EFSA Journal

CONCLUSION ON PESTICIDES PEER REVIEW

APPROVED: 28 July 2020

doi: 10.2903/j.efsa.2020.6232

Updated peer review of the pesticide risk assessment of the active substance cyazofamid

European Food Safety Authority (EFSA),
Maria Anastassiadou, Maria Arena, Domenica Auteri, Alba Brancato, Laszlo Bura, Luis Carrasco Cabrera, Eugenia Chaideftou, Arianna Chiusolo, Federica Crivellente, Chloe De Lentdecker, Mark Egsmose, Gabriella Fait, Luna Greco, Alessio Ippolito, Frederique Istace, Samira Jarrah, Dimitra Kardassi, Renata Leuschner, Alfonso Lostia, Christopher Lythgo, Oriol Magrans, Iris Mangas, Ileana Miron, Tunde Molnar, Laura Padovani, Juan Manuel Parra Morte, Ragnor Pedersen, Hermine Reich, Miguel Santos, Rachel Sharp, Juergen Sturma, Csaba Szentes, Andrea Terron, Manuela Tiramani, Benedicte Vagenende and Laura Villamar-Bouza

Abstract

The conclusions of the EFSA following the peer review of the initial risk assessments carried out by the competent authorities of the rapporteur Member State, France, and co-rapporteur Member State, Latvia, for the pesticide active substance cyazofamid are reported. The context of the peer review was that required by Commission Implementing Regulation (EU) No 844/2012. The conclusions were reached on the basis of the evaluation of the representative uses of cyazofamid as a fungicide on potato, tomato and cucurbits and were updated for non-target organisms. The reliable end points, appropriate for use in regulatory risk assessment, are presented. Missing information identified as being required by the regulatory framework is listed. Concerns are identified.

Keywords: cyazofamid, peer review, risk assessment, pesticide, fungicide

Requestor: European Commission

Question number: EFSA-Q-2020-00192

Correspondence: pesticides.peerreview@efsa.europa.eu

Update: This scientific output, approved on 28 July 2020, supersedes the previous output published on 15 June 2016 (EFSA, 2016).

Suggested citation: EFSA (European Food Safety Authority), Anastassiadou M, Arena M, Auteri D, Brancato A, Bura L, Carrasco Cabrera L, Chaideftou E, Chiusolo A, Crivellente F, De Lentdecker C, Egsmose M, Fait G, Greco L, Ippolito A, Istace F, Jarrah S, Kardassi D, Leuschner R, Lostia A, Lythgo C, Magrans O, Mangas I, Miron I, Molnar T, Padovani L, Parra Morte JM, Pedersen R, Reich H, Santos M, Sharp R, Sturma J, Szentes C, Terron A, Tiramani M, Vagenende B and Villamar-Bouza L, 2020. Updated peer review of the pesticide risk assessment of the active substance cyazofamid. EFSA Journal 2020;18(9):6232, 25 pp. https://doi.org/10.2903/j.efsa.2020.6232

ISSN: 1831-4732

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

Summary

Commission Implementing Regulation (EU) No 844/2012 (hereinafter referred to as 'the Regulation') lays down the procedure for the renewal of the approval of active substances submitted under Article 14 of Regulation (EC) No 1107/2009. The list of those substances is established in Commission Implementing Regulation (EU) No 686/2012. Cyazofamid is one of the active substances listed in Regulation (EU) No 686/2012.

In accordance with Article 1 of the Regulation, the rapporteur Member State (RMS), France, and co-rapporteur Member State (co-RMS), Latvia, received an application from ISK Biosciences Europe N.V. for the renewal of approval of the active substance cyazofamid. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicant, the co-RMS (Latvia), the European Commission and the European Food Safety Authority (EFSA) about the admissibility.

The RMS provided its initial evaluation of the dossier on cyazofamid in the renewal assessment report (RAR), which was received by EFSA on 23 June 2015. In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicant, ISK Biosciences Europe N.V., for comments on 22 July 2015. EFSA also provided comments. In addition, EFSA conducted a public consultation on the RAR. EFSA collated and forwarded all comments received to the European Commission on 21 September 2015.

Following consideration of the comments received on the RAR, it was concluded that additional information should be requested from the applicant, and that EFSA should conduct an expert consultation in the areas of mammalian toxicology, environmental fate and behaviour and ecotoxicology.

In accordance with Article 13(1) of the Regulation, EFSA should adopt a conclusion on whether cyazofamid can be expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009 of the European Parliament and of the Council.

Following the completion of the peer review, EFSA published on 15 June 2016 its conclusion on the pesticide peer review for cyazofamid (EFSA, 2016). The regulatory decision-making regarding cyazofamid could not be concluded due to certain open issues identified during the discussions at the Standing Committee on Plants, Animals, Food and Feed (PAFF Committee), which were considered crucial for taking a final regulatory decision. In particular, studies available only in the original dossier (supporting the first EU review of cyazofamid) were not considered during the peer review because not provided together with the supplementary dossier.

In February 2020, the European Commission asked EFSA to update the risk assessment for non-target arthropods, in particular for predatory mites, using a weight of evidence approach and taking into account all available information in the applicant's dossier including the studies available in the original dossier (supporting the first EU review of cyazofamid) and the supplementary dossier submitted for the renewal of the approval. Risk mitigation measures would be considered, if appropriate. A second expert meeting to discuss the risk assessment for non-target arthropods was held in May 2020. The conclusions laid down in this report were reached on the basis of the evaluation of the representative uses of cyazofamid as a fungicide on potato, tomato and cucurbits as proposed by the applicant. Full details of the representative uses can be found in Appendix A of this report.

Data were submitted to conclude that the uses of cyazofamid according to the representative uses proposed result in a sufficient fungicidal efficacy against the target organisms.

A data gap was identified for a more detailed assessment of the literature review for cyazofamid and its relevant metabolites in the residue section, dealing with side effects on health and published within 10 years before the date of submission of the dossier, to be conducted and reported in accordance with EFSA guidance.

In the area of identity, physical chemical properties and analytical methods data gaps were identified for a revised technical specification, residue method for the determination of metabolite CCIM in soil, a validation method for surface water and an independent laboratory validation (ILV) for residues in drinking water, methods for monitoring residue in air and body fluids and tissues and also for additional validation data for the residue method in processed commodities.

In the mammalian toxicology area, data gaps have been identified with regard to phototoxicity testing, the comparative *in vitro* metabolism study, the endocrine disruptor potential and the toxicological relevance of some impurities. In addition, data gaps for the metabolite CCIM were identified for the following studies: repeated dose toxicity, mammalian cell mutation and *in vitro* mutation.

In the residue area, data gaps were identified for a complete residue data set on cucumbers (southern outdoor use) and for additional residue trials on melon, respectively, for the southern outdoor use and the glasshouse use. Data gaps were also identified for a storage stability study in high water content commodities (cucurbits) analysing for cyazofamid and CCIM residues, for the magnitude of CCIM residues in cooked vegetables (courgettes) and for the determination of the residues in pollen and bee products for human consumption resulting from residues taken up by honeybees from crops at blossom. The consumer exposure assessment cannot be concluded on considering the identified data gaps, the outstanding data on the toxicity profile of CCIM and the finalisation of the residue definition for processed commodities.

The data available on environmental fate and behaviour are sufficient to carry out the required environmental exposure assessments at EU level for the representative uses, with the exception that information was not available regarding the effect of water treatment processes on the nature of residues that may be present in surface water at the point of abstraction for drinking water purposes. This results in it not being possible to finalise the consumer exposure and risk assessments. The potential for groundwater exposure by cyazofamid and its soil metabolites CCIM, CCIM-AM and CTCA from the representative uses above the parametric drinking water limit of 0.1 μg/L was concluded to be low in geoclimatic situations that are represented by all nine FOCUS groundwater scenarios.

In the ecotoxicology section, several data gaps were identified in the area of bees risk assessment. Further data gaps were identified for addressing the risk posed by the metabolites CCIM and CCIM-AM to soil macro- and microorganisms.

Regarding the outcome of the updated peer review of the risk assessment for non-target arthropods, a data gap for further data on predatory mites to complete the risk assessment was identified. Such data gap results in an assessment not finalised which is relevant for all representative uses. In the case, the use in glasshouses is confirmed to include applications to permanent greenhouses, then the risk for non-target arthropods for this type of use would be low.

Table of contents

Background

Commission Implementing Regulation (EU) No 844/2012[1] (hereinafter referred to as 'the Regulation') lays down the provisions for the procedure of the renewal of the approval of active substances, submitted under Article 14 of Regulation (EC) No 1107/2009[2]. This regulates for the European Food Safety Authority (EFSA) the procedure for organising the consultation of Member States, the applicant(s) and the public on the initial evaluation provided by the rapporteur Member State (RMS) and/or co-rapporteur Member State (co-RMS) in the renewal assessment report (RAR), and the organisation of an expert consultation where appropriate.

