 |
|             |             | Spray (bare soil), 1 × 0.26 kg/ha | 30, 120, 365 |

Studies performed with triazolyl- and carbinol-labelled flutriafol
Sources: EFSA, 2010a; United Kingdom, 2006, 2010a; FAO, 2011

### Processed commodities (hydrolysis study)

| Conditions                                 | Investigated? |
|--------------------------------------------|----------------|
| Pasteurisation (20 min, 90°C, pH 4)        | Yes            |
| Baking, brewing and boiling (60 min, 100°C, pH 5) | Yes            |
| Sterilisation (20 min, 120°C, pH 6)        | Yes            |

Source: EFSA, 2016a

DAT: days after treatment; PBI: plant-back interval.

**Can a general residue definition be proposed for primary crops?** Yes

**Rotational crop and primary crop metabolism similar?** Not applicable for the import tolerance

**Residue pattern in processed commodities similar to residue pattern in raw commodities?** Yes

**Plant residue definition for monitoring (RD-Mo)** Flutriafol only

**Plant residue definition for risk assessment (RD-RA)** Flutriafol only. Tentative residue definition, pending on the agreement on the approach for the assessment of TDMs.

**Conversion factor (monitoring to risk assessment)** Not applicable

**Methods of analysis for monitoring of residues (analytical technique, crop groups, LOQs)** Matrices with high water content, high oil content, high acid content and dry matrices: HPLC–MS/MS, with an LOQ of 0.01 mg/kg (EFSA, 2010a).
### B.1.1.2. Stability of residues in plants

| Plant products (available studies) | Category              | Commodity         | $T$ (°C) | Stability (months) |
|-----------------------------------|-----------------------|-------------------|----------|-------------------|
| High water content                | Wheat whole plant     | –23               | 12       |
| High oil content                  | Rape seed             | –18               | 12       |
| Dry/high starch                    | Wheat grain           | –23               | 12       |
| High acid content                 | Grapes                | –18               | 23       |

Source: EFSA, 2014
B.1.2. Magnitude of residues in plants

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

| Crop          | Region/ indoor<sup>a</sup> | Residue levels observed in the supervised residue trials (mg/kg)                                                                                     | Comments (OECD calculations)                                                                                                                                  | MRL proposals (mg/kg) | HR<sup>b</sup> (mg/kg) | STMR<sup>c</sup> (mg/kg) |
|---------------|-----------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|-------------------------|-------------------------|
| Hops          | USA                         | Flutriafol: 4.14, 4.64, 7.33, 7.96  
1,2,4-Triazole: < 0.01  
Triazole alanine: 0.091, 0.111, 0.121, 1.56  
Triazole acetic acid: < 0.01, 0.017, 0.024, 0.047 | MRL<sub>OECD</sub>: 18.05/20.00  
Residue trials on hops compliant with GAP. Results from the analysis of TDMs are reported for information only | 20                     | 7.96                     | 5.99                     |

MRL: maximum residue level; OECD: Organisation for Economic Co-operation and Development; GAP: good agricultural practice; TDMs: triazole derivative metabolites.

<sup>a</sup>: 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.

<sup>b</sup>: Highest residue according to the residue definition for monitoring.

<sup>c</sup>: Supervised trials median residue according to the residue definition for monitoring.

*: Indicates that the MRL is proposed at the limit of quantification.
B.1.2.2. Processing factors

| Processed commodity     | Number of valid studies | Processing Factor (PF) | Individual values | Median PF |
|-------------------------|-------------------------|------------------------|-------------------|-----------|
| Dried hops to Beer      | 4                       | 0.009, 0.021, 0.003, 0.003 | 0.006             |           |

B.2. Residues in livestock

Since hops are not fed to livestock, this section does not need further consideration under the current MRL application. The list of endpoints derived in the MRL review are still considered valid (EFSA, 2014).

B.3. Consumer risk assessment

| Assumption/Calculation                                                                 | Value/Details                                                   |
|----------------------------------------------------------------------------------------|-----------------------------------------------------------------|
| ARfD                                                                                   | 0.05 mg/kg bw (EFSA, 2010a)                                     |
| Highest IESTI, according to EFSA PRIMo                                                 | 3% ARfD                                                         |
| Assumptions made for the calculations                                                  | Only the residues at the highest residue (HR) level as observed in supervised field trials in hops has been considered in the acute exposure scenario |
| ADI                                                                                   | 0.01 mg/kg bw per day (EFSA, 2010a)                             |
| Highest IEDI, according to EFSA PRIMo                                                 | 34.5% ADI (WHO Cluster B)                                      |
| Assumptions made for the calculations                                                  | Hops contribution < 1% ADI                                      |
|                                                                                       | The long-term exposure assessment performed in the framework of the MRL review (EFSA, 2014) has been updated considering the STMR value derived from the residue trials submitted in support of this MRL application for hops and the STMRs derived in previous EFSA opinions published after the MRL review (EFSA, 2016a; EFSA, 2016b) |
|                                                                                       | The food commodities, for which MRLs were set at the LOQ in the Commission Regulation 2017/626, have been excluded from the exposure calculation, assuming that there is no use of flutriafol on these crops |

