Setting of import tolerance for cyflufenamid in hops

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Abstract

In accordance with Article 6 of Regulation (EC) No 396/2005, the applicant Nisso Chemical Europe GmbH submitted a request to the competent national authority in Greece to set an import tolerance for the active substance cyflufenamid in hops. The data submitted in support of the request were found to be sufficient to derive a maximum residue level (MRL) proposal for hops; however, further risk management considerations are required to decide on the appropriate MRL values considering that the MRL in the country of origin is lower than the MRL proposal derived from the residue trials. Adequate analytical methods for enforcement are available to control the residues of cyflufenamid in the crop under consideration at the validated limit of quantification (LOQ) of 0.01 mg/kg. Based on the consumer risk assessment results, EFSA concluded that the short-term and long-term intake of residues resulting from the use of cyflufenamid according to the reported agricultural practice in the country of origin is unlikely to present a risk to consumer health. This conclusion shall be regarded as indicative considering that some MRL proposals derived by EFSA during the MRL review require further confirmatory data.

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Keywords: Cyflufenamid, hops, pesticide, MRL, consumer risk assessment

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Question number: EFSA-Q-2019-00348
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Declarations of interest: The declarations of interest of all scientific experts active in EFSA's work are available at https://ess.efsa.europa.eu/doi/doiweb/doisearch.

Acknowledgments: EFSA wishes to thank: Stathis Anagnos, Laszlo Bura and Silvia Ruocco for the support provided to this scientific output.

Suggested citation: EFSA (European Food Safety Authority), Anastassiadou M, Bellisai G, Bernasconi G, Brancato A, Carrasco Cabrera L, Ferreira L, Greco L, Jarrah S, Kazocina A, Leuschner R, Magrans JO, Miron I, Nave S, Pedersen R, Reich H, Santos M, Scarlato AP, Theobald A, Vagenende B and Verani A, 2021. Reasoned Opinion on the setting of import tolerance for cyflufenamid in hops. EFSA Journal 2021;19(3):6492, 25 pp. https://doi.org/10.2903/j.efsa.2021.6492

ISSN: 1831-4732

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The EFSA Journal is a publication of the European Food Safety Authority, a European agency funded by the European Union.
Summary

In accordance with Article 6 of Regulation (EC) No 396/2005, Nisso Chemical Europe GmbH submitted an application to the competent national authority in Greece (evaluating Member State, EMS) to set an import tolerance for the active substance cyflufenamid 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 24 May 2019. The EMS proposed to establish an maximum residue level (MRL) for hops imported from the USA at the level of 5 mg/kg. EFSA assessed the application and the evaluation report as required by Article 10 of the MRL Regulation. EFSA identified data gaps that were requested from the EMS. On 7 December 2020, the EMS submitted the requested information in a revised evaluation report which replaced the previously submitted evaluation report.

Based on the conclusions derived by EFSA in the framework of Directive 91/414/EEC, the data evaluated under previous MRL assessments and the additional data provided by the EMS in the framework of this application, the following conclusions are derived.

The metabolism of cyflufenamid following foliar application was investigated in crops belonging to the groups of fruit crops (apples, cucumbers), cereals/grass (wheat) and pulses/oilseeds (rapeseeds). As the proposed use of cyflufenamid is on a permanent and imported crop, the nature of residues in rotational crops was not assessed. Investigation of the nature of residues in processed hops is not required because the contribution of hops to the overall cyflufenamid intake is low (0.03% of the acceptable daily intake (ADI)). Nevertheless, studies on processing with cyflufenamid radiolabelled in the fluorinated phenyl ring were submitted with the present application. The results from these studies show that the active substance is stable under standard processing conditions of pasteurisation, baking, brewing, boiling and sterilisation. Hydrolysis studies with the compound radiolabelled in the cyclopropyl ring were not provided.

Based on the metabolic pattern identified in metabolism studies, the toxicological significance of metabolites and the capability of the analytical method, EFSA proposed the residue definition for plant products as 'sum of cyflufenamid (Z-isomer) and its E-isomer' for enforcement and risk assessment. A slightly different wording for the residue definition for enforcement is currently reported in the MRL legislation. However, there is not a fundamental difference between the two expressions. The residue definition is applicable to primary and rotational crops.

EFSA concluded that for the crop assessed in this application, the metabolism of cyflufenamid has been sufficiently addressed and that the previously derived residue definitions are applicable.

An adequate analytical method based on high-performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) is available to quantify residues in hops. The method enables quantification of residues of cyflufenamid at or above the validated limit of quantification (LOQ) of 0.01 mg/kg in the crop assessed.

The number of available residue trials was sufficient to derive an MRL proposal for hops on the basis of the notified use of cyflufenamid in the USA. It was noted, however, that the samples from the USA field trials were analysed for residues of the parent cyflufenamid (Z-isomer) only. To take into account the possible contribution of the E-isomer in the absence of metabolism data on leafy crops (to which hop belongs), the analytical results for the Z-isomer were adjusted by a factor derived from the metabolism data on fruit crops. The approach used is characterised by a non-standard uncertainty which may impact the MRL calculation. However, the data available from the metabolism studies and from the residue trials on several crops assessed in the framework of the MRL review, suggest that the contribution of the E-isomer to the total residues in edible crops is very low. Currently, further risk management considerations are required to decide on the appropriate MRL value considering that the MRL in the country of origin is lower than the MRL proposal derived from the residue trials.

Specific studies investigating the magnitude of cyflufenamid residues in processed hop commodities were not submitted and are not required considering the low contribution of hops to the dietary intake and that a dilution of original residues is expected in beer, the main processing product of hops. Residues of cyflufenamid in commodities of animal origin were not assessed since the crop under consideration is normally not fed to livestock.

The toxicological profile of cyflufenamid was assessed in the framework of the EU pesticides peer review under Directive 91/414/EEC and the data were sufficient to derive an ADI of 0.04 mg/kg body weight (bw) per day and an acute reference dose (ARFD) of 0.05 mg/kg bw.

The consumer risk assessment was performed with revision 3.1 of the EFSA Pesticide Residues Intake Model (PRIMo). The short-term exposure assessment was performed only with regard to the

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commodity assessed in the present MRL application, in accordance with the internationally agreed methodology. For hops, the short-term exposure accounted for 0.8% of the ARfD. The long-term exposure assessment performed in the MRL review was updated with the risk assessment value derived from the residue trials on hops submitted in support of the present MRL application. The highest estimated long-term dietary intake accounted for 6% of the ADI (NL toddler). The contribution of residues of cyflufenamid from hops to the overall long-term exposure was up to 0.03% of the ADI (UK adults). Based on the very low intakes estimated for cyflufenamid from the notified use on hops, the impact of the non-standard uncertainty from the use of an adjustment factor derived from metabolism data on fruits to the short- and long-term exposure assessment would be expected to be minimal.

EFSA concluded that the proposed use of cyflufenamid on hops will not result in a consumer exposure exceeding the toxicological reference values and, therefore, is unlikely to pose a risk to consumers’ health. However, this conclusion shall be regarded as indicative considering that some MRL proposals derived by EFSA during the MRL review require further confirmatory data.