In accordance with Article 13 of the Regulation, unless formally informed by the European Commission that a conclusion is not necessary, EFSA is required to adopt a conclusion on whether the active substance can be expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009 within 5 months from the end of the period provided for the submission of written comments, subject to an extension of up to 8 months where additional information is required to be submitted by the applicant(s) in accordance with Article 13(3).

In accordance with Article 1 of the Regulation, the RMS, France, and co-RMS, Latvia, received an application from ISK Biosciences Europe N.V. for the renewal of approval of the active substance cyazofamid. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicant, the co-RMS (Latvia), the European Commission and EFSA about the admissibility.

The RMS provided its initial evaluation of the dossier on cyazofamid in the RAR, which was received by EFSA on 23 June 2015 (France, 2015).

In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicant, ISK Biosciences Europe N.V., for consultation and comments on 22 July 2015. EFSA also provided comments. In addition, EFSA conducted a public consultation on the RAR. EFSA collated and forwarded all comments received to the European Commission on 21 September 2015. At the same time, the collated comments were forwarded to the RMS for compilation and evaluation in the format of a reporting table. The applicant was invited to respond to the comments in column 3 of the reporting table. The comments and the applicant's response were evaluated by the RMS in column 3.

The need for expert consultation and the necessity for additional information to be submitted by the applicant in accordance with Article 13(3) of the Regulation were considered in a telephone conference between EFSA, the RMS on 9 November 2015. On the basis of the comments received, the applicant's response to the comments and the RMS's evaluation thereof, it was concluded that additional information should be requested from the applicant, and that EFSA should conduct an expert consultation in the areas of mammalian toxicology, environmental fate and behaviour and ecotoxicology.

The outcome of the telephone conference, together with EFSA's further consideration of the comments, is reflected in the conclusions set out in column 4 of the reporting table. All points that were identified as unresolved at the end of the comment evaluation phase and which required further consideration, including those issues to be considered in an expert consultation, were compiled by EFSA in the format of an evaluation table.

The conclusions arising from the consideration by EFSA, and as appropriate by the RMS, of the points identified in the evaluation table, together with the outcome of the expert consultation and the written consultation on the assessment of additional information, where these took place, were reported in the final column of the evaluation table.

A consultation on the conclusions arising from the peer review of the risk assessment took place with Member States via a written procedure in April–May 2016.

In February 2020, the European Commission asked EFSA to update the risk assessment for non-target arthropods, in particular for predatory mites, using a weight of evidence approach and taking into account all available information in the applicant's dossier including the studies available in the original dossier (supporting the first EU review of cyazofamid) and the supplementary dossier submitted for the renewal of the approval. Risk mitigation measures would be considered, if

[1] Commission Implementing Regulation (EU) No 844/2012 of 18 September 2012 setting out the provisions necessary for the implementation of the renewal procedure for active substances, as provided for in Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market. OJ L 252, 19.9.2012, p. 26–32.

[2] Regulation (EC) No 1107/2009 of 21 October 2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. OJ L 309, 24.11.2009, p. 1–50.

appropriate. A second expert meeting to discuss the risk assessment for non-target arthropods was held in May 2020.

A final consultation on the conclusions arising from the peer review of the risk assessment and the discussion on the risk assessment for non-target arthropods took place with Member States via a written procedure in July 2020.

This conclusion report summarises the outcome of the peer review of the risk assessment of the active substance and the representative formulation, evaluated on the basis of the representative uses of cyazofamid as a fungicide on potato, tomato and cucurbits, as proposed by the applicant. A list of the relevant end points for the active substance and the formulation is provided in Appendix A.

In addition, a key supporting document to this conclusion is the peer review report (EFSA, 2020), which is a compilation of the documentation developed to evaluate and address all issues raised in the peer review, from the initial commenting phase to the conclusion. The peer review report comprises the following documents, in which all views expressed during the course of the peer review, including minority views, where applicable, can be found:

- the comments received on the RAR;
- the reporting table (10 November 2015);
- the evaluation table (12 May 2016);
- the report(s) of the scientific consultation with Member State experts (where relevant);
- the comments received on the assessment of the additional information (where relevant);
- the comments received on the draft EFSA conclusion (April–May 2016);
- the comments received on the draft EFSA conclusion (July 2020).

Given the importance of the RAR, including its revisions (France, 2016, 2020), and the peer review report, both documents are considered as background documents to this conclusion and thus are made publicly available.

It is recommended that this conclusion report and its background documents would not be accepted to support any registration outside the EU for which the applicant has not demonstrated that it has regulatory access to the information on which this conclusion report is based.

The active substance and the formulated product

Cyazofamid is the ISO common name for 4-chloro-2-cyano-*N,N*-dimethyl-5-*p*-tolylimidazole-1-sulfonamide (IUPAC).

The representative formulated product for the evaluation was 'IKF-916 160SC-N' a suspension concentrate (SC) containing 160 g/L cyazofamid.

The representative uses evaluated were foliar applications against late blight on potato and tomato and against downy mildew on cucurbits, edible and inedible peel. Full details of the GAPs can be found in the list of end points in Appendix A.

Data were submitted to conclude that the uses of cyazofamid according to the representative uses proposed at EU level result in a sufficient fungicidal efficacy against the target organisms, following the guidance document SANCO/10054/2013 - rev. 3 (European Commission, 2013).

A data gap has been identified for a more detailed assessment of the literature review for cyazofamid and its relevant metabolites in the residue section, dealing with side effects on health and published within 10 years before the date of submission of the dossier, to be conducted and reported in accordance with EFSA guidance on the submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (EFSA, 2011).

Conclusions of the evaluation

1. Identity, physical/chemical/technical properties and methods of analysis

The following guidance documents were followed in the production of this conclusion: SANCO/3029/99-rev. 4 (European Commission, 2000a), SANCO/3030/99-rev. 4 (European Commission, 2000b), SANCO/10597/2003-rev. 10.1 (European Commission, 2012) and SANCO/825/00-rev. 8.1 (European Commission, 2010).

The minimum purity of the active substance as manufactured is 935 g/kg. The same reference specification was proposed as for the first approval; however, neither the batch data from industrial

scale production nor the quality control (QC) data fully supported the specification. As a consequence, a data gap was identified for an updated specification supported by data. The minimum purity of the technical material in the FAO Specification 653/TC (February 2015) is 935 g/kg.

The assessment of the data package revealed no issues that need to be included as critical areas of concern with respect to the identity, physical, chemical and technical properties of cyazofamid or the representative formulation. The main data regarding the identity of cyazofamid and its physical and chemical properties are given in Appendix A.

Adequate methods are available for the generation of pre-approval data required for the risk assessment; however, a data gap was identified for additional validation data for the residue method in processed commodities. Adequate analytical methods are available for the determination of cyazofamid in the technical material and in the representative formulation as well as for the determination of the respective impurities in the technical material.

Cyazofamid residues can be monitored in food and feed of plant origin by the QuEChERS method (liquid chromatography with tandem mass spectroscopy (LC-MS/MS)) with limits of quantification (LOQs) of 0.01 mg/kg in all plant commodity groups. An high-performance liquid chromatography with tandem mass spectroscopy (HPLC-MS/MS) method also exists with LOQs of 0.01 mg/kg in dry, high water content and high oil content commodities; however, the extraction efficiency was not fully addressed. For products of animal origin, a method of analysis is not required as maximum residue levels (MRLs) are not proposed for animal commodities.

Residues of cyazofamid in soil can be monitored by HPLC-UV with an LOQ of 0.01 mg/kg; however, the residue definition for monitoring in soil was defined as cyazofamid and its metabolite CCIM (see Section 4). As a consequence, a data gap was identified for a method for the determination of CCIM residues in soil. Cyazofamid can be determined in surface water and drinking water by HPLC-UV with an LOQ of 0.01 μg/L; however, data gaps were identified for the confirmatory method for surface water and for ILV for the method for residues in drinking water. An analytical method for the determination of residues of cyazofamid in air having an LOQ of at least 14 $\mu g/m^3$ was also identified as a data gap. A data gap was identified for a validated method of analysis in body fluids and tissues.

2. Mammalian toxicity

The following guidance documents were followed in the production of this conclusion: SANCO/221/2000-rev. 10-final (European Commission, 2003), SANCO/10597/2003-rev. 10.1 (European Commission, 2012) and Guidance on dermal absorption (EFSA PPR Panel, 2012).