Setting of import tolerance for flutriafol in hops
### Recommended MRLs

| Code<sup>(a)</sup> | Commodity | Existing EU MRL (mg/kg) | Proposed EU MRL (mg/kg) | Comment/justification |
|-------------------|-----------|------------------------|-------------------------|-----------------------|
| 070000            | Hops      | 0.05<sup>*</sup>       | 20                      | Import tolerance (USA) MRL derived from supervised residue trials in hops and for which no concern has been identified to European consumers |

**Enforcement residue definition:** flutriafol

MRL: maximum residue level.

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

<sup>*</sup>: Indicates that the MRL is set at the limit of analytical quantification (LOQ).
Appendix C – Pesticide Residue Intake Model (PRIMo)

| Flutriafol | Toxicological end points |
|------------|--------------------------|
| Status of the active substance: | Included |
| Code no. | Proposed LOQ |
| ADI (mg/kg bw per day) | 0.01 |
| Source of ADI | EFSA |
| Year of evaluation | 2010 |
| Source of ARfD | EFSA |
| Year of evaluation | 2010 |

| Toxicological end points | ADI (mg/kg bw per day): | LOQ (mg/kg bw): |
|--------------------------|--------------------------|----------------|
| ARfD (mg/kg bw) | 0.05 | 0.05 |

| No of diets exceeding ADI: | 5 |

| Chronic risk assessment – refined calculations |
|-----------------------------------------------|
| TMDI (range) in % of ADI | minimum – maximum |
| Commodity/ group of commodities | |
| **53.4** | WHO Cluster diet B | 12.4 | Maize | 6.1 | Wine grapes | 4.8 | Tomatoes |
| 25.6 | IE adult | 11.5 | Maize | 4.3 | Wine grapes | 1.0 | Strawberries |
| 24.6 | DE child | 8.4 | Apples | 2.7 | Table grapes | 2.1 | Strawberries |
| 20.1 | PT General population | 8.5 | Wine grapes | 3.1 | Rice | 2.4 | Maize |
| 19.9 | UK Infant | 5.1 | Maize | 3.9 | Milk and cream | 2.5 | Rice |
| 18.4 | NL child | 4.4 | Apples | 2.9 | Milk and cream | 1.6 | Table grapes |
| 17.7 | FR all population | 13.6 | Wine grapes | 0.7 | Tomatoes | 0.7 | Wheat |
| 16.3 | WHO Cluster diet E | 5.5 | Wine grapes | 2.8 | Maize | 0.8 | Rice |
| 14.3 | UK Toddler | 3.4 | Sugar beet (root) | 2.3 | Rice | 2.1 | Milk and cream |
| 13.0 | WHO Cluster diet D | 2.7 | Maize | 2.2 | Rice | 1.8 | Apples |
| 12.2 | DK child | 2.0 | Oats | 1.6 | Apples | 1.3 | Milk and cream |
| 11.1 | ES child | 1.9 | Rice | 1.5 | Tomatoes | 1.4 | Maize |
| 10.1 | WHO Cluster diet F | 2.0 | Wine grapes | 1.1 | Tomatoes | 0.8 | Rice |
| 9.6 | DA adult | 4.7 | Wine grapes | 0.6 | Tomatoes | 0.6 | Oats |
| 9.2 | WHO regional European diet | 1.7 | Tomatoes | 0.8 | Wine grapes | 0.8 | Rice |
| 9.0 | UK vegetarian | 2.8 | Wine grapes | 1.5 | Rice | 1.0 | Tomatoes |
| 8.9 | SE general population 90th percentile | 1.6 | Rice | 1.2 | Milk and cream | 1.2 | Tomatoes |
| 8.9 | UK Adult | 3.7 | Wine grapes | 1.4 | Rice | 0.7 | Tomatoes |
| 8.8 | FR infant | 2.6 | Milk and cream | 2.1 | Strawberries | 1.6 | Apples |
| 8.3 | NL general | 2.1 | Wine grapes | 0.8 | Apples | 0.7 | Tomatoes |
| 8.1 | ES adult | 1.4 | Wine grapes | 1.2 | Tomatoes | 0.9 | Rice |
| 7.9 | IT kids/toddler | 2.2 | Tomatoes | 1.3 | Wheat | 0.8 | Rice |
| 6.3 | IT adult | 1.8 | Tomatoes | 0.8 | Wheat | 0.7 | Rice |
| 5.4 | LT adult | 1.3 | Apples | 1.0 | Tomatoes | 0.8 | Rice |
| 4.9 | FI adult | 1.0 | Wine grapes | 0.7 | Tomatoes | 0.6 | Milk and cream |
| 4.8 | PL general population | 1.4 | Apples | 1.4 | Tomatoes | 0.7 | Table grapes |

