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

European Food Safety Authority (EFSA), Maria Anastassiadou, Alba Brancato, Daniela Brocca, Luis Carrasco Cabrera, Chloe De Lentdecker, Zoltan Erdos, Lucien Ferreira, Luna Greco, Samira Jarrah, Dimitra Kardassi, Renata Leuschner, Alfonso Lostia, Christopher Lythgo, Paula Medina, Ileana Miron, Tunde Molnar, Stefanie Nave, Ragnor Pedersen, Hermine Reich, Angela Sacchi, Miguel Santos, Alois Stanek, Juergen Sturma, Jose Tarazona, Anne Theobald, Benedicte Vagenende and Laura Villamar-Bouza

Abstract

The applicant ISK Biosciences Europe N.V. submitted a request to the competent national authority in France to evaluate the confirmatory data that were identified in the framework of the MRL review under Article 12 of Regulation (EC) No 396/2005 as not available. The data gap which was related to information on freezer storage conditions for the residue trials reported on potatoes, tomatoes and cucurbits with edible and inedible peel was considered satisfactorily addressed. The new information provided does not require a revision of risk assessment performed for cyazofamid.

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Keywords: cyazofamid, confirmatory data, pesticide, MRL review, risk assessment

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

In 2012, when the European Food Safety Authority (EFSA) reviewed the existing maximum residue levels (MRLs) for cyazofamid according to Article 12 of Regulation (EC) No 396/2005, EFSA identified some information as unavailable (data gap) and derived tentative MRLs for the uses on potatoes, tomatoes and cucurbits, edible and inedible peel which were not fully supported by data but for which no risk to consumers was identified. The following data gap was noted:

- information on freezer storage conditions for trials reported on potatoes, tomatoes and cucurbits (edible, inedible peel), to include not only the storage period but all conditions of storage and whether the samples were homogenised prior to storage.

The tentative MRL proposals derived for the crops concerned have been implemented in the MRL legislation by Commission Regulation (EU) No 398/2014, including the footnote, indicating the type of information that should be provided by a party having an interest in maintaining the proposed tentative MRLs by 23 April 2016.

In accordance with the agreed procedure set out in the working document SANTE/10235/2016, ISK Biosciences Europe N.V. submitted an application to the competent national authority in France (Rapporteur Member State (RMS)) to evaluate the confirmatory data identified during the MRL review. The RMS assessed the new information in an evaluation report, which was submitted to the European Commission and forwarded to EFSA on 8 March 2018. When assessing the evaluation report, EFSA identified points which needed further clarifications. On 18 May 2018, the RMS submitted a revised evaluation report which addressed the points for clarification.

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

It is highlighted that EFSA has published the conclusion on the peer review under Regulation (EC) No 1107/2009 where a number data gaps were identified. The decision on the renewal of the approval of cyazofamid has not yet been taken. The conclusions derived in this assessment may have to be reconsidered in the light of risk management measures taken in the framework of the approval process which may affect the authorised uses which are the basis of the current MRLs established under Regulation (EC) No 396/2005.

| Code(a) | Commodity                | Existing MRL(b) | Proposed MRL | Conclusion/recommendation |
|--------|--------------------------|-----------------|--------------|---------------------------|
| 211000 | Potatoes                 | 0.01* (ft)      | 0.01*        | The confirmatory data addressed the data gap identified by EFSA. The existing MRLs are confirmed. The risk assessment performed in the framework of the MRL review in 2012 is still valid |
| 231010 | Tomatoes                 | 0.6 (ft)        | 0.6          |                           |
| 232000 | Cucurbits with edible peel | 0.2 (ft)        | 0.2          |                           |
| 233000 | Cucurbits with inedible peel | 0.15 (ft)     | 0.15         |                           |

MRL: maximum residue level.
(a): Commodity code number according to Annex I of Regulation (EC) No 396/2005.
(b): Existing EU MRL and corresponding footnote on confirmatory data.
*: MRL is set at the limit of analytical quantification.
(ft): The European Food Safety Authority identified some information on residue trials as unavailable. When reviewing the MRL, the Commission will take into account the information referred to in the first sentence, if it is submitted by 23 April 2016, or, if that information is not submitted by that date, the lack of it. (Footnote related to data gap No 1).
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Assessment

The review of existing maximum residue levels (MRLs) for the active substance cyazofamid according to Article 12 of Regulation (EC) No 396/2005\(^1\) (MRL review) has been performed in 2012 (EFSA, 2012). The European Food Safety Authority (EFSA) identified some information as unavailable (data gap) and derived tentative MRLs for those uses not fully supported by data but for which no risk to consumers was identified. The following data gap was noted:

- information on freezer storage conditions for trials reported on potatoes, tomatoes and cucurbits (edible, inedible peel), to include not only the storage period but all conditions of storage and whether the samples were homogenised prior to storage.