Cyazofamid (IKF-916) was discussed at the Pesticides Peer Review Experts' Meeting 141 in February 2016.

The relevance of some individual impurities in comparison with the toxicological profile of the parent compound has not been fully addressed; therefore, a data gap has been identified to address the relevance of these impurities present in the technical specifications. The analytical profile of the batch used in all the toxicological studies is in compliance with the technical specifications provided.

Cyazofamid is rapidly absorbed after oral administration being mostly eliminated with urine and bile within 24 h. More than 90% of active dose is excreted within 48 h of dosing. Low acute toxicity was observed when cyazofamid was administered by the oral, dermal or inhalation routes; no skin irritation or eye irritation and no potential for skin sensitisation were attributed to the active substance. A comparative *in vitro* metabolism study has not been provided, and therefore, a data gap has been identified. Cyazofamid was classified as 'probably phototoxic' in an *in vitro* Neutral Red Uptake (NRU) phototoxicity study; on the basis of this, photogenotoxicity testing was identified as a data gap, acknowledging that validated test guidelines are not available. The main target organs of cyazofamid are kidney, liver and testes (via dermal route only) in the rat only, whilst no treatment-related effects were observed up to the highest dose in mice and dogs. The relevant short-term no adverse effect level (NOAEL) is 29.5 mg/kg body weight (bw) per day from the 90-day study in rats, based on kidney changes (increase in urinary proteins and urine volume, increased relative kidney weights and increased occurrence of renal basophilic tubules) and increased blood chloride, cholesterol and triglycerides levels. The relevant long-term NOAEL is 17 mg/kg bw per day from the 2-year study in rats based on kidney (weight increase, urinary parameters and biochemistry changes) and liver effects (weight increase). Cyazofamid did not present genotoxic potential *in vivo* and in the overall *in vitro* studies. No evidence of carcinogenicity was observed in rats or mice. The reproduction, fertility and developmental parameters were not affected by cyazofamid administration. There was no evidence of neurotoxic effects or immunotoxicity induced by cyazofamid treatment in studies provided. Cyazofamid

is not classified or proposed to be classified as carcinogenic or toxic for the reproduction category 2 (ECHA, 2015) in accordance with the provisions of Regulation (EC) No 1272/2008 (harmonised classification supported by the present assessment). No adverse effects that could be related to an endocrine disruptor mode of action were observed. However, considering that a number of parameters (including sperm evaluation, sexual maturation, functional observation battery (FOB) of offspring etc.) were not assessed in the two-generation study, an endocrine-disrupting potential of cyazofamid cannot be ruled out in the absence of mechanistic studies, and therefore, a data gap is identified. Acute oral toxicity studies and an *in vitro* bacterial mutation assay were provided on four cyazofamid metabolites, CCIM, CCIM-AM, CTCA and DMSA. Amongst all metabolites, CCIM and CTCA were found more acutely toxic than cyazofamid. All the metabolites were considered non-mutagenic to bacteria under the conditions of the studies. An acute reference dose (ARfD) of 0.2 mg/kg bw on the basis of the higher acute toxicity of CCIM compared to cyazofamid was agreed by JMPR (JMPR, 2015) and also agreed during the Experts' meeting 141. However, considering that a data gap was identified with regard to the lack of genotoxicity testing (mammalian cell mutation assay, *in vitro* mutation test using mouse lymphoma L518Y cells) for the metabolite CCIM, EFSA after the expert meeting considered preferable not to set an acute reference dose (ARfD) for CCIM until its genotoxic potential is clarified; the RMS expressed disagreement, considering the information sufficient for setting an ARfD of 0.2 mg/kg bw for CCIM. The lack of specific toxicity data on metabolite CCIM did not allow concluding on the consumer risk assessment of this metabolite relevant for processed commodities (data gap). A mammalian cell mutation assay, an *in vitro* mutation test using mouse lymphoma L518Y cells and a repeated dose toxicity study for the metabolite CCIM to conclude on the toxicological relevance of CCIM has not been submitted (data gap for these three studies). The acceptable daily intake (**ADI**) of cyazofamid is 0.17 mg/kg bw per day with no change in the ADI value compare to SANCO/10379/2002-final (European Commission, 2002c), based on the NOAEL of 17 mg/kg bw per day for kidney and liver effects observed in the 2-year study in rats and applying an uncertainty factor (UF) of 100. JMPR derived a similar ADI (0.2 mg/kg bw per day) based on the 2-year toxicity and carcinogenicity study in the rat and applying an uncertainty factor (UF) of 100. The differences between the two values are due to rounding by the JMPR evaluation. The acceptable operator exposure level (**AOEL**) is 0.045 mg/kg bw per day, based on the NOAEL of 29.5 mg/kg bw per day for the kidney and biochemistry changes observed in the 90-day study in rat and applying a correction factor to account for the limited oral absorption of 15%; in the previous Review Report assessment (European Commission, 2002a), AOEL was set at 0.3 mg/kg bw per day since a standard correction factor of 100 was considered without taking into account the limited oral absorption. An **ARfD** was not considered necessary, and therefore, it was not allocated for cyazofamid.

Based on human skin *in vitro* dermal absorption study, dermal absorption values for the representative formulation are 0.1% for the concentrate and 3% for the aqueous dilution. To obtain a level of exposure below the AOEL, no personal protective equipment (PPE) is required for operators according to both the German and UK POEM models. The estimated bystander and residential exposure levels were below the AOEL according to the EUROPOEM II data and BfR model. No exceedance of AOEL was anticipated for the unprotected worker wearing adequate work clothing (but no PPE).

3. Residues

The assessment in the residue section is based on the European Commission guideline document on MRL setting (European Commission, 2015), the Joint Meeting on Pesticide Residues (JMPR) recommendations on livestock burden calculations (JMPR, 2004, 2007) and the OECD publication on MRL calculations (OECD, 2011).

Metabolism in primary crops was investigated upon foliar application on fruits (tomato, grapes), leafy crops (lettuce) and root crops (potatoes), using [U-^{14}C]-Phenyl- and [4-^{14}C]-imidazole rings labelled cyazofamid, respectively. Cyazofamid was the major compound of the terminal residues in fruits, lettuce and potato foliage accounting for 58–96% total radioactive residue (TRR) and occurred at a lower proportion in potato tuber (9.5% TRR) where a significant fraction of the total residues was characterised as polar neutral and acidic components (20–44% TRR). CCIM metabolite resulting from the hydrolysis of the sulphonamide group of the parent compound accounted for 3–7.4% TRR in all the edible parts of the crops and also under its conjugated form in grapes only (2.4% TRR). All the other identified metabolites were structurally related to the parent compound and were recovered at negligible levels (< 10% TRR; < 0.01 mg/kg). A significant fraction of the radioactive residues was

shown to be incorporated into natural plant constituents (bound residues) mainly in potato tubers (16–54% TRR) and to a minor extend in the other crops (2.6–25% TRR).

In a confined rotational crop study, the metabolism of [U-^{14}C]-Phenyl and [4-^{14}C]-imidazole cyazofamid was investigated in rotated cereals (wheat), leafy vegetables (lettuce) and root vegetables (carrot) after bare soil application at a 1N rate using plant back intervals (PBIs) of 30, 120 and 360 days. The highest TRR values were observed at the 30-day PBI and decrease substantially by the 120-day and 365-day PBIs. Identification of metabolites was not attempted in lettuce and carrot root in view of the low residue levels (< 0.01–0.015 mg eq/kg and < 0.01–0.018 mg eq/kg, respectively). The maximum residue levels accounted for 0.5 mg eq/kg in wheat forage and straw and 0.09 mg eq/kg in wheat grain at the 30-day PBI. In wheat forage and straw, cyazofamid and their structurally related compounds (CCBA, CCIM, CCIM-AM) were tentatively identified and each accounted for a level below 0.01 mg/kg whilst the major part of the radioactive residues were characterised as polar fractions. In wheat grain, most of the radioactive residues were found to be incorporated into natural plant constituents. Based on these data, the metabolic pattern of cyazofamid can be considered as similar in primary and in succeeding crops and a specific residue definition for rotational crops is not deemed necessary. Furthermore, in view of the very low residue levels recovered for each individual component and considering also that a situation of crop failure is not relevant for the representative uses, it can reasonably be assumed that cyazofamid residues are not expected to be present in rotational crops, provided that cyazofamid is applied according to the representative uses.

Based on the metabolism data in primary and rotational crops, a general residue definition for monitoring and risk assessment for plants is proposed as cyazofamid only.