Conclusion: The estimated Theoretical Maximum Daily Intakes (TMDI), based on pTMRLs were below the ADI. A long-term intake of residues of Flutriafol is unlikely to present a public health concern.
### Acute risk assessment/children – refined calculations

| Highest % of ARfD/ADI for processed commodities | pTMRL/threshold MRL (mg/kg) | Highest % of ARfD/ADI for processed commodities | pTMRL/threshold MRL (mg/kg) | Highest % of ARfD/ADI for processed commodities | pTMRL/threshold MRL (mg/kg) | Highest % of ARfD/ADI for processed commodities | pTMRL/threshold MRL (mg/kg) |
|---|---|---|---|---|---|---|---|
| HOPS (dried) | 7.96 | - | HOPS (dried) | 7.96 | - | HOPS (dried) | 7.96 | - |
| Grape juice | 0.89 | - | Peach juice | 0.41 | - | Peach preserved with | 0.41 | - |
| Apple juice | 0.24 | - | Peach juice | 0.24 | - | Tomato (preserved- | 0.24 | - |
| Peach juice | 0.41 | - | Tomato juice | 0.24 | - | Bread/pizza | 0.1 | - |

**No of critical MRLs (IESTI 1):**

- No exceedance of the ARfD/ADI was identified for any unprocessed commodity.
- The results of the IESTI calculations are reported for at least 5 commodities. If the ARfD is exceeded for more than 5 commodities, all IESTI values > 90% of ARfD are reported.

**pTMRL:** provisional temporary MRL

**Conclusion:**

- For Flutriafol, IESTI 1 and IESTI 2 were calculated for food commodities for which pTMRLs were submitted and for which consumption data are available.
- No exceedance of the ARfD was identified for any processed commodity.
- For processed commodities, no exceedance of the ARfD/ADI was identified.
### Appendix D – Input values for the exposure calculations

| Commodity                        | Chronic exposure assessment | Acute exposure assessment |
|----------------------------------|-----------------------------|---------------------------|
|                                  | Input (mg/kg)               | Comment                    | Input (mg/kg)               | Comment                                      |
| Risk assessment residue definition: flutriafol |                             |                           |                             |                                             |
| Hops                             | 5.99                        | STMR (Table B.1.2.1)      | 7.96                        | HR (Table B.1.2.1)                          |
| Strawberries                     | 0.42                        | STMR (EFSA, 2016a)        |                             |                                              |
| Cucumber                         | 0.05                        | STMR (EFSA, 2016b)        |                             |                                              |
| Gherkins                         | 0.05                        | STMR (EFSA, 2016b)        |                             |                                              |
| Courgettes                       | 0.05                        | STMR (EFSA, 2016b)        |                             |                                              |
| Other cucurbits (edible peel)    | 0.05                        | STMR (EFSA, 2016b)        |                             |                                              |
| Other commodities of plant and animal origin | See table 4-2 in reasoned opinion on Art 12. MRLs review (EFSA, 2014) |                                           |

STMR: supervised trials median residue; HR: highest residue; MRL: maximum residue level.
## Appendix E – Used compound code(s)

| Code/trivial name | Chemical name/SMILES notation (a)                                                                 | Structural formula (a)                                      |
|-------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------|
| Flutriafol        | (RS)-2,4′-Difluoro-α-(1H-1,2,4-triazol-1-ylmethyl)benzhydryl alcohol MW: 301.3 g/mol             | ![Flutriafol Structure](image)                               |
|                   |                                                                                                  |                                                             |
| **Triazole derivative metabolites** |                                                                                                  |                                                             |
| 1,2,4-Triazole    | 1H-1,2,4-Triazole (free triazole) (CAS number 288-88-0)                                          | ![1,2,4-Triazole Structure](image)                           |
| TA                | (RS)-2-amino-3-(1H-1,2,4 triazol-1-yl) propanoic acid or 3-(1H-1,2,4-Triazol-1-yl)-a,L-alanine (CAS number 86362-20-1) | ![Triazole Alanine Structure](image)                        |
| TAA               | 1H-1,2,4-Triazol-1-ylacetic acid (CAS number 28711-29-7)                                         | ![Triazole Acetic Acid Structure](image)                    |
| TLA               | (R,S)-2-Hydroxy-3-(1H-1,2,4-triazol-1-yl) propanoic acid                                        | ![Triazole Lactic Acid Structure](image)                    |

SMILES: simplified molecular-input line-entry system; CAS: Chemical Abstracts Service; MW: molecular weight.
(a): (ACD/ChemSketch, Advanced Chemistry Development, Inc., ACD/Labs Release: 12.00 Product version: 12.00 (Build 29305, 25 November 2008).