EFSA proposes to amend the existing MRL as reported in the summary table below. Full details of all endpoints and the consumer risk assessment can be found in Appendices B-D.

| Code\(^{(a)}\) | Commodity | Existing EU MRL (mg/kg) | Proposed EU MRL (mg/kg) | Comment/justification |
|----------------|------------|------------------------|------------------------|-----------------------|
| 7000000 Hops   | 0.05\(^{*}\) | Further risk management considerations are required | The submitted data are sufficient to derive an MRL proposal for the notified USA GAP. The MRL of 6 mg/kg is calculated using an adjustment factor derived from the metabolism data on fruit crops. The USA MRL is set at 5 mg/kg. Further risk management considerations are required to decide on the appropriate MRL value considering that the MRL in the country of origin is lower than the MRL proposal derived from the residue trials. Risk for consumer unlikely. |

MRL: maximum residue level; GAP: Good Laboratory Practice.
\(^{*}\): Indicates that the MRL is set at the limit of analytical quantification (LOQ).
\(^{(a)}\): Commodity code number according to Annex I of Regulation (EC) No 396/2005.
**Table of contents**

| Section                                                                 | Page |
|------------------------------------------------------------------------|------|
| Abstract                                                               | 1    |
| Summary                                                                | 3    |
| Assessment                                                             | 6    |
| 1. Residues in plants                                                | 7    |
| 1.1. Nature of residues and methods of analysis in plants             | 7    |
| 1.1.1. Nature of residues in primary crops                            | 7    |
| 1.1.2. Nature of residues in rotational crops                         | 7    |
| 1.1.3. Nature of residues in processed commodities                    | 7    |
| 1.1.4. Methods of analysis in plants                                  | 7    |
| 1.1.5. Storage stability of residues in plants                        | 8    |
| 1.1.6. Proposed residue definitions                                   | 8    |
| 1.2. Magnitude of residues in plants                                  | 8    |
| 1.2.1. Magnitude of residues in primary crops                         | 8    |
| 1.2.2. Magnitude of residues in rotational crops                       | 9    |
| 1.2.3. Magnitude of residues in processed commodities                 | 9    |
| 1.2.4. Proposed MRLs                                                 | 9    |
| 2. Residues in livestock                                              | 9    |
| 3. Consumer risk assessment                                           | 9    |
| 4. Conclusion and Recommendations                                     | 10   |
| References                                                             | 10   |
| Abbreviations                                                         | 11   |
| Appendix A: Summary of notified GAP triggering the amendment of existing EU MRLs | 13   |
| Appendix B: List of end points                                        | 14   |
| Appendix C: Pesticide Residue Intake Model (PRIMo)                    | 20   |
| Appendix D: Input values for the exposure calculations                | 23   |
| Appendix E: Used compound codes                                       | 25   |
Assessment

The European Food Safety Authority (EFSA) received an application to set an import tolerance for the active substance cyufenamid in hops. The detailed description of the authorised use in the USA in hops, which is the basis for the current import tolerance application, is reported in Appendix A.

Cyufenamid is the ISO common name for (Z)-N-[((cyclopropylmethoxyimino)-2,3-difluoro-6-(trifluoromethyl)benzyl]-2-phenylacetamide (IUPAC). The chemical structures of the active substance and its main metabolites are reported in Appendix E.

Cyufenamid was evaluated in the framework of Directive 91/414/EEC1 with the United Kingdom designated as rapporteur Member State (RMS) for the representative uses as foliar applications on wheat, rye and barley. The draft assessment report (DAR) prepared by the RMS has been peer reviewed by EFSA (2009). Cyufenamid was approved2 for the use as a fungicide only on 1 April 2010.

The EU maximum residue levels (MRLs) for cyufenamid are established in Annex II of Regulation (EC) No 396/20053. The review of existing MRLs according to Article 12 of Regulation (EC) No 396/2005 (MRL review) has been performed (EFSA, 2018b) and the proposed modifications have been implemented in the MRL legislation.4

In accordance with Article 6 of Regulation (EC) No 396/2005, Nisso Chemical Europe GmbH submitted an application to the competent national authority in Greece (evaluating Member State, EMS) to set an import tolerance for the active substance cyufenamid 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 EFSA on 24 May 2019. The EMS proposed to establish a new MRL for cyufenamid in hops imported from USA at the level of 5 mg/kg.

EFSA assessed the application and the evaluation report as required by Article 10 of the MRL Regulation. EFSA identified data gaps and points which needed further clarification that were requested from the EMS. On 7 December 2020, the EMS submitted the requested information in a revised evaluation report which replaced the previously submitted evaluation report.

EFSA based its assessment on the evaluation report submitted by the EMS (Greece, 2019), the DAR (and its addendum) (United Kingdom, 2006, 2008) prepared under Directive 91/414/EEC, the Commission review report on cyufenamid (European Commission, 2009), the conclusion on the peer review of the pesticide risk assessment of the active substance cyufenamid (EFSA, 2009), as well as the conclusion from the previous EFSA opinions, including the opinion on the review of the existing maximum residue levels for cyufenamid according to Article 12 of Regulation (EC) No 396/2005 (EFSA, 2011, 2014, 2016, 2018b).

For this application, the data requirements established in Regulation (EU) No 544/20115 and the guidance documents applicable at the date of submission of the application to the EMS are applicable (European Commission, 1997a–q, 2000, 2010a,b, 2017; OECD, 2011). 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 546/20116.

A selected list of end points of the studies assessed by EFSA in the framework of this MRL application, including the end points of relevant studies assessed previously, is presented in Appendix B.

The evaluation report submitted by the EMS (Greece, 2019) 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.
1. Residues in plants

1.1. Nature of residues and methods of analysis in plants

1.1.1. Nature of residues in primary crops

The metabolism of cyflufenamid following foliar applications in primary crops belonging to the groups of fruit crops (apples and cucumbers), cereals/grass (wheat) and pulses/oilseeds (rapeseeds) has been investigated in the framework of the EU pesticides peer review and previous MRL applications (EFSA, 2009, 2011, 2016). These studies were re-assessed during the MRL review under Article 12 of Regulation (EC) No 396/2005 (EFSA, 2018b). Although the metabolism of cyflufenamid radiolabelled in both the phenyl ring and the cyclopropyl ring was investigated in one crop only (wheat), EFSA concluded that the metabolic pathway of cyflufenamid was sufficiently elucidated and was similar in all three crop groups. This conclusion is also applicable for the notified use in hops.

1.1.2. Nature of residues in rotational crops

As the proposed use of cyflufenamid is on a permanent crop, the nature of residues in rotational crops was not assessed. Additionally, studies on rotational crops are not required for imported crops.

1.1.3. Nature of residues in processed commodities

Based on the low contribution of hops to the overall cyflufenamid intake (0.03% of the acceptable daily intake (ADI)) (see Section 3), investigation of the nature of residues in processed hops is not required. However, studies investigating the effect of processing on the nature of cyflufenamid were submitted with the current application (Greece, 2019) and assessed by EFSA.

The studies, which were performed with cyflufenamid radiolabelled in the fluorinated phenyl ring, showed that the parent compound is hydrolytically stable under standard processing conditions of pasteurisation, baking, brewing, boiling and sterilisation: 91–92% of applied radioactivity (AR) was represented as unchanged cyflufenamid and up to the 6.9% AR was converted to the (E)-isomer. Under sterilisation conditions, the compound 149-F (1.2% AR) and an additional degradation product (1.7% AR) were observed.

It was noted that studies with the compound radiolabelled in the cyclopropyl ring or arguments for waiving the requirement were not provided. The relevance of the need to generate additional studies on the effect of processing shall be investigated in the framework of the peer review for the renewal of the approval of the active substance.