A sufficient number of residue field trials conducted according to the cGAP conditions are available for potatoes, tomatoes and cucumbers (glasshouse), determining residues of parent compound and metabolite CCIM, respectively. Eight residue trials on cucumber (southern outdoor use) are requested with a possible extrapolation to the whole group of cucurbits, edible peel (data gap). For melon, four additional residue trials compliant with the glasshouse use and one additional residue trial compliant with the southern outdoor use are also requested with a possible extrapolation to the whole group of cucurbits, inedible peel (data gap). The results of the residue trials on the crops under consideration are supported by validated analytical methods. Acceptable storage stability study was provided on potatoes and tomatoes and covered the maximum storage period of the residue samples from the trials on these crops. However, based on the current guidance recommendations and considering the results discrepancies observed in the storage stability study submitted on cucumber, cantaloupe and squash compared to the storage stability study on tomatoes, a second storage stability study in high water content commodities (cucurbits) and analysing for cyazofamid and CCIM residues is still needed to confirm the validity of the results of the residue trials on cucumber and melon (data gap).

Under standard hydrolysis conditions, 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. Currently, insufficient specific toxicological data are available to adequately evaluate the relevance of CCIM as a 90-day rat study is required (see data gaps in Section 2). Furthermore, although this compound was identified at a very low proportion in the primary crop and was not detected in the residue field trials on the crops under consideration, data are available that give the actual occurrence of CCIM in tomato processed commodities. Quantifiable residues of this compound were observed in tomato juice (0.02 mg/kg), tomato paste (0.02–0.05 mg/kg) and tomato ketchup (0.01–0.03 mg/kg). Therefore, CCIM has to be considered relevant for the consumer risk assessment and its inclusion in a separate residue definition for processed commodities is proposed. Thus the finalisation of the residue definition for processed commodities is pending the outcome of the requested toxicological data on CCIM. Furthermore, since CCIM was found to be more acutely toxic than cyazofamid (see Section 2), a data gap was identified to address the occurrence of CCIM in cooked vegetables (courgettes).

Although not triggered according to the representative uses, ruminant and poultry metabolism studies were conducted at a dosing rate of 10 mg/kg diet and total residues were shown to be below 0.01 mg/kg in all matrices except in milk, liver and kidney (up to 0.05 mg eq/kg, 0.125 mg eq/kg and 0.1 mg eq/kg, respectively). The parent compound was extensively degraded into numerous minor metabolites and accounted only for a level of < 5% TRR. CCBA (free and cysteine conjugates) was identified as a predominant compound of the total residues in milk (42% TRR), kidney (70% TRR), muscle (24% TRR) and in fat (57% TRR). In muscle and fat and besides the CCBA conjugates, CCIM was also identified predominantly in these matrices (up to 27% TRR and 33% TRR, respectively). In liver, CCIM-AM and a mixture of conjugates of CHCN and a minor unidentified metabolite were

identified each at a level of 12% TRR. Since these studies clearly indicate that residues are not expected in animal matrices based on the calculated dietary burden, EFSA proposes for monitoring and risk assessment to set the residue definition by default as cyazofamid only. No MRLs are required.

It is noted that the proposed residue definition for monitoring and risk assessment for primary crops has not been changed compared to the residue definition proposed in the framework of the review of the existing maximum residue levels (MRLs) for cyazofamid (EFSA, 2012) but has been extended to all categories of crops considering the additional metabolism study on leafy crops submitted for the renewal of the approval of cyazofamid. Since the residue definition for processed commodities cannot be finalised with regard to CCIM in view of the outstanding data regarding the toxicity profile of this compound, it is not excluded that the consumer dietary risk assessment may have to be revised accordingly. Finally, a livestock exposure assessment was also not triggered based on the European authorised uses and the toxicological reference values for cyazofamid remain unchanged. The established MRLs under Article 12 of Regulation (EC) No 396/2005[3] may therefore need to be revised pending upon the outcome of the outstanding toxicological data on CCIM metabolite.

The consumer dietary risk assessment was performed with revision 2 of the EFSA Pesticides Residues Intake Model (PRIMo). No long-term intake concern was identified (TMDI < 1% ADI, WHO Cluster diet B). No short-term intake calculation was conducted as an ARfD was not allocated for cyazofamid. The consumer exposure assessment cannot be concluded on considering the outstanding data on the toxicity profile of CCIM and the finalisation of the residue definition for processed commodities.

Since all the crops under consideration may be visited by honey bees for pollen and/or nectar collection and considering that application of cyazofamid on the representative crops can take place at flowering, a data gap was identified for the determination of the residues in pollen and bee products for human consumption resulting from residues taken up by honeybees from crops at blossom.

4. Environmental fate and behaviour

Cyazofamid was discussed at the Pesticides Peer Review Expert's teleconference 126 in February 2016.

The rates of dissipation and degradation in the environmental matrices investigated were estimated using FOCUS (2006) kinetics guidance. In soil laboratory incubations under aerobic conditions in the dark, cyazofamid exhibited low persistence, forming the major (> 10% applied radioactivity (AR)) CCIM (max. 31% AR), CCIM-AM (max. 14% AR) and CTCA (max. 21% AR), which exhibited low to moderate, low to high and moderate to high persistence, respectively. Mineralisation of the phenyl and imidazole ring ^{14}C radiolabels to carbon dioxide accounted for 12–14% AR after 45–59 days. The formation of unextractable residues (not extracted by acetonitrile/water followed by sodium chloride solution) for these radiolabels accounted for 48–64% AR at these times. In an anaerobic soil incubation, the route and rate of degradation of cyazofamid were comparable to that which occurred in aerobic incubations. In a laboratory air-dried soil photolysis experiment the major transformation product CCBA (max. 38–54% AR) was identified in both the light exposed and dark control samples. For the representative uses being assessed, prolonged periods of dry topsoil would not be anticipated, as these crops would all require irrigation in dry periods. So for the representative uses, further assessment of CCBA is considered unnecessary. For other uses where dry soil conditions might be anticipated, additional information to complete exposure assessments for CCBA may be necessary. Cyazofamid exhibited low mobility in soil. CTCA and CCIM exhibited medium to low soil mobility and CCIM-AM exhibited low to slight soil mobility. It was concluded that the adsorption of all these compounds was not pH dependent. The dossier contains no information from field dissipation studies. Consequently, the available exposure assessment has been completed using the information from just laboratory investigations. Field dissipation and/or degradation time values (or field residue levels should the derivation of reliable kinetics be not possible) for CTCA and CCIM-AM should have been made available according to the data requirements. As such data were not available; this has been identified as a data gap (see Section 7).

In laboratory incubations in dark aerobic natural sediment water systems, cyazofamid exhibited moderate persistence, forming the major metabolites CCIM (max. 28% AR in water and 19% AR in

[3] Regulation (EC) No 396/2005 of the European 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.

sediment, exhibiting moderate persistence), CCIM-AM (max. 11% AR as sum of both water and sediment, exhibiting moderate persistence) and CTCA (max. 8% AR in water and 22% max. in sediment, still increasing at study end that also exhibited moderate persistence). The unextractable sediment fraction (not extracted by acetonitrile/water) was a sink for the phenyl and imidazole ring ^{14}C radiolabels, accounting for 45–46% AR at study end (100 days). Mineralisation of these radiolabels accounted for only 0.6–3.2% AR at the end of the study. The rate of decline of cyazofamid in a laboratory sterile aqueous photolysis experiment was more rapid than occurred in the aerobic sediment water incubations. The major transformation products identified were CCIM (max. 40% AR), CCTS (max. 38% AR), HTID (max. 18% AR), *p*-toluamide (max. 12% AR) and CDTS (max. 10% AR). The necessary surface water and sediment exposure assessments (predicted environmental concentrations (PEC) calculations) were carried out for the metabolites/phototransformation products CCIM, CCIM-AM, CTCA, CCTS, CDTS, HTID and *p*-toluamide, using the FOCUS (FOCUS, 2001) step 1 and step 2 approach (version 2.1 of the Steps 1–2 in FOCUS calculator). For the active substance cyazofamid, appropriate step 3 (FOCUS, 2001) simulations were available.[4] For the phototransformation product CDTS, step 3 results for the active substance precursor were used to calculate exposure assessments for it, considered equivalent to a step 3 assessment.

The necessary groundwater exposure assessments were appropriately carried out using FOCUS (FOCUS, 2009) scenarios and the models PEARL 4.4.4 and PELMO 5.5.3[5] for the active substance cyazofamid and its soil transformation products CCIM, CCIM-AM and CTCA. The potential for groundwater exposure from the representative uses by cyazofamid and these three transformation products above the parametric drinking water limit of 0.1 μg/L was concluded to be low in geoclimatic situations that are represented by all nine FOCUS groundwater scenarios.