Tentative MRL proposals have been implemented in Regulation (EC) No 396/2005 by Commission Regulation (EU) No 398/2014\(^2\), including a footnote that specified for the relevant MRLs the type of information that was identified as missing. Any party having an interest in maintaining the proposed tentative MRL was requested to address the confirmatory data by 23 April 2016.

In accordance with the specific provisions set out in the working document of SANTE/10235/2016 (European Commission, 2016), the applicant, ISK Biosciences Europe N.V. submitted an application to the competent national authority in France (designated rapporteur Member State (RMS)) to evaluate the data identified during the MRL review as missing. In order to address data gaps related to the national authorisations, the applicant submitted eight residue trials compliant with the northern Europe (NEU) outdoor GAP on tomatoes, eight residue trials compliant with the southern Europe (SEU) outdoor Good Agricultural Practice (GAP) on cucumber with a possible extrapolation to the whole subgroup of cucurbits, edible peel and nine residue trials compliant with the SEU outdoor GAP on melon and with a possible extrapolation to the cucurbits, inedible peel. Since these data are not expected to have an impact on the validity of the previously derived MRL proposals and risk assessment values derived for tomatoes, cucumbers and for melons, these residue trials were not assessed in the framework of this reasoned opinion.

The RMS assessed the new information related to the data gap related to the freezer storage conditions of residue trials in potatoes, tomatoes and cucurbits in an evaluation report, which was submitted to the European Commission and forwarded to EFSA on 8 March 2018 (France, 2018). EFSA assessed the application as requested by the European Commission in accordance with Article 9 of Regulation (EC) No 396/2005. During the detailed assessment, EFSA identified points which needed further clarifications. On 18 May 2018 the RMS submitted a revised evaluation report which addressed the points for clarification (France, 2018).

It is noted that in 2016, the EFSA conclusion on the peer review for the renewal of the approval of cyazofamid under Regulation (EC) No 1107/2009\(^3\) was issued (EFSA, 2016). EFSA identified a number of data gaps and the consumer dietary risk assessment could not be finalised. The decision on the renewal of the approval of cyazofamid has not yet been taken. The conclusions derived under this assessment may have to be reconsidered in the light of risk management measures taken in the framework of the approval process which may affect the authorised uses which are the basis of the current MRLs established under Regulation (EC) No 396/2005.

EFSA based its assessment on the evaluation report submitted by the RMS (France, 2018), the reasoned opinion on the MRL review according to Article 12 of Regulation (EC) No 396/2005 (EFSA, 2012) and the EFSA conclusion on the peer review (EFSA, 2016).

For this application, the data requirements established in Regulation (EU) No 544/2011\(^4\) and the guidance documents at the date of implementation of the confirmatory data requirements by Regulation (EU) No 398/2014 are applicable. The assessment is performed in accordance with the legal provisions of the Uniform Principles for the Evaluation and the Authorisation of Plant Protection Products adopted by Commission Regulation (EU) No 546/2011\(^5\).
An updated list of endpoints, including the endpoints of relevance in the framework of this confirmatory data, is presented in Appendix B.

The evaluation report submitted by the RMS (France, 2018) is considered a supporting document to this reasoned opinion and, thus, is made publicly available as background document.

1. **Residues in plants**

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

Not relevant for the current assessment.

1.2. **Magnitude of residues in plants**

The MRLs for plant commodities in the MRL regulation were tentatively set at 0.01* mg/kg (potatoes), 0.6 mg/kg (tomatoes), 0.2 mg/kg (cucurbits with edible peel) and 0.15 mg/kg (cucurbits with inedible peel), requesting additional information on freezer storage conditions for the trials reported on potatoes, tomatoes and cucurbits, to include not only the storage period but all conditions of storage and whether the samples were homogenised prior to storage.

In the framework of the peer review for the renewal of the approval of cyazofamid, acceptable storage stability for cyazofamid residues has been demonstrated for up to 26 months in homogenised samples of tomatoes (high water content matrices) and for up to 6 months in homogenised samples of potatoes (high starch content matrices) (EFSA, 2016).

All the residue trials on potatoes and most of the residue trials on tomatoes, cucumbers and melons that were assessed under the MRL review under Article 12 of Regulation (EC) No 396/2005 have been re-assessed in the framework of the renewal of the approval of cyazofamid and were found to be acceptable in terms of storage conditions and maximum storage time period (EFSA, 2016).

Regarding the residue trials on tomatoes, cucumbers and melons that were not assessed under the peer review and that were submitted in the framework of the MRL review under Article 12 of Regulation (EC) No 396/2005, it can reasonably be assumed that the samples and extracts of samples from these trials have not been stored under frozen conditions for more than 2 years.

The confirmatory data regarding the freezer storage conditions for the trials reported on potatoes, tomatoes and cucurbits can therefore be considered as sufficiently addressed.

