CONCLUSION ON PESTICIDES PEER REVIEW

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Peer review of the pesticide risk assessment of the active substance *Trichoderma atroviride* strain AT10

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Abstract

The conclusions of the European Food Safety Authority (EFSA) following the peer review of the initial risk assessments carried out by the competent authority of the rapporteur Member State, France, for the pesticide active substance *Trichoderma atroviride* strain AT10 and the considerations as regards the inclusion of the substance in Annex IV of Regulation (EC) No 396/2005 are reported. The context of the peer review was that required by Regulation (EC) No 1107/2009 of the European Parliament and of the Council. The conclusions were reached on the basis of the evaluation of the representative use of *Trichoderma atroviride* strain AT10 as a fungicide on lettuce (field use). The reliable endpoints, 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: *Trichoderma atroviride* strain AT10, peer review, risk assessment, pesticide, fungicide

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Summary

Trichoderma atroviride strain AT10 is a new active substance for which, in accordance with Article 7 of Regulation (EC) No 1107/2009 of the European Parliament and of the Council, the rapporteur Member State (RMS), France, received an application from Agrotecnologías Naturales S.L. on 30 October 2018 for approval. In addition, the applicant submitted an application for inclusion of the substance in Annex IV of Regulation (EC) No 396/2005. Complying with Article 9 of the Regulation, the completeness of the dossier was checked by the RMS and the date of admissibility of the application was recognised as being 15 February 2019.

An initial evaluation of the dossier on *Trichoderma atroviride* strain AT10 was provided by the RMS in the draft assessment report (DAR), and subsequently, a peer review of the pesticide risk assessment on the RMS evaluation was conducted by EFSA in accordance with Article 12 of Regulation (EC) No 1107/2009. The following conclusions are derived.

The use of *Trichoderma atroviride* strain AT10 by drip irrigation according to the representative use as a fungicide on lettuce, as proposed at EU level results in a sufficient fungicidal efficacy against the target *Sclerotinia* sp. Considering the limited data provided, more detailed consideration will be fully assessed in the context of subsequent applications for products authorisation.

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 the representative formulation.

In the area of mammalian toxicology, the risk assessment for metabolites including peptaibols and 6-pentyl-2H-pyran-2-one (6-pentyl-2-pyrone) from non-dietary exposure could not be finalised due to lack of identification/quantification and toxicological assessment.

In the area of residues, for non-viable residues on lettuce following treatment according to the representative field use lettuce (drip irrigation, up to five applications ($1 \times (5 \times 10^{11})$ CFU/ha + $4 \times (2.5 \times 10^{11})$ CFU/ha); BBCH 10–49), a data gap was identified for qualitative and quantitative information on possible occurrence of metabolites (e.g. peptaibols) of potential health concern, leading to the consumer risk assessment not finalised. Further risk management considerations are required to decide whether *Trichoderma atroviride* strain AT10 can be included into Annex IV of Regulation (EC) No 396/2005.

Satisfactory information was not provided to demonstrate that, under the conditions of the proposed representative use, any secondary metabolites/toxins produced by *Trichoderma atroviride* strain AT10 will not occur in the environmental compartments in concentrations considerably higher than under natural conditions. Consequently, further data on the persistence, transformation and mobility of these compounds may be needed in order to assess the potential level of environmental exposure including the exposure of groundwater.

The risk assessment to non-target organisms: birds, wild mammals, aquatic organisms, non-target soil arthropods, earthworms and other soil macro- and microorganisms could not be finalised.

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Background

Regulation (EC) No 1107/2009 of the European Parliament and of the Council[1] (hereinafter referred to as 'the Regulation') lays down, *inter alia*, the detailed rules as regards the procedure and conditions for approval of active substances. This regulates for the European Food Safety Authority (EFSA) the procedure for organising the consultation of Member States and the applicant(s) for comments on the initial evaluation in the draft assessment report (DAR), provided by the rapporteur Member State (RMS), and the organisation of an expert consultation, where appropriate.

In accordance with Article 12 of the Regulation, EFSA is required to adopt a conclusion on whether an active substance can be expected to meet the approval criteria provided for in Article 4 of the Regulation (also taking into consideration recital (10) of the Regulation) within 120 days from the end of the period provided for the submission of written comments, subject to an extension of 30 days where an expert consultation is necessary, and a further extension of up to 150 days where additional information is required to be submitted by the applicant(s) in accordance with Article 12(3).