The applicant did not provide appropriate information to address the effect of water treatments processes on the nature of the residues that might be present in surface water, when surface water is abstracted for drinking water. This has led to the identification of a data gap (see Section 7) and results in the consumer risk assessment not being finalised (see Section 9).

The PEC in soil, surface water, sediment and groundwater covering the representative uses assessed can be found in Appendix A of this conclusion.

5. Ecotoxicology

The risk assessment was based on the following documents: European Commission (2002b,c), SETAC (2001), EFSA (2009), EFSA PPR Panel (2013) and EFSA (2013). According to Regulation (EU) No. 283/2013[6], data should be provided regarding the acute and chronic toxicity to honeybees and data to address the development of honeybee brood and larvae. As the European Commission (2002b) does not provide a risk assessment scheme which is able to use the chronic toxicity data for adult honeybees and the honeybee brood, when performing the risk assessment according to European Commission (2002b), the risk to adult honeybees from chronic toxicity and the risk to bee brood, could not be finalised due to the lack of a risk assessment scheme. Therefore, the EFSA (2013) was used for risk assessment in order to reach a conclusion for the representative uses.

Cyazofamid was discussed at the Pesticide Peer Review Experts' Meeting 142 in February 2016. A second expert meeting to discuss the risk assessment for non-target arthropods was held in May 2020.

No separate risk assessment was presented for field and protected uses on tomato and cucurbits. Therefore, the present evaluation is focused on the worst case (field uses).

As mentioned in Section 2, the relevance of some individual impurities in comparison with the toxicological profile of the parent compound has not been fully addressed (data gap).

Based on the available data and risk assessment, a low acute and chronic risk via dietary exposure to **birds** and **wild mammals** was concluded for all representative uses of cyazofamid. A low risk was also concluded from secondary poisoning and from exposure via contaminated water.

A low risk to all **aquatic organisms** was concluded for all representative uses of cyazofamid by using PECsw estimated with FOCUS step 1–3. Based on the available data, a low risk was also concluded for the metabolites CCIM, CCIM-AM, CTCA, CCTS and HTID. No experimental toxicity data were available for the metabolites p-toluamide and CDTS. The screening assessment carried out

[4] Simulations correctly utilised the agreed Q10 of 2.58 (following EFSA, 2008) and Walker equation coefficient of 0.7.
[5] Simulations correctly utilised the agreed Q10 of 2.58 (following EFSA, 2007) and Walker equation coefficient of 0.7.
[6] Regulation (EU) No 283/2013 of the European Parliament and of the Council of 1 March 2013 setting out the data requirements for active substances in accordance with Regulation (EC) No 1107/2009 concerning the placing of plant protection products on the market. OJ L 93, 3.4.2013, p. 1–84.

considering these metabolites 10 times more toxic than the parent was sufficient to conclude a low risk for all representative uses.

The risk assessment to bees was performed by EFSA in accordance with EFSA (2013). Based on the available acute and chronic data, a low risk to adult **honeybees** could be concluded at the screening level for all representative uses. No standard laboratory data were available for estimating the toxicity of cyazofamid to honeybee larvae. However, a higher tier study (tunnel test) was performed in accordance with the OECD 75 guideline (OECD, 2007). The test was carried out with an application of 256 g cyazofamid/ha (close to 3x single application rate according to the current GAP) on *Phacelia*. This is regarded as acceptable since the six applications of cyazofamid foreseen for the representative uses are likely to be performed in two blocks of maximum three applications each. Brood termination rate and the foraging activity were significantly decreased with respect to the control. A slight (non-significant) decrease was also seen for the brood index. The brood compensation index was comparable to the control, giving some indications that the colonies could be able to recover from temporary effect of the test item. However, the number of observations and the length of the study are considered insufficient for concluding a low risk. A data gap is therefore identified.

No assessment was available for sublethal effects (i.e. HPG) (data gap). No assessment for accumulative effects was available. No information was available regarding metabolites occurring in pollen and nectar (data gap).

A low acute and chronic risk to honeybees was concluded on the basis of the screening assessment for exposure via residues in guttation fluid and surface water. A high margin of safety (three orders of magnitude) was identified. No data were submitted to estimate cyazofamid concentration in puddle water. However, a low risk was also concluded for exposure via residues in puddle water, as the concentration needed to trigger a high risk would have to be three orders of magnitude higher than the solubility limit of cyazofamid. Due to the lack of endpoint for larvae, no risk assessment could be performed for exposure via residues in contaminated water.

A tunnel test study similar to the one performed with honeybees was also available for **bumblebees**. None of the measured endpoint showed appreciable differences between the treated colonies and the controls. However, the number of observations and the length of the study are considered insufficient for concluding a low risk. Furthermore, it was noted that reservoirs of sucrose solution and pollen were made available to the colonies before the exposure phase. It is unclear how this could have influenced the foraging behaviour of the bees, and the consequent exposure to the active substance.

No data were available to perform a risk assessment for solitary bees.

Regarding the risk assessment for **non-target terrestrial arthropods,** standard and extended laboratory data were available for several species. These studies were performed with cyazofamid, the representative product (IKF-916 160SC-N) or the representative product used in the previous EU assessment (IKF-916 400 SC and adjuvant). The experts at the meeting discussed and agreed the scientific validity of the available studies (Pesticides Peer Review TC 14[7]). Several studies were considered not to be reliable as the control performance was not within the expected range or criteria specified in the test guidelines were not fulfilled. It was also discussed whether the data for the representative product used in the previous EU assessment (IKF-916 400 SC and adjuvant) were comparable to the representative formulation currently under assessment (IKF-916 160SC-N). However, as some of the key studies needed for such comparison were not deemed as reliable and those studies which were reliable were not performed to comparable methodologies, it was agreed that no conclusion could be reached (Pesticides Peer Review TC 14[8]).

The risk assessment for non-target arthropods encompasses several steps and an overall weight-of-evidence assessment. All aspects of the risk assessment were discussed in detail during the experts meeting. Owing to the lack of reliable toxicity data with either cyazofamid or representative formulation (IKF-916 160SC-N), no tier 1 or tier 2 risk assessment could be performed for one of the standard test species (*Typhlodromus pyri*). The data for the other tested species (*Aphidius rhopalosiphi, Chrysoperla carnea and Coccinella septempunctata*) indicated a low risk (Pesticides Peer Review TC 14[9]).

[7] Point 1 of the discussion.
[8] Point 2 of the discussion.
[9] Point 3 of the discussion.

A field study with predatory mites was available and proposed to be used for a higher tier in-field risk assessment. The study was discussed at the meeting (Pesticides Peer Review TC 14[10]). The experts agreed that the study was unreliable and could not be used to draw conclusions on the recovery of non-target arthropods as the lack of statistical significance was owing to a decrease in the size of the control population and not recovery of the population of mites in the treatment plots. Furthermore, the experts raised concerns regarding the lack of detected effects in the plots treated with reference item which further questions the sensitivity of the test system to be able to properly assess the effects of the test item. No further refinements were available for the in-field risk assessment.

No data were available to perform a higher tier off-field risk assessment. Furthermore, owing to the lack of reliable tier 1 and tier 2 data for *Typhlodromus pyri*, it was not possible to quantify the mitigation needed to conclude a low off-field risk (Pesticides Peer Review TC 14[11]).

The experts at the meeting also constructed a weight-of-evidence assessment putting together all of the available evidence to assess whether a low risk to non-target arthropods could be concluded from either the representative formulation (IKF-916 160SC-N) or from cyazofamid. Details of the evidence and the integration of such evidence can be found in the meeting report (Pesticides Peer Review TC 14[12]). Overall, all the experts agreed that there was insufficient evidence to conclude a low risk to non-target arthropods from either the representative formulation (IKF-916 160SC-N) or from cyazofamid. Therefore, a data gap is identified for further data on predatory mites to address both the in-field and off-field risk to non-target arthropods (relevant to the representative uses to potatoes, tomatoes and cucurbits grown in the field). This also leads to an assessment not finalised for these uses.

It is not clear whether the representative uses to tomatoes and cucurbits in glasshouses are restricted to permanent greenhouses. Owing to the lack of exposure, a low risk to non-target arthropods would be concluded for applications made in permanent greenhouses. For other types of structures, exposure to non-target arthropods is expected and therefore the above data gap and assessment not finalised are relevant for the representative uses to tomatoes and cucurbits grown in protected structures other than permanent greenhouses.

Toxicity data on **earthworms** and other **soil macro-organisms** were available for cyazofamid and the metabolite CTCA. Based on these data, a low risk could be concluded for all representative uses for cyazofamid and the metabolite CTCA. No data were available for the metabolites CCIM-AM and CCIM. Therefore, a screening risk assessment was carried out assuming the metabolites as 10 times more toxic than the parent. A low risk to both earthworms and other soil macro-organisms was concluded for CCIM-AM (all representative uses of cyazofamid) and for CCIM (uses on tomatoes and cucurbits). For CCIM, a low risk to earthworms could not be demonstrated for the representative use of cyazofamid on potatoes (data gap).