1.1.4. Methods of analysis in plants

Analytical methods for the determination of residues of cyflufenamid in plants were assessed during the EU pesticides peer review, previous MRL applications and the MRL review (EFSA, 2009, 2011, 2016, 2018b). According to the MRL review, the available methods which quantify residues at or above an limit of quantification (LOQ) of 0.01 mg/kg in high water, high acid, high oil content and dry commodities could cover both isomers measured as Z-isomer.

Hop is considered to be a complex matrix and a full validation package for enforcement purposes shall be presented for this commodity (European Commission, 2010b). A new analytical method was submitted for the enforcement of cyflufenamid in dried hop cones (Greece, 2019). The method is based on high-performance liquid chromatography with tandem mass spectrometry (HPLC–MS/MS) and quantifies residues of cyflufenamid (Z-isomer) at an LOQ of 0.01 mg/kg. It is validated at one primary transition (m/z 413–> 295) and one confirmatory transition (m/z 413–> 241) and is highly specific; therefore, a confirmatory method is not required. The method was validated for the Z-isomer only but not for the E-isomer which is also part of the residue definition for enforcement.

EFSA noted that no independent laboratory validation (ILV) was submitted for the determination of cyflufenamid residues in hops. Considering, however, that (i) two ILVs based on HPLC-MS/MS are available for different types of matrices and were validated at the same LOQ as the one in hops (0.01 mg/kg), (ii) the method used to quantify residues of cyflufenamid in hops in the context of the trials uses the same methodology, preparation technique and extraction solvent (methanol) with the newly developed method proposed for enforcement (see Section 1.2.1) and (iii) the levels of residues in the hop samples taken in the context of the trials are two orders of magnitude higher than the LOQ,
setting that possible uncertainties which might have been captured by an ILV at low levels would not affect the validity of measurement at the anticipated concentrations of cyflufenamid in hops (see Section 1.2.1), the missing ILV for cyflufenamid in hops, although desirable, can be considered a minor deficiency.

Based on the above, the method for enforcement of cyflufenamid in hops can be considered to be fully validated as enforcement method in terms of specificity, linearity, accuracy and precision based on the provisions of the SANCO/825/00 rev 8.1 guidance document (European Commission, 2010b).

Details on the analytical methods available are presented in Appendix B.1.1.1.

1.1.5. Storage stability of residues in plants

The storage stability of cyflufenamid (Z-isomer) and its (E)-isomer in plants stored under frozen conditions was investigated in the framework of the EU pesticides peer review and in a previous MRL application (EFSA, 2009, 2014).

EFSA noted that for storage stability purposes, hops are classified as high oil content matrices. In high oil content matrices (oilseed rape), cyflufenamid (Z-isomer) and the E-isomer residues were stable for at least 18 months when stored at −18°C. For the E-isomer, recoveries below 70% were observed at 3 (63% recovery) and 18 months of storage (67%). Although it remains unclear whether these low recoveries are related to isomerisation to the Z-isomer, the EFSA MRL review concluded that this would not be expected to impact the assessment as no degradation was observed for the sum of isomers (EFSA, 2018b).

1.1.6. Proposed residue definitions

Based on the metabolic pattern identified in metabolism studies, the toxicological significance of metabolites, the capabilities of enforcement analytical methods, the residue definition for enforcement and risk assessment proposed for cereals in the EU pesticides peer review as ‘sum of cyflufenamid (Z-isomer) and its E-isomer’ was extended to all plants in the MRL review (EFSA, 2018b).

A slightly different wording for the residue definition for enforcement is currently reported in the MRL legislation: ‘sum of cyflufenamid (Z-isomer) and its E-isomer, expressed as cyflufenamid’. However, there is not a fundamental difference between the two expressions. The residue definitions are also applicable to rotational crops.

EFSA concluded that these residue definitions are appropriate for the crop under assessment.

1.2. Magnitude of residues in plants

1.2.1. Magnitude of residues in primary crops

In support of the authorised use on hops in the USA, the applicant submitted four residue trials on hops, which were performed in the USA over the growing season of 2015. All trials were independent and compliant with the authorised GAP. None of the trials was designed as decline trial and the possibility that residues might be higher at a longer PHI cannot be excluded. As the trials were performed within the same growing season and were limited in the north-western part of the country, they may not be representative for hops growing in different seasons and in other parts of the USA.

Samples were analysed for the parent compound only (Z-isomer) and not for the E-isomer which is also part of the residue definition for enforcement and risk assessment. To take into account the possible contribution of the E-isomer, the EMS proposed to multiply the analytical results for the Z-isomer by a factor of 1.0387 derived from the metabolism study in a high oil content commodity (oilseed rape) (Greece, 2019). This study was assessed by EFSA in a previous opinion (EFSA, 2016).

Considering, however, that hops belong to the group of leafy crops and that no metabolism study matching the notified PHI in a leafy crop is available, EFSA is of the opinion that the results from the metabolism studies on fruit crops assessed in a previous opinion (EFSA, 2011) are closer to the notified use on hops. This because in the studies in fruit crops the leaves of the plants were also analysed, additionally, the study parameters in oilseeds (5 × 60 g/ha, last application at BBCH 69 before the consumable part of the crop is formed with seeds harvested 52 days after) were very

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7 The EMS calculated a mean factor of 1.038 taking into consideration the peak areas of the HPLC chromatograms generated from the oilseed rape sample extracts (forage/plant and seed). The derived mean factor of 1.067 was then further corrected by subtracting a factor of 0.029 obtained from the chromatograms of the analysis of the radiochemical purity for the E-isomer amounts present in the test item before and after applications to rapeseed (Greece, 2019).
different from the notified GAP on hops (2 × 60 g/ha, BBCH 87, PHI 6 days). Based on the calculation proposed by EFSA a slightly lower adjustment factor of 1.025 was derived for the E-isomer. The adjustment factor represents the average of the individual factors obtained in the leaves and the fruits of each crop (see Table B.1.2.1 for details).

The use of an adjustment factor from metabolism studies in fruit instead of leafy crops is characterised by a non-standard uncertainty which may impact the estimation of the risk assessment values and the MRL calculation. However, the data available from the metabolism studies and from the residue trials on several crops assessed in that framework of the MRL review suggest that the contribution of the E-isomer to the total residues is very low (EFSA, 2018b). Nonetheless, in future applications to set MRLs on leafy crops or any other crop, samples shall be analysed according to the residue definition set in the EU.

Samples were stored under conditions ensuring stability of residues under storage. The method used in the analysis of samples in the context of the residue trials is based on HPLC–MS/MS and was found to be sufficiently validated to support the determination of residues of cyflufenamid (Z-isomer) in the crop under assessment at an LOQ of 0.01 mg/kg.

The number of submitted trials is sufficient to derive an MRL proposal. Applying the adjustment factor, an MRL of 6 mg/kg is derived for cyflufenamid in hops.

1.2.2. Magnitude of residues in rotational crops

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

1.2.3. Magnitude of residues in processed commodities

Specific studies investigating the magnitude of cyflufenamid residues in processed commodities were not submitted and are not required considering the low contribution of hops to the dietary intake and that a dilution of original residues is expected in beer, the main processing product of hops.

