REASONED OPINION

APPROVED: 26 October 2018

doi: 10.2903/j.efsa.2018.5487

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

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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.

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

Requestor: European Commission

Question numbers: EFSA-Q-2018-00239

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Suggested citation: European Food Safety Authority (EFSA), Anastassiadou M, Brancato A, Brocca D, Carrasco Cabrera L, De Lentdecker C, Erdos Z, Ferreira L, Greco L, Jarrah S, Kardassi D, Leuschner R, Lostia A, Lythgo C, Medina P, Miron I, Molnar T, Nave S, Pedersen R, Reich H, Sacchi A, Santos M, Stanek A, Sturma J, Tarazona J, Theobald A, Vagenende B and Villamar-Bouza L, 2018. Reasoned opinion on the evaluation of confirmatory data following the Article 12 MRL review for cyazofamid. EFSA Journal 2018;16 (11):5487, 11 pp. https://doi.org/10.2903/j.efsa.2018.5487

ISSN: 1831-4732

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

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
Enforcement residue definition: cyazofamid				
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).

Table of contents

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].

[1] Regulation (EC) No 396/2005 of the Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC. OJ L 70, 16.3.2005, p. 1–16.

[2] Commission Regulation (EU) No 398/2014 of 22 April 2014 amending Annexes II and III to Regulation (EC) No 396/2005 of the European Parliament and of the Council as regards maximum residue levels for benthiavalicarb, cyazofamid, cyhalofop-butyl, forchlorfenuron, pymetrozine and silthiofam in or on certain products. OJ L 119, 23.4.2014, p. 3–39.

[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 309, 24.11.2009, p. 1–50.

[4] Commission Regulation (EU) No 544/2011 of 10 June 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards the data requirements for active substances. OJ L 155, 11.6.2011, p. 1–66.

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

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

ADI	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) Metabolism studies conducted using [U-^{14}C]-phenyl- and [4-^{14}C]-imidazole rings labelled cyazofamid, respectively (EFSA, 2012, 2016)
	Leafy crops	Lettuce	Indoor, 500 g/ha	30; 120; 360	
	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	T (°C)	Stability (month)		
			Cyazofamid	CCIM	
High water content	Tomato (homogenised samples)	−25°C	26	36	EFSA (2012, 2016)
High oil content	Oilseed rape (whole sample)	−20°C	12	12	EFSA (2016)
High protein content	Dry bean (whole sample)	−20°C	12	12	EFSA (2016)
High starch content	Potato (homogenised samples)	−25°C	6	6	EFSA (2012, 2016)
High acid content	Grape (homogenised samples)	−20°C	12	12	EFSA (2012, 2016)
	Grape (homogenised samples)	−20°C	3	3	
	Wine	−20°C	3	36	

B.1.1.3. Magnitude of residues in plants

Not applicable.

B.2. Residues in livestock

Not relevant.

B.3. Consumer risk assessment

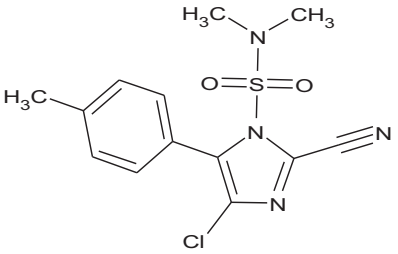
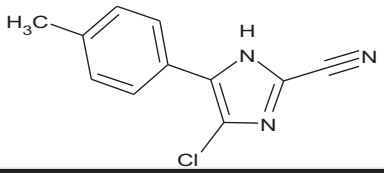
Not applicable.

B.4. Recommended MRLs

Code[(a)]	Commodity	Existing MRL[(b)]	Proposed MRL	Conclusion/recommendation
Enforcement residue definition: cyazofamid				
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[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
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 YXKMMRDKEKCERS-UHFFFAOYSA-N	
CCIM	4-chloro-5-(4-methylphenyl)-1*H*-imidazole-2-carbonitrile Clc1nc(C#N)[NH]c1c1ccc(C)cc1 AHLIZUWPYRQFHY-UHFFFAOYSA-N	

IUPAC: International Union of Pure and Applied Chemistry; SMILES: simplified molecular-input line-entry system; InChiKey: International Chemical Identifier Key.
(a): The metabolite name in bold is the name used in the conclusion.
(b): ACD/Name 2017.2.1 ACD/Labs 2017 Release (File version N40E41, Build 96719, 6 September 2017).
(c): ACD/ChemSketch 2017.2.1 ACD/Labs 2017 Release (File version C40H41, Build 99535, 14 February 2018).