Toxicity data on **soil microorganisms** were available for the representative formulation of cyazofamid and the metabolite CTCA. Based on these data, a low risk could be concluded for all representative uses for cyazofamid and the metabolite CTCA. No data were available for the metabolites CCIM-AM and CCIM (data gap); however, it is likely that these metabolites were formed in the study with the representative formulation.

A low risk to **non-target terrestrial plants** and **biological methods for sewage treatment** was concluded for all representative uses.

For the ecotoxicological assessments, no other studies were available to address the potential endocrine activity of cyazofamid. Pending on the outcome of the data gap in Section 2, further ecotoxicological tests might be necessary to address the potential endocrine-disrupting properties of cyazofamid.

[10] Point 4 of the discussion.
[11] Point 5 of the discussion.
[12] Point 6 of the discussion.

6. Overview of the risk assessment of compounds listed in residue definitions triggering assessment of effects data for the environmental compartments (Tables 1–4)

Table 1: Soil

Compound (name and/or code)	Persistence	Ecotoxicology
Cyazofamid	Low persistence Biphasic kinetics DT_{50} 3.3–5 days (DT_{90} 16–35 days, 20°C 40–45% MWHC)	Low risk to soil organisms
CCIM	Low to moderate persistence Single first-order and biphasic kinetics DT_{50} 1–10 days (DT_{90} 10–64 days, 20°C 45% MWHC)	Data gap
CCIM-AM	Low to high persistence Single first-order and biphasic kinetics DT_{50} 2–18 days (DT_{90} 24–563 days, 20°C 45% MWHC)	Data gap
CTCA	Moderate to high persistence Single first-order and biphasic kinetics DT_{50} 4.3–339 days (DT_{90} 69–1130 days, 20°C 45% MWHC)	Low risk to soil organisms

Table 2: Groundwater

Compound (name and/or code)	Mobility in soil	> 0.1 µg/L at 1 m depth for the representative uses[(a)]	Pesticidal activity	Toxicological relevance	Ecotoxicology
Cyazofamid	Low mobility K_{Foc} 657–1,444 mL/g	No	Yes	Yes	Low risk to aquatic organisms living in surface water
CCIM	Medium to low mobility K_{Foc} 333–1,651 mL/g	No	Assessment not triggered	Assessment not triggered	Low risk to aquatic organisms living in surface water
CCIM-AM	Low to slight mobility K_{Foc} 1,513–2,136 mL/g	No	Assessment not triggered	Assessment not triggered	Low risk to aquatic organisms living in surface water
CTCA	Medium to low mobility K_{Foc} 321–1,138 mL/g	No	Assessment not triggered	Assessment not triggered	Low risk to aquatic organisms living in surface water

(a): At least one FOCUS scenario or relevant lysimeter.

Table 3: Surface water and sediment

Compound (name and/or code)	Ecotoxicology
Cyazofamid	Low risk to aquatic organisms
CCIM	Low risk to aquatic organisms
CCIM-AM	Low risk to aquatic organisms
CTCA	Low risk to aquatic organisms
CCTS	Low risk to aquatic organisms
CDTS	Low risk to aquatic organisms
HTID	Low risk to aquatic organisms
p-toluamide	Low risk to aquatic organisms

Table 4: Air

Compound (name and/or code)	Toxicology
Cyazofamid	Rat inhalation LC_{50} > 5.5 mg/L air (4 h exposure, whole-body), no classification required

7. Data gaps

This is a list of data gaps identified during the peer review process, including those areas in which a study may have been made available during the peer review process but not considered for procedural reasons (without prejudice to the provisions of Article 56 of Regulation (EC) No 1107/2009 concerning information on potentially harmful effects).

- Updated technical specification supported by data (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 1).
- Method for the determination of CCIM residues in soil (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Sections 1 and 5).
- Confirmatory method for the determination of cyazofamid residues in surface water and for ILV for the method for residues in drinking water (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 1).
- Analytical method for the determination of residues of cyazofamid in air having an LOQ of at least 14 $\mu g/m^3$ (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Sections 1 and 2).
- Method of analysis of cyazofamid residues in body fluids and tissues (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 1).
- Additional validation data for the residue method in processed commodities (relevant for representative use in tomato; submission date proposed by the applicant: unknown; see Sections 1 and 3).
- Photogenotoxicity testing (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- A comparative *in vitro* metabolism study (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- Genotoxicity potential of the metabolite CCIM should be fully addressed by providing a mammalian cell mutation assay, an *in vitro* mutation test using mouse lymphoma L518Y cells and a repeated dose toxicity study to conclude on the toxicological relevance of CCIM (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Sections 2 and 3).
- Toxicological relevance of individual impurities present in the technical specifications in comparison with the toxicity profile of the parent compound (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Sections 2 and 5).
- Further investigations of the potential endocrine-disrupting properties of cyazofamid, according to the OECD Conceptual Framework (OECD, 2012) and the EFSA Scientific Opinion on the hazard assessment of endocrine disruptors (EFSA Scientific Committee, 2013) (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2 and 5).
- Eight residue trials on cucumber compliant with the southern outdoor GAP (relevant for the representative uses evaluated on cucurbits, edible peel; submission date proposed by the applicant: unknown; see Section 3).
- Four additional residue trials on melon compliant with the glasshouse GAP and one additional residue trial on melon compliant with the southern outdoor GAP (relevant for the representative uses evaluated on cucurbits, inedible peel; submission date proposed by the applicant: unknown; see Section 3).
- A storage stability study in high water commodities (cucurbits) and analysing for cyazofamid and CCIM residues (relevant for cucurbits; submission date proposed by the applicant: unknown; see Section 3).
- The magnitude of CCIM residues in cooked vegetables (courgettes) (relevant for the representative uses evaluated on cucurbits, edible peel; submission date proposed by the applicant: unknown; see Section 3).
- Determination of the residues in pollen and bee products for human consumption resulting from residues taken up by honeybees from crops at blossom (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).
- A more detailed assessment of the literature review for cyazofamid and its relevant metabolites in the residue section, dealing with side effects on health and published within 10 years before

the date of submission of the dossier, to be conducted and reported in accordance with EFSA guidance on the submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (EFSA, 2011) (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown, see Section 3).

- Field dissipation and or degradation time values (or field residue levels should the derivation of reliable kinetics be not possible) for CTCA and CCIM-AM should be available according to the data requirements and such data are not available (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 4).
- Information to address the effect of water treatment processes on the nature of residues present in surface water when surface water is abstracted for drinking water was not available. Probably in the first instance, a consideration of the processes of ozonation and chlorination would appear appropriate. If an argumentation is made that concentrations at the point of abstraction for drinking water purposes will be low, this argumentation should cover metabolites predicted to be in surface water, as well as the active substance. Should this consideration indicate novel compounds might be expected to be formed from water treatment, the risk to human or animal health through the consumption of drinking water containing them would need to be addressed (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Sections 3 and 4).
- Based on EFSA (2013), information to address the chronic risk to honeybee larvae (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).
- Based on EFSA (2013), suitable data to address the risk of sublethal effects (i.e. HPG development effects) to honeybees (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).
- Information to assess the risk to honeybees due to plant metabolites occurring in pollen and nectar (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).
- Further information to address the risk to predatory mites (relevant for all representative uses evaluated except for the uses to tomatoes and cucurbits in permanent greenhouses; submission date proposed by the applicant: April–May 2016; see Section 5).
- Further information to address the risk to earthworms for the metabolite CCIM (relevant for the representative use on potatoes; submission date proposed by the applicant: unknown; see Section 5).
- Information to assess the toxicity of the metabolites CCIM and CCIM-AM to soil microorganisms (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).

8. Particular conditions proposed to be taken into account to manage the risk(s) identified

No particular conditions are proposed for the representative uses evaluated.

9. Concerns

9.1. Issues that could not be finalised

An issue is listed as 'could not be finalised' if there is not enough information available to perform an assessment, even at the lowest tier level, for the representative uses in line with the uniform principles in accordance with Article 29(6) of Regulation (EC) No 1107/2009 and as set out in Commission Regulation (EU) No 546/2011[13] and if the issue is of such importance that it could, when finalised, become a concern (which would also be listed as a critical area of concern if it is of relevance to all representative uses).

[13] 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 issue is also listed as 'could not be finalised' if the available information is considered insufficient to conclude on whether the active substance can be expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009.