1.2.4. Proposed MRLs

The available data are considered sufficient to derive an MRL proposal as well as risk assessment values for cyflufenamid in hops (see Appendix B). The tolerance of cyflufenamid in the USA8 is set at 5 mg/kg for hops since the residue definition for enforcement is cyflufenamid (Z-isomer) only. A higher MRL of 6 mg/kg is obtained based on theoretical calculations on the possible contribution of the E-isomer (see Section 1.2.1). Therefore, additional risk management considerations are required to decide on the most appropriate value also considering that the MRL in the country of origin is lower. In Section 3, EFSA assessed whether residues on this crop resulting from the uses authorised in the USA are likely to pose a consumer health risk.

2. Residues in livestock

Not relevant as hops are not used for feed purposes.

3. Consumer risk assessment

EFSA performed a dietary risk assessment using revision 3.1 of the EFSA PRIMo (EFSA, 2018a, 2019). This exposure assessment model contains food consumption data for different sub-groups 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 cyflufenamid used in the risk assessment (i.e. ADI and acute reference dose (ARfD) values) were derived in the framework of the EU pesticides peer review (European Commission, 2009). The E-isomer, as included in the risk assessment residue definition in plants is considered to be of similar toxicity as the parent.

Short-term (acute) dietary risk assessment

The short-term exposure assessment was performed for the commodity assessed in this application in accordance with the internationally agreed methodology. The calculations were based on the HR derived from supervised field trials which was multiplied by an adjustment factor to take into account the contribution of the E-isomer. The input value can be found in Appendix D.1.

8 https://www.govinfo.gov/content/pkg/FR-2018-02-09/pdf/2018-02670.pdf
The short-term exposure to cyflufenamid from hops accounts for 0.8% of the ARfD (see Appendix B.3).

**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 (EFSA, 2018b). EFSA updated the calculation with the relevant STMR value derived from the residue trials submitted in support of this MRL application for hops. In hops, an adjustment factor derived from the metabolism data on fruit crops was used to take into consideration possible contribution of the E-isomer. The input values used in the exposure calculations are summarised in Appendix D.1.

The estimated long-term dietary intake was up to 6% of the ADI (NL toddlers). The contribution of residues expected in hops to the overall long-term exposure is 0.03% of the ADI (UK adults). Considering the very low intake estimated for cyflufenamid from hops, the impact of the non-standard uncertainty from the use of an adjustment factor for the E-isomer would be expected to be minimal.

EFSA concluded that the long-term exposure to residues of cyflufenamid resulting from the existing and the notified uses is unlikely to present a risk to consumer health. This conclusion, however, shall be regarded as indicative considering that some MRL proposals derived by EFSA during the MRL review require further confirmatory data.

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

4. **Conclusion and Recommendations**

The data submitted in support of this MRL application were found to be sufficient to derive an MRL proposal for hops imported from the USA. However, further risk management considerations are required to decide on the most appropriate value because a higher MRL of 6 mg/kg is obtained from theoretical calculations on the possible contribution of the E-isomer and the MRL in the country of origin is set at 5 mg/kg for cyflufenamid.

EFSA concluded that the notified use of cyflufenamid on hops will not result in a consumer exposure exceeding the toxicological reference values and, therefore, is unlikely to pose a risk to consumers’ health. This conclusion, however, shall be regarded as indicative considering that some MRL proposals derived by EFSA during the MRL review require further confirmatory data.

The MRL recommendations are summarised in Appendix B.4.

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9 Dietary data from the UK were included in PRIMo when the UK was a member of the European Union.
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Abbreviations

a.s. active substance
ADIR acceptable daily intake
AR applied radioactivity
ARfD acute reference dose
BBCH growth stages of mono- and dicotyledonous plants
bw body weight
CF conversion factor for enforcement to risk assessment residue definition
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
GC gas chromatography
GC–MS gas chromatography with mass spectrometry
Setting of an import tolerance for cyflufenamid in hops

HPLC–MS/MS  high performance liquid chromatography with tandem mass spectrometry
HR           highest residue
IEDI         international estimated daily intake
IESTI        international estimated short-term intake
ILV          independent laboratory validation
InChIKey     International Chemical Identifier Key
ISO          International Organisation for Standardisation
IUPAC        International Union of Pure and Applied Chemistry
LC-MS/MS     liquid chromatography with tandem mass spectrometry
LOQ          limit of quantification
MRL          maximum residue level
MS            Member States
NEU          northern Europe
OECD         Organisation for Economic Co-operation and Development
PBI          plant-back interval
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
RAC          raw agricultural commodity
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
WHO          World Health Organization
### Appendix A – Summary of notified GAP triggering the amendment of existing EU MRLs

| Crop and/or situation | NEU, SEU, MS or country | F G or I<sup>(a)</sup> | Pests or group of pests controlled | Preparation | Application | Application rate per treatment | Remarks |
|-----------------------|-------------------------|----------------------|-----------------------------------|-------------|-----------------|-----------------------------|---------|
| 700000 HOPS (dried)   | USA                     | F                    | Powdery mildew                    | SC 100 g/L  | Foliar treatment – broadcast spraying | 2-14  | 60 g a.s./ha | 6 |

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

| Primary crops (available studies) | Crop groups | Crop(s) | Application(s) | Sampling (DAT) | Comment/Source |
|-----------------------------------|-------------|---------|----------------|----------------|----------------|
| Fruit crops                       |            |         |                |                |                |
| Cucumbers                         | Not specified: 1 x 50 g a.s./ha | 0-31 (fruit, leaf) |
| Cucumbers                         | Not specified: 1 x 200 g a.s./ha | 7-35 (fruit, leaf) |
| Cereals/grass                     | Wheat      | Foliar: 2 x 25 or 100 g a.s./ha; BBCH 32/59 (Study C) | 0 (forage and root) At maturity (straw, husk, grain) | Fluorinated phenyl-U-14C labelled cyflufenamid (EFSA, 2009). |
| Cereals/grass                     | Wheat      | Foliar: 2 x 25 g a.s./ha; BBCH 32/59 (Study A) | 0 (forage and root) At maturity (straw, husk, grain) | Fluorinated phenyl-U-14C labelled cyflufenamid (EFSA, 2009). |
| Cereals/grass                     | Wheat      | Foliar: 2 x 25 g a.s./ha; BBCH 32/39 (Study B) | 0 (forage and root) At maturity (straw, husk, grain) | Fluorinated phenyl-U-14C labelled cyflufenamid (EFSA, 2009). |
| Pulses/oilseeds                   | Rapeseeds  | Foliar: 1 x 12.5 g a.s./ha; BBCH 14 or 69 | 14 (whole plant) At maturity (seed) | Fluorinated phenyl-U-14C labelled cyflufenamid (EFSA, 2016). |
| Pulses/oilseeds                   | Rapeseeds  | Foliar: 5 x 12.5 g a.s./ha; BBCH 69 | 14 (whole plant) At maturity (seed) | Fluorinated phenyl-U-14C labelled cyflufenamid (EFSA, 2016). |

| Rotational crops (available studies) | Crop groups | Crop(s) | Application(s) | PBI (DAT) | Comment/Source |
|--------------------------------------|-------------|---------|----------------|-----------|----------------|
| Root/tuber crops                     | Carrot      | Bare soil application: 1 x 50 g a.s./ha | 30, 120 | Fluorinated phenyl-U-14C labelled cyflufenamid (EFSA, 2009). |
| Leafy crops                          | Lettuces    | Bare soil application: 1 x 50 g a.s./ha | 30 | Fluorinated phenyl-U-14C labelled cyflufenamid (EFSA, 2009). |
| Cereal (small grain)                 | Wheat       | Bare soil application: 1 x 50 g a.s./ha | 30, 120, 270 |                   |