Trichoderma atroviride strain AT10 is a new active substance for which, in accordance with Article 7 of the Regulation, the RMS, France (hereinafter referred to as the 'RMS'), received an application from Agrotecnologías Naturales S.L. on 30 October 2018 for approval. In addition, the applicant submitted an application for inclusion of the substance in Annex IV of Regulation (EC) No 396/2005[2]. Complying with Article 9 of the Regulation, the completeness of the dossier was checked by the RMS and the date of admissibility of the application was recognised as being 15 February 2019.

The RMS provided its initial evaluation of the dossier on *Trichoderma atroviride* strain AT10 in the DAR, which was received by EFSA on 18 September 2020 (France, 2020). The peer review was initiated on 28 October 2020 by dispatching the DAR to the Member States and the applicant, Agrotecnologías Naturales S.L., for consultation and comments. EFSA also provided comments. In addition, EFSA conducted a public consultation on the DAR. The comments received were collated by EFSA and 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 12(3) of the Regulation were considered in a telephone conference between EFSA and the RMS on 24 February 2021. 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 there was no need to conduct an expert consultation.

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 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 written consultation on the assessment of additional information, where these took place, were reported in the final column of the evaluation table.

In accordance with Article 12 of the Regulation, EFSA should adopt a conclusion on whether *Trichoderma atroviride* strain AT10 can be expected to meet the approval criteria provided for in Article 4 of the Regulation, taking into consideration recital (10) of the Regulation.

A final consultation on the conclusions arising from the peer review of the risk assessment and on the considerations as regards the inclusion of the substance in Annex IV of Regulation (EC) No 396/2005 took place with Member States via a written procedure in January–February 2022.

This conclusion report summarises the outcome of the peer review of the risk assessment on the active substance and the representative formulation evaluated on the basis of the representative use of *Trichoderma atroviride* strain AT10 as a fungicide on lettuce (field use) as proposed by the applicant. In accordance with Article 12(2) of Regulation (EC) No 1107/2009, risk mitigation options identified in the DAR and considered during the peer review, if any, are presented in the conclusion.

[1] 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.

[2] 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.

Furthermore, this conclusion also addresses the requirement for an assessment by EFSA under Article 12 of Regulation (EC) No 396/2005 provided that the active substance will be approved under Regulation (EC) No 1107/2009 without restrictions affecting the residue assessment. In the event of a non-approval of the active substance or an approval with restrictions that have an impact on the residue assessment, the Annex IV proposal, if any, from this conclusion might no longer be relevant and a new assessment under Article 12 of Regulation (EC) No 396/2005 will be required.

A list of the relevant end points for the active substance and the formulation is provided in Appendix A.

A key supporting document to this conclusion is the peer review report (EFSA, 2022), 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 DAR;
- the reporting table (25 February 2021);
- the evaluation table (11 February 2022);
- the comments received on the assessment of the additional information;
- the comments received on the draft EFSA conclusion.

Given the importance of the DAR, including its revisions (France, 2022), 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 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 identity of the microorganism and the properties of the formulated product

Trichoderma atroviride strain AT10 is a filamentous fungus deposited at the Spanish type culture collection under the accession number CECT 20951. It is a wild-type strain isolated from the soil in Tarragona, Spain.

The representative formulated product for the evaluation was 'TRICOTEN WP', a wettable powder (WP) containing 5×10^{11} CFU/kg *Trichoderma atroviride* strain AT10.

The representative use evaluated comprises field applications by drip irrigation on lettuce, as a fungicide against *Sclerotinia* sp. Full details of the good agricultural practice (GAP) can be found in the list of end points in Appendix A.

Data were submitted to conclude that the use of *Trichoderma atroviride* strain AT10 according to the representative use proposed at EU level results in a sufficient fungicidal efficacy against the target organisms, following the guidance document SANCO/10054/2013 – rev. 3 (European Commission, 2013). Considering the limited data provided, more detailed consideration will be fully assessed in the context of subsequent applications for products authorisation.

A data gap has been identified for a search of the scientific peer-reviewed open literature on the active substance and its relevant metabolites, dealing with side effects on human and animal health focusing on metabolites as well as the environment to support the viability/population dynamics of *Trichoderma atroviride* strain AT10 in natural water and sediment systems and published within the 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) (see Section 9).