1) The consumer exposure assessment cannot be concluded on considering the identified data gaps, the outstanding data on the toxicity profile of CCIM and the finalisation of the residue definition for processed commodities (see Section 3).
2) The consumer risk assessment from consumption of drinking water could not be finalised whilst the nature of residues in drinking water following water treatment had not been addressed (see Sections 3 and 4).
3) The risk assessment to non-target arthropods could not be finalised for, the field uses to potato, tomato and cucurbits, and the uses to tomato and cucurbits in protected structures other than permanent greenhouses.

9.2. Critical areas of concern

An issue is listed as a critical area of concern if there is enough information available to perform an assessment for the representative uses in line with the uniform principles in accordance with Article 29(6) of Regulation (EC) No 1107/2009 and as set out in Commission Regulation (EU) No 546/2011, and if this assessment does not permit the conclusion that, for at least one of the representative uses, it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater, or any unacceptable influence on the environment.

An issue is also listed as a critical area of concern if the assessment at a higher tier level could not be finalised due to lack of information, and if the assessment performed at the lower tier level does not permit the conclusion that, for at least one of the representative uses, it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater, or any unacceptable influence on the environment.

An issue is also listed as a critical area of concern if, in the light of current scientific and technical knowledge using guidance documents available at the time of application, the active substance is not expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009.

9.3. Overview of the concerns identified for each representative use considered (Table 5)

Table 5: Overview of concerns

Representative use		Potatoes	Tomato field/ protected	Cucurbits field/ protected
Operator risk	Risk identified			
	Assessment not finalised			
Worker risk	Risk identified			
	Assessment not finalised			
Resident/bystander risk	Risk identified			
	Assessment not finalised			
Consumer risk	Risk identified			
	Assessment not finalised	X[2]	X[1,2]	X[1,2]
Risk to wild non-target terrestrial vertebrates	Risk identified			
	Assessment not finalised			
Risk to wild non-target terrestrial organisms other than vertebrates	Risk identified			
	Assessment not finalised	X[3(c)]	X[3(c)]	X[3(c)]
Risk to aquatic organisms	Risk identified			
	Assessment not finalised			

Representative use		Potatoes	Tomato field/ protected	Cucurbits field/ protected
Groundwater exposure to active substance	Legal parametric value breached			
	Assessment not finalised			
Groundwater exposure to metabolites	Legal parametric value breached[(a)]			
	Parametric value of 10 μg/L[(b)] breached			
	Assessment not finalised			

Columns are grey if no safe use can be identified. The superscript numbers relate to the numbered points indicated in Sections 9.1 and 9.2. Where there is no superscript number, see Sections 2–6 for further information.

(a): When the consideration for classification made in the context of this evaluation under Regulation (EC) No 1107/2009 is confirmed under Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008.

(b): Value for non-relevant metabolites prescribed in SANCO/221/2000-rev. 10 final, European Commission (2003).

(c): It is not clear whether the representative uses to tomatoes and cucurbits in glasshouses are restricted to permanent greenhouses. Owing to the lack of exposure, a low risk to non-target arthropods would be concluded for applications made in permanent greenhouses.

References

ECHA (European Chemicals Agency), 2015. Guidance on the Application of the CLP Criteria; Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures. Version 4.1, June 2015. Reference: ECHA-15-G-05-EN; ISBN: 978-92-9247-413-3. Available online: http://echa.europa.eu/documents/10162/13562/clp_en.pdf

EFSA (European Food Safety Authority), 2008. Opinion on a request from EFSA related to the default Q10 value used to describe the temperature effect on transformation rates of pesticides in soil. EFSA Journal 2008;6(1):622, 32 pp. https://doi.org/10.2903/j.efsa.2008.622

EFSA (European Food Safety Authority), 2009. Guidance on Risk Assessment for Birds and Mammals on request from EFSA. EFSA Journal 2009;7(12):1438, 358 pp. https://doi.org/10.2903/j.efsa.2009.1438

EFSA (European Food Safety Authority), 2011. Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009. EFSA Journal 2011;9(2):2092, 49 pp. https://doi.org/10.2903/j.efsa.2011.2092

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), 2013. EFSA Guidance Document on the risk assessment of plant protection products on bees (*Apis mellifera, Bombus* spp. and solitary bees). EFSA Journal 2013;11(7):3295, 268 pp. https://doi.org/10.2903/j.efsa.2013.3295

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

EFSA (European Food Safety Authority), 2020. Peer review report to the conclusion regarding the peer review of the pesticide risk assessment of the active substance cyazofamid. Available online: www.efsa.europa.eu

EFSA PPR Panel (EFSA Panel on Plant Protection Products and their Residues), 2012. Guidance on dermal absorption. EFSA Journal 2012;10(4):2665, 30 pp. https://doi.org/10.2903/j.efsa.2012.2665

EFSA PPR Panel (EFSA Panel on Plant Protection Products and their Residues), 2013. Guidance on tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters. EFSA Journal 2013;11(7):3290, 186 pp. https://doi.org/10.2903/j.efsa.2013.3290

EFSA Scientific Committee, 2013. Scientific Opinion on the hazard assessment of endocrine disruptors: scientific criteria for identification of endocrine disruptors and appropriateness of existing test methods for assessing effects mediated by these substances on human health and the environment. EFSA Journal 2013;11(3):3132, 84 pp. https://doi.org/10.2903/j.efsa.2013.3132

European Commission, 2000a. Residues: guidance for generating and reporting methods of analysis in support of pre-registration data requirements for Annex II (Part A, Section 4) and Annex III (Part A, Section 5) of Directive 91/414. SANCO/3029/99-rev. 4, 11 July 2000.

European Commission, 2000b. Technical material and preparations: guidance for generating and reporting methods of analysis in support of pre- and post-registration data requirements for Annex II (Part A, Section 4) and Annex III (Part A, Section 5) of Directive 91/414. SANCO/3030/99-rev. 4, 11 July 2000.

European Commission, 2002a. Review Report on the active substance cyazofamid. SANCO/10379/2002-final, 27 November 2002.

European Commission, 2002b. Guidance Document on Terrestrial Ecotoxicology Under Council Directive 91/414/EEC. SANCO/10329/2002-rev. 2 final, 17 October 2002.

European Commission, 2002c. Guidance Document on Aquatic Ecotoxicology Under Council Directive 91/414/EEC. SANCO/3268/2001-rev. 4 final, 17 October 2002.
European Commission, 2003. Guidance Document on Assessment of the Relevance of Metabolites in Groundwater of Substances Regulated under Council Directive 91/414/EEC. SANCO/221/2000-rev. 10 final, 25 February 2003.
European Commission, 2010. Guidance Document on residue analytical methods. SANCO/825/00-rev. 8.1, 16 November 2010.
European Commission, 2012. Guidance document on the assessment of the equivalence of technical materials of substances regulated under Regulation (EC) No 1107/2009. SANCO/10597/2003-rev. 10.1, 13 July 2012.
European Commission, 2013. Guidance document on data requirements on efficacy for the dossier to be submitted for the approval of new active substances contained in plant protection products. SANCO/10054/2013-rev. 3, 11 July 2013.
European Commission, 2015. Guidelines on comparability, extrapolation, group tolerances and data requirements for setting MRLs. SANCO 7525/VI/95-rev. 10.1. December 2015. pp. 1–56.
FOCUS (Forum for the Co-ordination of Pesticide Fate Models and their Use), 2001. FOCUS surface water scenarios in the EU evaluation process under 91/414/EEC. Report of the FOCUS Working Group on Surface Water Scenarios. EC Document Reference SANCO/4802/2001-rev. 2, 245 pp., as updated by Generic guidance for FOCUS surface water scenarios, v. 1.1, March 2012.
FOCUS (Forum for the Co-ordination of Pesticide Fate Models and their Use), 2006. Guidance document on estimating persistence and degradation kinetics from environmental fate studies on pesticides in EU Registration Report of the FOCUS Work Group on Degradation Kinetics. EC Document Reference SANCO/10058/2005-v. 2.0, 434 pp.
FOCUS (Forum for the Co-ordination of Pesticide Fate Models and their Use), 2009. Assessing potential for movement of active substances and their metabolites to ground water in the EU. Report of the FOCUS Workgroup. EC Document Reference SANCO/13144/2010-v. 1, 604 pp., as outlined in Generic guidance for tier 1 FOCUS groundwater assessment, v. 2.0, January 2011.
France, 2015. Renewal Assessment Report (RAR) on the active substance cyazofamid prepared by the rapporteur Member State France in the framework of Regulation (EU) No 844/2012, June 2015. Available online: www.efsa.europa.eu
France, 2016. Revised Renewal Assessment Report (RAR) on cyazofamid prepared by the rapporteur Member State France in the framework of Regulation (EU) No 844/2012, March 2016. Available online: www.efsa.europa.eu
France, 2020. Revised Renewal Assessment Report (RAR) on cyazofamid prepared by the rapporteur Member State France in the framework of Regulation (EU) No 844/2012, May 2020. Available online: www.efsa.europa.eu
JMPR (Joint Meeting on Pesticide Residues), 2004. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues, Rome, Italy, 20–29 September 2004, 383 pp.
JMPR (Joint Meeting on Pesticide Residues), 2007. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues, Geneva, Switzerland, 18–27 September 2007, 164 pp.
JMPR (Joint Meeting on Pesticide Residues), 2015. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues, Geneva, Switzerland, 15–24 September 2015, 103 pp.
OECD (Organisation for Economic Co-operation and Development), 2007. Guidance document on the honey bee (*Apis mellifera l.*) brood test under semi-field conditions. OECD Series on Testing and Assessment, No. 75, OECD Publishing, Paris. ENV/JM/MONO(2007)22, 27 pp.
OECD (Organisation for Economic Co-operation and Development), 2011. OECD MRL calculator: spreadsheet for single data set and spreadsheet for multiple data set, 2 March 2011. In: Pesticide Publications/Publications on Pesticide Residues.
OECD (Organisation for Economic Co-operation and Development), 2012. Series on Testing and Assessment: Guidance document on standardised test guidelines for evaluating chemicals for endocrine disruption, No. 150, OECD Publishing, Paris. ENV/JM/MONO(2012)22, 524 pp.
SETAC (Society of Environmental Toxicology and Chemistry), 2001. Guidance document on regulatory testing and risk assessment procedures for plant protection products with non-target arthropods. ESCORT 2.