| Processed commodities (hydrolysis study) | Conditions | Stable? | Comment/Source |
|------------------------------------------|------------|---------|----------------|
|                                        | Pasteurisation (20 min, 90°C, pH 4) | Yes | Fluorinated phenyl-U-14C labelled a.s. cyflufenamid (92.4% AR); (E)-isomer (6.7% AR) (Greece, 2019) |
Baking, brewing and boiling (60 min, 100°C, pH 5) & Yes & Fluorinated phenyl-U-14C labelled a.s. cyflufenamid (91.1% AR); (E)-isomer (5.8% AR) (Greece, 2019) \\
Sterilisation (20 min, 120°C, pH 6) & Yes & Fluorinated phenyl-U-14C labelled a.s. cyflufenamid (91% AR); (E)-isomer (5.7% AR), 149-F (1.2% AR), others/unknown (4.9% AR) (Greece, 2019) \\
Other processing conditions & – & –

| Can a general residue definition be proposed for primary crops? | Yes | EFSA, 2018b |
| Rotational crop and primary crop metabolism similar? | Yes | EFSA, 2018b |
| Residue pattern in processed commodities similar to residue pattern in raw commodities? | Not triggered | Hydrolysis study with fluorinated phenyl-radiolabelled cyflufenamid available (Greece, 2019) |
| Plant residue definition for monitoring (RD-Mo) | Regulation (EC) No 396/2005: Cyflufenamid (sum of cyflufenamid (Z-isomer) and its E-isomer, expressed as cyflufenamid) EFSA, 2018b: Sum of cyflufenamid (Z-isomer) and its E-isomer |
| Plant residue definition for risk assessment (RD-RA) | Sum of cyflufenamid (Z-isomer) and its E-isomer |
| Methods of analysis for monitoring of residues (analytical technique, matrix groups, LOQs) | High water and high acid content commodities (EFSA, 2011):  
  • GC-MS  
  LOQ = 0.01 mg/kg for the sum of isomers: cyflufenamid (Z-isomer) and its E-isomer.  
  Confirmation by monitoring 2 additional fragment ions.  
  ILV available (GC-MS)  
  • QuEChERS (LC-MS/MS), LOQ = 0.01 mg/kg for cyflufenamid (Z-isomer) (EFSA, 2018b). |
| | High oil content commodities:  
  • QuOil (LC-MS-QToF), LOQ = 0.01 mg/kg for cyflufenamid (Z-isomer) (EFSA, 2018b). |
| | Dry commodities (EFSA, 2009):  
  • GC-MS  
  LOQ = 0.01 mg/kg for the sum of isomers: cyflufenamid (Z-isomer) and its E-isomer.  
  Confirmation by monitoring 2 additional fragment ions.  
  ILV available (GC-MS)  
  • QuEChERS (LC-MS/MS) LOQ = 0.01 mg/kg for cyflufenamid (Z-isomer) (EFSA, 2018b). |
| | Hops (Greece, 2019):  
  • HPLC-MS/MS  
  LOQ = 0.01 mg/kg for cyflufenamid (Z-isomer)  
  Confirmation by monitoring 1 additional fragment ion.  
  ILV not available and not strictly necessary since ILV available in high water, high acid, high oil content and dry matrices. |

a.i.: active ingredient; DAT: days after treatment; PBI: plant-back interval; HPLC–MS/MS: high-performance liquid chromatography with tandem mass spectrometry; LC–MS/MS: liquid chromatography with tandem mass spectrometry; LC-MS-QToF: liquid chromatography quadrupole time-of-flight mass spectrometry; QuEChERS: Quick, Easy, Cheap, Effective, Rugged, and Safe (analytical method); QuOil: variation of QuEChERS method for vegetable oil samples; LOQ: limit of quantification; ILV: independent laboratory validation.
## B.1.1.2. Stability of residues in plants

| Plant products (available studies) | Category | Commodity               | T (°C) | Stability period Value | Unit | Compounds covered | Comment/Source |
|-----------------------------------|----------|-------------------------|--------|------------------------|------|-------------------|----------------|
| High water content                | Immature barley shoots | –18 | 25 Months              |       | Sum of cyflufenamid (Z-isomer) and its E-isomer | EFSA (2009) |
| High oil content                  | Oilseed rape          | –18 | 18 Months              |       | Sum of cyflufenamid (Z-isomer) and its E-isomer | Residues were analysed for each isomer separately (EFSA, 2014). |
| High protein content              | Dry beans             | –18 | 24 Months              |       | Sum of cyflufenamid (Z-isomer) and its E-isomer | Residues were analysed for each isomer separately (EFSA, 2014). |
| High starch content               | Wheat grain           | –18 | 24 Months              |       | Sum of cyflufenamid (Z-isomer) and its E-isomer | Residues were analysed for each isomer separately (EFSA, 2014). |
| High acid content                 | Grape                | –18 | 24 Months              |       | Sum of cyflufenamid (Z-isomer) and its E-isomer | Residues were analysed for each isomer separately (EFSA, 2014). |
### B.1.2. Magnitude of residues in plants

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

| Commodity          | Region/Indoor<sup>(a)</sup> | Residue levels observed in the supervised residue trials (mg/kg) | Comments/Source                                                                 | Calculated MRL (mg/kg) | HR<sup>(b)</sup> (mg/kg) | STMR<sup>(c)</sup> (mg/kg) | CF<sup>(d)</sup> |
|--------------------|------------------------------|-----------------------------------------------------------------|---------------------------------------------------------------------------------|------------------------|--------------------------|---------------------------|-----------------|
| Hops, dried cones | USA                          | Z-isomer: 0.82, 1.60, 2.08, 2.24                                | Sum Z-isomer and E-isomer: 0.84, 1.64, 2.13, 2.30                              | 5                      | 2.20                     | 1.84                      | –               |
|                    |                              |                                                                  | Residue trials on hops conducted at harvest over a single season and compliant with USA GAP. Samples analysed for cyflufenamid (Z-isomer) only. Individual residue levels where recalculated to consider potential contribution of the E-isomer (included in the residue definition) using a factor of 1.025<sup>(e)</sup> |                        |                          |                           |                 |

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

<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. The highest residue for risk assessment refers to the whole commodity and not to the edible portion.

<sup>(c)</sup>: Supervised trials median residue. The median residue for risk assessment refers to the whole commodity and not to the edible portion.

<sup>(d)</sup>: Conversion factor to recalculate residues according to the residue definition for monitoring to the residue definition for risk assessment.

<sup>(e)</sup>: The adjustment factor represents the average of the individual factors derived from the metabolism studies with cyflufenamid in fruit crops (apple leaves and fruits; cucumber leaves and fruits) applying the formula $(Z\text{-isomer } \% \text{ TRR} + E\text{-isomer } \% \text{ TRR})/Z\text{-isomer } \% \text{ TRR})$. 

www.efsa.europa.eu/efsajournal 17 EFSA Journal 2021;19(3):6492
B.1.2.2. Residues in rotational crops

| Residues in rotational and succeeding crops expected based on confined rotational crop study? | Not triggered | Hops do not grow in rotation |
| Residues in rotational and succeeding crops expected based on field rotational crop study? | Not triggered | See above |

B.1.2.3. Processing factors

No processing studies were submitted in the framework of the present MRL application.