Conclusions of the evaluation

1. Identity of the microorganism/biological properties/physical and technical properties and methods of analysis

The following guidance documents were followed in the production of this conclusion (European Commission, 2000,2012; EFSA FEEDAP Panel, 2018).

The microbial pest control agent (MPCA) manufactured is identical with the formulated product, containing min. 1×10^{11} to max. 1×10^{12} CFU/kg *Trichoderma atroviride* strain AT10.

The levels of contaminating microorganisms in commercially produced batches comply with the requirements of SANCO/12116/2012 rev.0 (European Commission, 2012).

Molecular methods are available to distinguish *Trichoderma atroviride* strain AT10 from other strains of the same species. Internal transcribed spacer (ITS) and translation-elongation factor 1 (tef-1) full length sequences obtained by whole genome sequencing (WGS) were used for identification at species level of *Trichoderma atroviride* strain AT10. A specific primer pair was developed to specifically amplify a strain-specific gene. A genotype high resolution melting (HRM) profile and an amplicon of specific length can be used to distinguish *Trichoderma atroviride* strain AT10 from other *Trichoderma atroviride* strains.

There is no evidence of relationships of *Trichoderma atroviride* strain AT10 to known plant, animal or human pathogens.

Trichoderma species have been reported to produce many toxins/secondary metabolites. The *Trichoderma atroviride* strain AT10 was screened for the presence of peptaibols-related non-ribosomal peptide synthetase (NRPS) and polyketide synthase (PKS) clusters, and in addition, the genome of strain AT10 was screened with search translated nucleotide databases (TBLASTN) using a protein query. *Trichoderma atroviride* strain AT10 lacks the capacity to produce anthraquinones, cytochalasin, camptothecin, glio-toxins, sorbicillinoids including trichodimerol, sirodesmin, tricholignans and trichothecenes including harzianum A and trichodermin as well as calonectrins/deoxynivalenols. *Trichoderma atroviride* strain AT10 has the potential for producing two peptaibols, a 19-mer atroviridin-like peptaibol and a short peptaibol like compound. The strain has the capacity to produce 6-pentyl-2H-pyran-2-one (6-pentyl-2-pyrone) and a conidial pigment.

Five batches of the product 'TRICOTEN WP' were analysed for the content of peptaibols and seven peptaibols were found in detectable quantities in the formulation, three of them below the limit of quantification (LOQ). The content of all peptaibols in five batches of the product 'TRICOTEN WP' was below 1 g/kg. To decide on the relevance of the peptaibols found, the determination of their identity is required, and as a consequence, a data gap was identified (See Sections 2 and 8.1). For *Trichoderma atroviride* strain, AT10 indicative data were available on the production of 6-pentyl-2-pyrone. A data gap was identified for the quantification of 6-pentyl-2*H*-pyran-2-one (6-pentyl-2-pyrone) in the MPCA (see Sections 2 and 8.1).

Information on production of potentially toxic metabolites *in situ* was missing.

Trichoderma atroviride strain AT10 was able to grow at temperatures between 15°C and 30°C, the optimum growth conditions were: 22°C and pH 5.0; 25°C and pH 6.0; 30°C and pH 4.0. It was unable to grow at 0°C, 7°C, 37°C and 40°C. It should be noted, however, that the study was not conducted according to GLP; as a consequence, a data gap was identified (see Section 9).

Trichoderma atroviride strain AT10 is susceptible to amphotericin B, voriconazole and caspofungin, and it is resistant to ketoconazole, fluconazole and itraconazole.

The supported shelf-life of the product is 1 year at 4 ± 2°C in the original packaging.

Acceptable methods are available for the determination of the microorganism in the technical material, formulation, for the determination of the content of contaminating microorganisms and for the determination of metabolites.

Residue definitions were not applicable for *Trichoderma atroviride* strain AT10; therefore, post-registration monitoring methods are not needed.

2. Mammalian toxicity

General data

From the **medical data**, no adverse **health effects** have been reported in workers as a result of exposure to *Trichoderma atroviride* strain AT10 during production and handling. There is no evidence that *Trichoderma atroviride* species cause infection in immunocompetent healthy humans. One case of infection with *Trichoderma atroviride* was reported in a severely immunocompromised transplanted patient, due to possible contamination.

Trichoderma atroviride species are not recommended for the **Qualified Presumption of Safety list** (EFSA BIOHAZ Panel, 2020).