2. **Residues in livestock**

Not relevant for the current assessment.

The confirmatory data requirement for cyazofamid identified in Commission Regulation (EU) No 398/2014 does not relate to residues in commodities of animal origin.

3. **Consumer risk assessment**

The submitted confirmatory data did not trigger a modification of previous risk assessment performed in the framework of the MRL review under Article 12 of Regulation (EC) No 396/2005 for cyazofamid (EFSA, 2012). The highest chronic exposure was calculated for France (all population) representing 0.7% of the acceptable daily intake (ADI). No short-term intake calculation was conducted as an acute reference dose (ARfD) was not allocated for cyazofamid.

4. **Conclusion and Recommendations**

The data gap regarding information on freezer storage conditions for the trials reported on potatoes, tomatoes and cucurbits (edible and inedible peel) has been sufficiently addressed.

The previously derived MRL proposals and risk assessment values are confirmed. The risk assessment performed in the framework of the review of the existing MRLs under Article 12 of Regulation (EC) No 396/2005 is still valid. However, it is highlighted that the conclusions derived in the framework of the renewal of the approval (EFSA, 2016) may trigger a revision of the authorised uses, which will have an impact on the existing European Union (EU) MRLs and therefore require revisiting the MRLs.
References

EFSA (European Food Safety Authority), 2012. Reasoned opinion on the review of the existing maximum residue levels (MRLs) for cyazofamid according to Article 12 of Regulation (EC) No 396/2005. EFSA Journal 2012;10 (12):3065, 38 pp. https://doi.org/10.2903/j.efsa.2012.3065

EFSA (European Food Safety Authority), 2016. Conclusion on the peer review of the pesticide risk assessment of the active substance cyazofamid. EFSA Journal 2016;14(6):4503, 24 pp. https://doi.org/10.2903/j.efsa.2016.4503

European Commission, 2016. Commission staff working document on the evaluation of data submitted to confirm MRLs following the review of existing MRLs Finalised in the Standing Committee on Plants, Animals, Food and Feed at its meeting on 17 June 2016. Brussels, SANTE/E4/VW 10235/2016 - Rev. 2, 3pp. 17 June 2016.

France, 2018. Evaluation report on the evaluation of confirmatory data for cyazofamid following review according to Article 12 of Regulation (EC) No 396/2005. February 2018, updated in May 2018, 63 pp.

Abbreviations

ADl acceptable daily intake
AR applied radioactivity
ARfD acute reference dose
DAR draft assessment report
DAT days after treatment
DM dry matter
GAP Good Agricultural Practice
InChiKey International Chemical Identifier Key
MRL maximum residue level
NEU northern Europe
PBI plant-back interval
RA risk assessment
RD residue definition
RMS rapporteur Member State
SEU southern Europe
SMILES simplified molecular-input line-entry system
Appendix A – Summary of GAPs assessed in the evaluation of confirmatory data

Not relevant for the current assessment.
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\(^{(a)}\) | Comment/source |
|-----------------------------------|-------------|---------|----------------|------------------|---------------|
| Fruit crops                       | Tomato      | Foliar  | (4x 100–400 g/ha) | 1 DAT\(_4\) | Studies conducted with [U-\(^{14}\)C]-phenyl- and [4-\(^{14}\)C]-imidazole rings labelled cyazofamid, respectively (EFSA, 2012, 2016) |
|                                  | Grape       | Foliar  | (5x 100 g/ha)    | 44 DAT\(_5\) |               |
| Root crops                        | Potato      | Foliar  | (2–3x 100 g/ha; 3–5x 400 g/ha) | 7 DAT\(_3,5\) |               |
| Leafy crops                       | Lettuce     | Foliar  | (3x 100 g/ha)    | 14 DAT\(_3\) | EFSA (2016) |

| Rotational crops (available studies) | Crop groups | Crop(s) | Application(s) | PBI (DAT) | Comment/Source |
|--------------------------------------|-------------|---------|----------------|-----------|---------------|
| Root/tuber crops                     | Carrot      | Indoor  | 500 g/ha       | 30; 120; 360 | Bare soil application (total dose rate: 500 g/ha) |
| Leafy crops                          | Lettuce     | Indoor  | 500 g/ha       | 30; 120; 360 | Metabolism studies conducted using [U-\(^{14}\)C]-phenyl- and [4-\(^{14}\)C]-imidazole rings labelled cyazofamid, respectively (EFSA, 2012, 2016) |
| Cereal (small grain)                 | Wheat       | Indoor  | 500 g/ha       | 30; 120; 360 |               |

| Processed commodities (hydrolysis study) | Conditions | Stable? | Comment/Source |
|------------------------------------------|------------|--------|----------------|
|                                          | Pasteurisation (20 min, 90°C, pH 4) | No | Cyazofamid was completely degraded into CCIM under baking/brewing/boiling and sterilisation conditions (100% of the applied radioactivity (AR)) and up to 81% of AR under pasteurisation processing (EFSA, 2016) |
|                                          | Baking, brewing, boiling (60 min, 100°C, pH 5) | No | |
|                                          | Sterilisation (20 min, 120°C, pH 6) | No | |

PBI: plant-back interval.
(a): DAT\(_x\), days after treatment x, e.g. DAT\(_2\): day after second treatment.