B.2. Residues in livestock

Not relevant

B.3. Consumer risk assessment

ARfD

0.05 mg/kg bw (European Commission, 2009)

Highest IESTI, according to EFSA PRIMo

Hops: 0.8% of ARfD

Assumptions made for the calculations

The calculation is performed using PRIMo version 3.1. The short-term exposure assessment focused on the commodity under assessment using the highest residue level expected as found in the available residue trials and multiplied by a factor of 1.025 derived from the metabolism data on fruit crops to take into consideration possible contribution of E-isomer.

ADI

0.04 mg/kg bw per day (European Commission, 2009)

Highest IEDI, according to EFSA PRIMo

6% ADI (NL toddler)

Contribution of crops assessed:

Hops: 0.03% of ADI (UK adults)\(^9\)

Assumptions made for the calculations

The calculation is performed using PRIMo version 3.1. The calculation is based on the median residue (STMR) level derived for the crop under consideration from the submitted residue trials and the STMR values reported in the MRL review (EFSA, 2018b). The residues on hops were multiplied by a factor of 1.025 derived from the metabolism data on fruit crops to take into consideration possible contribution of E-isomer. The contributions of commodities where no GAP was reported in the framework of the MRL review were not included in the calculation. The consumer risk assessment is indicative considering that some MRL proposals derived by EFSA during the MRL review require further confirmatory data.

ARfD: acute reference dose; bw: body weight; IESTI: international estimated short-term intake; PRIMo: (EFSA) Pesticide Residues Intake Model; ADI: acceptable daily intake; IEDI: international estimated daily intake; STMR: supervised trials median residue; GAP: Good Agricultural Practice; MRL: maximum residue level.

10 Dietary data from the UK were included in PRIMo when UK was a member of the European Union.
### B.4. Recommended MRLs

| Code(a) | Commodity | Existing EU MRL (mg/kg) | Proposed EU MRL (mg/kg) | Comment/justification |
|---------|-----------|-------------------------|-------------------------|-----------------------|
| 7000000 | Hops      | 0.05*                   |                         | Further risk management considerations are required |

**Enforcement residue definition:** Cyflufenamid (sum of cyflufenamid (Z-isomer) and its E-isomer, expressed as cyflufenamid)

The submitted data are sufficient to derive an MRL proposal for the notified USA GAP. The MRL of 6 mg/kg is calculated using an adjustment factor derived from the metabolism data on fruit crops to take into consideration possible contribution of the E-isomer. The USA MRL is set at 5 mg/kg. Further risk management considerations are required to decide on the appropriate MRL value considering that the MRL in the country of origin is lower than the MRL proposal derived from the residue trials. Risk for consumer unlikely.

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

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

(a): Commodity code number according to Annex I of Regulation (EC) No 396/2005.
### Appendix C – Pesticide Residue Intake Model (PRIMo)

#### Cyflufenamid

| Input values | Toxicological reference values |
|--------------|-------------------------------|
| Details – chronic risk assessment | EC (group 2A) |
| Details – acute risk assessment | 2009 Year of evaluation |
| Details – acute risk assessment/children | 2009 Year of evaluation |

#### Toxicological reference values

- **ADI** (mg/kg bw per day): 0.01
- **ARfD** (mg/kg bw): 0.05

#### Source of ADI

- EC (group 2A)

#### Year of evaluation

- EFSA PRIMo revision 3.1; 2019/03/19

#### Comments

- Refined calculation mode
- Chronic risk assessment: JMPR methodology (IEDI/TMDI)
- No of diets exceeding the ADI: –––
- Exposure resulting from commodities not MRLs set at under assessment
- Expsoure (in % of ADI)
- Highest contributor to exposure
- 2nd contributor to exposure
- 3rd contributor to exposure

#### Calculated exposure (in % of ADI)

| Commodity/group of commodities | MS Diet 6% 2.35 4% 0.4% 0.2% Wheat 0.2% 6% NL toddler 3% 1.36 3% 0.1% 0.1% Bovine: Muscle/meat 0.1% 3% DE adult 3% 1.06 2% 0.2% 0.2% Apples 0.1% 3% NL child 2% 0.98 2% 0.2% 0.1% Bovine: Muscle/meat 0.1% 2% FR toddler 2 3 yr 3% 1.08 1% 0.5% 0.2% Wheat 0.1% 3% DE child 3% 1.06 2% 0.2% 0.2% Apples 0.1% 3% FR child 3 15 yr 2% 0.84 2% 0.2% 0.1% Bovine: Muscle/meat 0.1% 2% UK toddler 3% 1.08 1% 0.5% 0.2% Wheat 0.1% 3% FR infant 1% 0.59 1% 0.1% 0.0% Wheat 0.0% 1% DE general 3% 1.06 2% 0.2% 0.2% Apples 0.1% 3% NL general 2% 0.98 2% 0.2% 0.1% Bovine: Muscle/meat 0.1% 2% FR adult 1% 0.59 0.9% 0.3% 0.2% Wheat 0.1% 3% DE adult 1% 0.59 0.9% 0.3% 0.2% Wheat 0.1% 3% NL adult 1% 0.59 0.9% 0.3% 0.2% Wheat 0.1% 3% IE adult 1% 0.59 0.9% 0.3% 0.2% Wheat 0.1% 3% IE child 1% 0.59 0.9% 0.3% 0.2% Wheat 0.1% 3% ES child 1% 0.59 0.9% 0.3% 0.2% Wheat 0.1% 3% UK adult 1% 0.59 0.9% 0.3% 0.2% Wheat 0.1% 3% FI child 1% 0.59 0.9% 0.3% 0.2% Wheat 0.1% 3% FI adult 1% 0.59 0.9% 0.3% 0.2% Wheat 0.1% 3% PT general 0.5% 0.23 0.2% Wheat 0.2% 3% UK toddler 0.5% 0.23 0.2% Wheat 0.2% 3% IT toddler 0.5% 0.23 0.2% Wheat 0.2% 3% IT adult 0.5% 0.23 0.2% Wheat 0.2% 3% IE child 0.4% 0.15 0.3% Wheat 0.1% 3% IE adult 0.4% 0.15 0.3% Wheat 0.1% 3%