Abbreviations

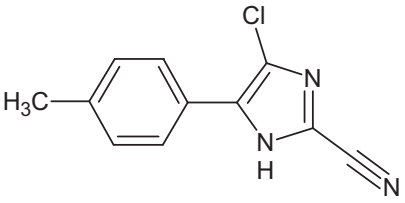
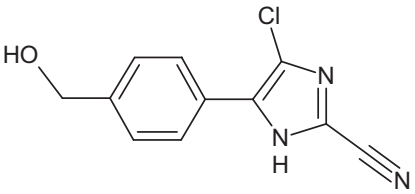
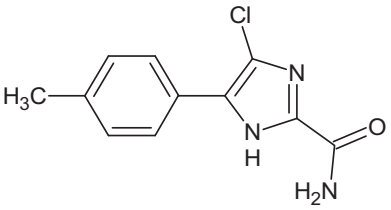
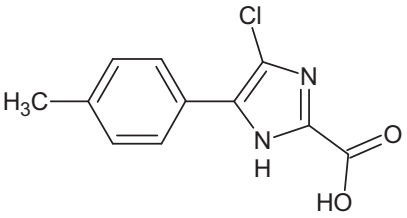
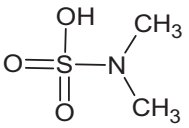
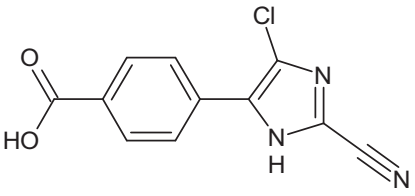
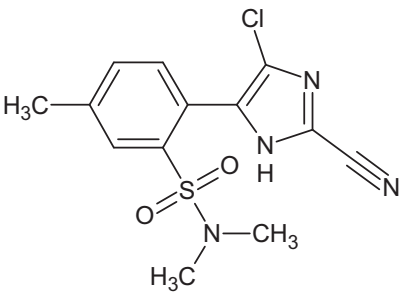
1/*n*	slope of Freundlich isotherm
λ	wavelength
ε	decadic molar extinction coefficient
a.s.	active substance
ADI	acceptable daily intake
ARfD	Acute Reference Dose

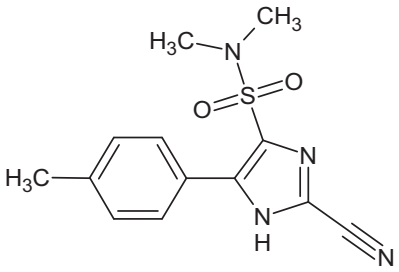
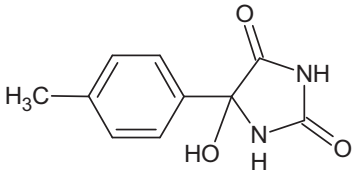
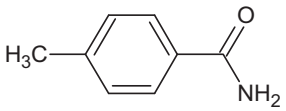
AOEL	acceptable operator exposure level
AR	applied radioactivity
ARfD	acute reference dose
bw	body weight
CAS	Chemical Abstracts Service
DAR	draft assessment report
DAT	days after treatment
DM	dry matter
DT_{50}	period required for 50% dissipation (define method of estimation)
DT_{90}	period required for 90% dissipation (define method of estimation)
ECHA	European Chemicals Agency
EEC	European Economic Community
EUROPOEM	European Predictive Operator Exposure Model
FAO	Food and Agriculture Organization of the United Nations
FOB	functional observation battery
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
GAP	Good Agricultural Practice
HPLC	high-pressure liquid chromatography or high-performance liquid chromatography
HPLC-MS	high-pressure liquid chromatography–mass spectrometry
HPLC-MS/MS	high performance liquid chromatography with tandem mass spectrometry
HPLC-UV	high performance liquid chromatography with ultra violet detector
HQ	hazard quotient
HR	hazard rate
ILV	independent laboratory validation
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
JMPR	Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
K_{Foc}	Freundlich organic carbon adsorption coefficient
LC_{50}	lethal concentration, median
LC-MS	liquid chromatography–mass spectrometry
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LOQ	limit of quantification
MRL	maximum residue level
MS	mass spectrometry
MWHC	maximum water-holding capacity
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NRU	Neutral Red Uptake
OECD	Organisation for Economic Co-operation and Development
Pa	pascal
PEC	predicted environmental concentration
PECsw	predicted environmental concentration in surface water
PHI	preharvest interval
PPE	personal protective equipment
QuEChERS	quick, easy, cheap, effective and safe method
RA	Risk assessment
SC	suspension concentrate
SMILES	simplified molecular-input line-entry system
TMDI	theoretical maximum daily intake
TRR	total radioactive residue
TWA	time-weighted average
UF	uncertainty factor
UV	ultraviolet
WHO	World Health Organization

Appendix A – List of end points for the active substance and the representative formulation

Appendix A can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2020.6232

Appendix B – Used compound codes

Code/trivial name[a]	Chemical name/SMILES notation[b]	Structural formula[b]
CCIM	4-chloro-5-(4-methylphenyl)-1*H*-imidazole-2-carbonitrile Clc2nc(C#N)nc2c1ccc(C)cc1	
CHCN	4-chloro-5-[4-(hydroxymethyl)phenyl]-1*H*-imidazole-2-carbonitrile Clc2nc(C#N)nc2c1ccc(CO)cc1	
CCIM-AM	4-chloro-5-(4-methylphenyl)-1*H*-imidazole-2-carboxamide Clc2nc(nc2c1ccc(C)cc1)C(=O)N	
CTCA	4-chloro-5-(4-methylphenyl)-1*H*-imidazole-2-carboxylic acid Clc2nc(nc2c1ccc(C)cc1)C(O)=O	
DMSA	dimethylsulfamic acid CN(C)S(=O)(=O)O	
CCBA	4-(4-chloro-2-cyano-1*H*-imidazol-5-yl)benzoic acid Clc2nc(C#N)nc2c1ccc(cc1)C(=O)O	
CCTS	2-(4-chloro-2-cyano-1*H*-imidazol-5-yl)-*N*,*N*,5-trimethylbenzenesulfonamide Clc2nc(C#N)nc2c1ccc(C)cc1S(=O)(=O)N(C)C	

Code/trivial name[a]	Chemical name/SMILES notation[b]	Structural formula[b]
CDTS	2-cyano-*N*,*N*-dimethyl-4-(4-methylphenyl)-1*H*-imidazole-5-sulfonamide O=S(=O)(c1nc(C#N)nc1c2ccc(C)cc2)N(C)C	
HTID	5-hydroxy-5-(4-methylphenyl)imidazolidine-2,4-dione OC1(NC(=O)NC1=O)c2ccc(C)cc2	
***p*-toluamide**	4-methylbenzamide Cc1ccc(cc1)C(=O)N	

(a): The compound name in bold is the name used in the conclusion.
(b): ACD/Labs 2015 Release, Advanced Chemistry Development, Inc., Toronto, ON, Canada, www.acdlabs.com, 2015.