Plant residue definition for monitoring (RD-Mo)

| Cyazofamid |
|------------|
| Processed commodities: cyazofamid and CCIM\(^{(1)}\) |

Plant residue definition for risk assessment (RD-RA)

| Cyazofamid |
|------------|
| Processed commodities: cyazofamid and CCIM\(^{(1)}\) |

\(^{(1)}\): Whether or not these compounds are expressed as the sum or considered separately is pending a finalised assessment of the toxicological profile of CCIM (EFSA, 2016).
B.1.1.2. Stability of residues in plants

| Plant products (category) | Commodity (category) | T (°C) | Stability (month) Cyazofamid | Stability (month) CCIM |
|--------------------------|----------------------|--------|-----------------------------|------------------------|
| High water content       | Tomato (homogenised samples) | $-25^\circ$C | 26 | 36 EFSA (2012, 2016) |
| High oil content         | Oilseed rape (whole sample) | $-20^\circ$C | 12 | 12 EFSA (2016) |
| High protein content     | Dry bean (whole sample) | $-20^\circ$C | 12 | 12 EFSA (2016) |
| High starch content      | Potato (homogenised samples) | $-25^\circ$C | 6 | 6 EFSA (2012, 2016) |
| High acid content        | Grape (homogenised samples) | $-20^\circ$C | 12 | 12 EFSA (2012, 2016) |
|                          | Grape (homogenised samples) | $-20^\circ$C | 3 | 3 |
|                          | Wine | $-20^\circ$C | 3 | 3 |

B.1.1.3. Magnitude of residues in plants

Not applicable.

B.2. Residues in livestock

Not relevant.

B.3. Consumer risk assessment

Not applicable.

B.4. Recommended MRLs

| Code(a) | Commodity | Existing MRL(b) | Proposed MRL | Conclusion/recommendation |
|---------|-----------|----------------|--------------|----------------------------|
| 211000  | Potatoes  | 0.01* (ft)     | 0.01*        | The confirmatory data addressed the data gap identified by EFSA. The existing MRLs are confirmed. The risk assessment performed in the framework of the MRL review in 2012 is still valid |
| 231010  | Tomatoes  | 0.6 (ft)       | 0.6          |                            |
| 232000  | Cucurbits with edible peel | 0.2 (ft) | 0.2 |                            |
| 233000  | Cucurbits with inedible peel | 0.15 (ft) | 0.15 |                            |

MRL: maximum residue level.
(a): Commodity code number according to Annex I of Regulation (EC) No 396/2005.
(b): Existing EU MRL and corresponding footnote on confirmatory data.
*: MRL is set at the limit of analytical quantification.
(ft): The European Food Safety Authority identified some information on residue trials as unavailable. When reviewing the MRL, the Commission will take into account the information referred to in the first sentence, if it is submitted by 23 April 2016, or, if that information is not submitted by that date, the lack of it. (Footnote related to data gap No 1).
### Appendix C – Used compound codes

| Code/trivial name<sup>(a)</sup> | IUPAC name/SMILES notation/InChiKey<sup>(b)</sup> | Structural formula<sup>(c)</sup> |
|-------------------------------|-----------------------------------------------|---------------------------------|
| Cyazofamid                    | 4-chloro-2-cyano-N,N-dimethyl-5-p-tolylimidazole-1-sulfonamide  
N#Cc1nc(Cl)c(c2ccc(C)cc2)n1S(=O)(=O)N(C)C  
YXKMMRDKEKERS-UHFFFAOYSA-N | ![Structural formula for Cyazofamid](attachment:image.png) |
| CCIM                          | 4-chloro-5-(4-methylphenyl)-1H-imidazole-2-carbonitrile  
Clc1nc(C#N)[NH]c1c1ccc(C)cc1  
AHLIZUWYPQFHY-UHFFFAOYSA-N | ![Structural formula for CCIM](attachment:image.png) |

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

<sup>(a)</sup> The metabolite name in bold is the name used in the conclusion.

<sup>(b)</sup> ACD/Name 2017.2.1 ACD/Labs 2017 Release (File version N40E41, Build 96719, 6 September 2017).

<sup>(c)</sup> ACD/ChemSketch 2017.2.1 ACD/Labs 2017 Release (File version C40H41, Build 99535, 14 February 2018).