#### Exposure resulting from commodities

| Commodity/group of commodities | MS Diet 6% 2.35 4% 0.4% 0.2% Wheat 0.2% 6% NL toddler 3% 1.36 3% 0.1% 0.1% Bovine: Muscle/meat 0.1% 3% DE adult 3% 1.06 2% 0.2% 0.2% Apples 0.1% 3% NL child 2% 0.98 2% 0.2% 0.1% Bovine: Muscle/meat 0.1% 2% FR toddler 2 3 yr 3% 1.08 1% 0.5% 0.2% Wheat 0.1% 3% DE child 3% 1.06 2% 0.2% 0.2% Apples 0.1% 3% FR child 3 15 yr 2% 0.84 2% 0.2% 0.1% Bovine: Muscle/meat 0.1% 2% UK toddler 3% 1.08 1% 0.5% 0.2% Wheat 0.1% 3% FR infant 1% 0.59 0.9% 0.3% 0.2% Wheat 0.1% 3% DE general 3% 1.06 2% 0.2% 0.2% Apples 0.1% 3% NL general 2% 0.98 2% 0.2% 0.1% Bovine: Muscle/meat 0.1% 2% FR adult 1% 0.59 0.9% 0.3% 0.2% Wheat 0.1% 3% DE adult 1% 0.59 0.9% 0.3% 0.2% Wheat 0.1% 3% NL adult 1% 0.59 0.9% 0.3% 0.2% Wheat 0.1% 3% IE adult 1% 0.59 0.9% 0.3% 0.2% Wheat 0.1% 3% IE child 1% 0.59 0.9% 0.3% 0.2% Wheat 0.1% 3% ES child 1% 0.59 0.9% 0.3% 0.2% Wheat 0.1% 3% UK adult 1% 0.59 0.9% 0.3% 0.2% Wheat 0.1% 3% FI child 1% 0.59 0.9% 0.3% 0.2% Wheat 0.1% 3% FI adult 1% 0.59 0.9% 0.3% 0.2% Wheat 0.1% 3% PT general 0.5% 0.23 0.2% Wheat 0.2% 3% UK toddler 0.5% 0.23 0.2% Wheat 0.2% 3% IT toddler 0.5% 0.23 0.2% Wheat 0.2% 3% IT adult 0.5% 0.23 0.2% Wheat 0.2% 3% IE child 0.4% 0.15 0.3% Wheat 0.1% 3% IE adult 0.4% 0.15 0.3% Wheat 0.1% 3%

#### Conclusion

The estimated long-term dietary intake (TMDI/NEDI/IEDI) was below the ADI. The long-term intake of residues of Cyflufenamid is unlikely to present a public health concern.
The acute risk assessment is based on the ARfD. The calculation is based on the large portion of the most critical consumer group.

| Commodity          | ARfD/ADI (mg/kg) | Exposure (µg/kg bw) | Highest % of ARfD/ADI | Commodity          | ARfD/ADI (mg/kg) | Exposure (µg/kg bw) | Highest % of ARfD/ADI |
|--------------------|------------------|---------------------|-----------------------|--------------------|------------------|---------------------|-----------------------|
| Table grapes       | 0.2/0.12         | 8.8                 | 8%                    | Table grapes       | 0.2/0.12         | 4.1                 | 3%                    |
| Pears              | 0.06/0.04        | 4.8                 | 6%                    | Wine grapes        | 0.2/0.12         | 2.8                 | 3%                    |
| Apples             | 0.06/0.04        | 3.8                 | 2%                    | Watermelons        | 0.05/0.03        | 1.2                 | 2%                    |
| Pears              | 0.2/0.12         | 8.8                 | 8%                    | Table grapes       | 0.2/0.12         | 4.1                 | 3%                    |
| Watermelons        | 0.05/0.03        | 3.7                 | 2%                    | Cucumbers          | 0.05/0.04        | 1.1                 | 3%                    |
| Pears              | 0.2/0.12         | 8.8                 | 8%                    | Table grapes       | 0.2/0.12         | 4.1                 | 3%                    |
| Watermelons        | 0.05/0.03        | 3.7                 | 2%                    | Cucumbers          | 0.05/0.04        | 1.1                 | 3%                    |
| Pears              | 0.2/0.12         | 8.8                 | 8%                    | Table grapes       | 0.2/0.12         | 4.1                 | 3%                    |
| Watermelons        | 0.05/0.03        | 3.7                 | 2%                    | Cucumbers          | 0.05/0.04        | 1.1                 | 3%                    |

Results for children
No. of commodities for which ARfD/ADI is exceeded (IESTI):

| Commodity          | ARfD/ADI (mg/kg) | Exposure (µg/kg bw) | Highest % of ARfD/ADI |
|--------------------|------------------|---------------------|-----------------------|
| Table grapes       | 0.2/0.12         | 8.8                 | 8%                    |
| Pears              | 0.06/0.04        | 4.8                 | 6%                    |
| Apples             | 0.06/0.04        | 3.8                 | 2%                    |
| Pears              | 0.2/0.12         | 8.8                 | 8%                    |
| Watermelons        | 0.05/0.03        | 3.7                 | 2%                    |
| Pears              | 0.2/0.12         | 8.8                 | 8%                    |
| Watermelons        | 0.05/0.03        | 3.7                 | 2%                    |
| Pears              | 0.2/0.12         | 8.8                 | 8%                    |
| Watermelons        | 0.05/0.03        | 3.7                 | 2%                    |

Results for adults
No. of commodities for which ARfD/ADI is exceeded (IESTI):

| Commodity          | ARfD/ADI (mg/kg) | Exposure (µg/kg bw) | Highest % of ARfD/ADI |
|--------------------|------------------|---------------------|-----------------------|
| Table grapes       | 0.2/0.12         | 8.8                 | 8%                    |
| Pears              | 0.06/0.04        | 4.8                 | 6%                    |
| Apples             | 0.06/0.04        | 3.8                 | 2%                    |
| Pears              | 0.2/0.12         | 8.8                 | 8%                    |
| Watermelons        | 0.05/0.03        | 3.7                 | 2%                    |
| Pears              | 0.2/0.12         | 8.8                 | 8%                    |
| Watermelons        | 0.05/0.03        | 3.7                 | 2%                    |
| Pears              | 0.2/0.12         | 8.8                 | 8%                    |
| Watermelons        | 0.05/0.03        | 3.7                 | 2%                    |

Details – acute risk assessment/children
Details – acute risk assessment/adults
### Setting of an import tolerance for cyflufenamid in hops

#### Results for children

| Processed commodities | MRL/ADI (mg/kg) | Exposure (µg/kg bw) |
|-----------------------|-----------------|---------------------|
| Pumpkins/boiled       | 0.05/0.03       | 2.7                 |
| Courgettes/boiled     | 0.05/0.04       | 1.4                 |
| Wine grapes/juice      | 0.2/0.03        | 1.2                 |
| Gherkins/pickled      | 0.05/0.04       | 0.92                |
| Apples/juice          | 0.06/0.02       | 0.84                |
| Peaches/canned        | 0.06/0.03       | 0.78                |
| Pears/juice           | 0.06/0.02       | 0.51                |
| Tomatoes/juice        | 0.04/0.02       | 0.38                |
| Peaches/juice         | 0.06/0.02       | 0.33                |
| Wheat/milling (flour) | 0.04/0.02       | 0.24                |
| Maize/oil             | 0.01/0.02       | 0.23                |
| Tomatoes/sauce/puree  | 0.04/0.02       | 0.19                |
| Plums/juice           | 0.07/0.02       | 0.19                |
| Wheat/milling (wholemeal) | 0.04/0.02 | 0.11               |
| Buckwheat/bulgur and grits | 0.15/0.02 | 0.11               |

#### Results for adults

| Processed commodities | MRL/ADI (mg/kg) | Exposure (µg/kg bw) |
|-----------------------|-----------------|---------------------|
| Pumpkins/boiled       | 0.05/0.03       | 1.7                 |
| Wine grapes/wine      | 0.2/0.03        | 1.1                 |
| Courgettes/boiled     | 0.05/0.04       | 0.91                |
| Table grapes/raisins  | 0.2/0.03        | 0.69                |
| Wine grapes/juice     | 0.2/0.03        | 0.56                |
| Apples/juice          | 0.06/0.02       | 0.52                |
| Peaches/canned        | 0.06/0.02       | 0.27                |
| Peaches/canned        | 0.06/0.03       | 0.25                |
| Tomatoes/sauce/puree  | 0.04/0.02       | 0.16                |
| Maize/oil             | 0.00/0.03       | 0.14                |
| Barley/beer           | 0.1/0.01        | 0.14                |
| Wheat/bread/pizza     | 0.04/0.02       | 0.09                |
| Wheat/pasta           | 0.04/0.02       | 0.08                |
| Wheat/bread (wholemeal) | 0.04/0.02    | 0.07                |
| Rice/milling (polishing) | 0.01/0.01 | 0.04                |

#### Conclusion

No exceedance of the toxicological reference value was identified for any unprocessed commodity. A short term intake of residues of Cyflufenamid is unlikely to present a public health risk. For processed commodities, no exceedance of the ARfD/ADI was identified.
## Appendix D – Input values for the exposure calculations

### D.1. Consumer risk assessment

| Commodity                             | Chronic risk assessment | Acute risk assessment |
|---------------------------------------|-------------------------|-----------------------|
|                                       | Input value (mg/kg)     | Comment               | Input value (mg/kg) | Comment               |
| **Risk assessment residue definition for plant commodities:** sum of cyflufenamid (Z-isomer) and its E-isomer |                         |                       |                       |                       |
| Hops                                  | 1.89                    | STMR\(^{(a)}\)        | 2.30\(^{(a)}\)      | HR                    |
| Pome fruits                           | 0.02                    | STMR (EFSA, 2018b)    |                       |                       |
| Apricots and peaches                  | 0.02                    | STMR (EFSA, 2018b)    |                       |                       |
| Cherries (sweet)                      | 0.04                    | STMR (EFSA, 2018b)    |                       |                       |
| Plums                                 | 0.02                    | STMR (EFSA, 2018b)    |                       |                       |
| Table and wine grapes                 | 0.03                    | STMR (EFSA, 2018b)    |                       |                       |
| Strawberries                          | 0.02                    | STMR (EFSA, 2018b)    |                       |                       |
| Tomatoes                              | 0.02                    | STMR (EFSA, 2018b)    |                       |                       |
| Sweet peppers/bell peppers           | 0.02                    | STMR (EFSA, 2018b)    |                       |                       |
| Aubergines/eggplants                  | 0.02                    | STMR (EFSA, 2018b)    |                       |                       |
| Cucumbers, gherkins and courgettes   | 0.02                    | STMR (EFSA, 2018b)    |                       |                       |
| Melons and pumpkins                   | 0.02                    | STMR (EFSA, 2018b)    |                       |                       |
| Watermelons                           | 0.02                    | STMR (EFSA, 2018b)    |                       |                       |
| Globe artichokes                      | 0.02                    | STMR (EFSA, 2018b)    |                       |                       |
| Barley, buckwheat, oat grains         | 0.02                    | STMR (EFSA, 2018b)    |                       |                       |
| Maize/corn grains                     | 0.01                    | EU MRL (LOQ)          |                       |                       |
| Common millet/proso millet grains     | 0.01                    | EU MRL(LOQ)           |                       |                       |
| Rice grains                           | 0.01                    | EU MRL (LOQ)          |                       |                       |
| Sorghum grains                        | 0.01                    | EU MRL (LOQ)          |                       |                       |
| Wheat and rye grains                  | 0.02                    | STMR (EFSA, 2018b)    |                       |                       |
| **Risk assessment residue definition for animal commodities:** sum of cyflufenamid (Z-isomer), its E-isomer and metabolite 149-F1, expressed as cyflufenamid |                         |                       |                       |                       |
| Bovine and equine meat                | 0.03                    | 0.8 × STMR muscle + 0.2 × STMR fat\(^{(b)}\) (EFSA, 2018b) |                       |                       |
| Bovine and equine fat                 | 0.03                    | STMR (EFSA, 2018b)    |                       |                       |
| Bovine and equine liver               | 0.03                    | STMR (EFSA, 2018b)    |                       |                       |
| Bovine and equine kidney              | 0.03                    | STMR (EFSA, 2018b)    |                       |                       |
| Sheep and goat meat                   | 0.03                    | 0.8 × STMR muscle + 0.2 × STMR fat\(^{(b)}\) (EFSA, 2018b) |                       |                       |
| Sheep and goat fat                    | 0.03                    | STMR (EFSA, 2018b)    |                       |                       |
| Sheep and goat liver                  | 0.03                    | STMR (EFSA, 2018b)    |                       |                       |
| Sheep and goat kidney                 | 0.03                    | STMR (EFSA, 2018b)    |                       |                       |
| Poultry meat                          | 0.02                    | EU MRL (LOQ)\(^{(c)}\) |                       |                       |
| Poultry fat                           | 0.02                    | EU MRL(LOQ)\(^{(c)}\) |                       |                       |
| Poultry liver                         | 0.02                    | EU MRL(LOQ)\(^{(c)}\) |                       |                       |
| Cattle and horse milk                 | 0.03                    | STMR (EFSA, 2018b)    |                       |                       |
| Sheep and goat milk                   | 0.03                    | STMR (EFSA, 2018b)    |                       |                       |
| Birds eggs                            | 0.02                    | EU MRL (LOQ)\(^{(c)}\) |                       |                       |

\(^{(a)}\): An adjustment factor of 1.025 obtained from the metabolism data on fruit crops was used to take into consideration possible contribution of E-isomer, which was not analysed for in the samples from the US field trials.

Acute risk assessment was performed only for the crops under consideration.
(b): Consumption figures in the EFSA PRIMo are expressed as meat. Since the a.s. is a fat-soluble pesticide, STMR and HR residue values were calculated considering a 80%/90% muscle and 20%/10% fat content for mammal/poultry meat respectively (FAO, 2016).

(c): For poultry, since no metabolism study is available (data gap), EFSA could not derive a residue definition and MRL proposals (EFSA, 2018b).
## Appendix E – Used compound codes

| Code/trivial name | IUPAC name/SMILES notation/InChiKey<sup>(a)</sup> | Structural formula<sup>(b)</sup> |
|------------------|-----------------------------------------------|---------------------------------|
| Cyflufenamid 149-(Z)-FB | (Z)-N-\(\text{cyclopropylmethoxyimino}\)-2,3-difluoro-6-( trifluoromethyl)benzyl]-2-phenylacetamide | ![Structural formula](image) |
|                  | FC(F)(F)c1ccc(F)c(F)c1C\(\text{NC}(\text{=O})\text{C}(\text{ccc}c1\text{ccc}c1)=\text{N}\ \text{OCC1CC1})\)ACMXQHF NODYQAT-TWGOXAJXNA-N | |
| 149-F            | N'-\(\text{cyclopropylmethoxy}\)-2,3-difluoro-6-(trifluoromethyl)benzene-1-carboximidamide | ![Structural formula](image) |
|                  | N/C(\text{=N}\ \text{OCC1CC1})c1c(ccc(F)c1F)c(F)(F)F| GATGRGDKTXQMNK-UHFFFAOYSA-N |
| 149-F1           | 2,3-difluoro-6-(trifluoromethyl)benzene-1-carboximidamide | ![Structural formula](image) |
|                  | Fc1c(C(\text{=N})N)c(ccc1F)c(F)(F)F | JYSBNIJWTHMPOC-UHFFFAOYSA-N |

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

<sup>(a)</sup> ACD/Name 2019.1.3 ACD/Labs 2019 Release (File version N05E41, Build 111418, 3 September 2019).

<sup>(b)</sup> ACD/ChemSketch 2019.1.3 ACD/Labs 2019 Release (File version C05H41, Build 111302, 27 August 2019).