Toxicity/Infectivity/Pathogenicity studies

The available methods for testing **dermal sensitisation** are not suitable for testing microorganisms and there are no validated test methods for sensitisation by inhalation. Based on their

characteristics, microorganisms such as *Trichoderma atroviride* strain AT10 may have the potential to provoke sensitising reactions.

No signs of **toxicity, pathogenicity or infectivity** have been detected with the formulated product 'TRICOTEN WP' (containing *T. atroviride* strain AT10) after high dose acute administration by oral, dermal, intraperitoneal or intratracheal routes. The microorganism is rapidly cleared. No skin or eye irritation potential has been identified.

Secondary metabolites/toxins

As described in Section 1, *Trichoderma atroviride* strain AT10 has the genomic capacity to produce different secondary metabolites: genes for peptaibols, 6-pentyl-2-pyrone and a conidial pigment have been identified. No (geno)toxicity testing has been performed on any metabolite. quantitative structure–activity relationship (QSAR) analysis for peptaibols did not reveal any alert for potential adverse effects. However, considering the results of the literature review for other *Trichoderma* species, toxicity of **peptaibols** cannot be excluded and should be further considered pending the identification and quantification of *in situ* production (data gap).

With regard to **6-pentyl-2*H*-pyran-2-one (6-pentyl-2-pyrone)**, it is noted that it is a volatile organic compound (of low concern by diet), which is approved as a food flavouring substance (FL no. 10.031) by Commission Implementing Regulation (EU) No 872/2012[3] adopting the list of flavouring substances provided for by Regulation (EC) No 2232/96. However, considering that the metabolite is potentially involved in the microorganism's mode of action and its production *in situ* is thus plausible, more information is needed to conclude on the toxicity profile of 6-pentyl-2-pyrone by inhalation (data gap). Reports of potential adverse effects including irritation and effects on histamine release in the respiratory tract are available in the published literature (see e.g. Larsen et al., 1998, not included in the DAR; Polizzi et al., 2011).

Trichoderma atroviride strain AT10 has the capacity to produce a **conidial pigment**; however, the exposure to the amount present in the product is not expected to be a concern, considering also the lack of concern from the toxicological studies with the microorganism. Moreover, it is acknowledged that once the conidia germinate the pigment is not expected to be in the environment (see Section 4); therefore, no further data are required for this pigment.

Reference values and non-dietary exposure

For the **microorganism *per se***, the data package is insufficient to derive reference values, nevertheless acceptable daily intake (ADI), acceptable operator exposure level (AOEL) or acute reference dose (ARfD) values are not needed as *Trichoderma atroviride* strain AT10 is considered to be of low toxicological concern. Therefore, exposure considerations are not necessary. In the absence of a quantitative risk assessment, the use of personal protective equipment (PPE) and respiratory protective equipment (RPE) for the operators and workers might be considered to reduce the non-dietary exposure (dermal and inhalation).

Concerning the potential **secondary metabolites**, with specific reference to **peptaibols**, the exposure of operators and bystanders during the representative use on lettuce is considered unlikely due to low volatility combined with low drift from application by drip irrigation. The risk assessment for workers and residents cannot be finalised pending the identification and quantification of peptaibols after *in situ* production. Regarding other secondary metabolites, e.g. **6-pentyl-2*H*-pyran-2-one** (6-pentyl-2-pyrone) (only by inhalation), the risk assessment for operators, workers, residents and bystanders cannot be finalised in the absence of identification/quantification of their levels in the technical product and produced *in situ* by the microorganism after application.

3. Residues

A representative use on lettuce has been proposed for *Trichoderma atroviride* strain AT10. The field use foresees up to five treatments by drip irrigation at growth stages of BBCH 10 up to BBCH 49 with intervals of 10 days. The first application has a maximum application rate of 5×10^{11} CFU/ha, whereby the four subsequent applications are performed at a rate of maximum 2.5×10^{11} CFU/ha.

[3] Commission Implementing Regulation (EU) No 872/2012 of 1 October 2012 adopting the list of flavouring substances provided for by Regulation (EC) No 2232/96 of the European Parliament and of the Council, introducing it in Annex I to Regulation (EC) No 1334/2008 of the European Parliament and of the Council and repealing Commission Regulation (EC) No 1565/2000 and Commission Decision 1999/217/EC. OJ L 267, 2.10.2012, p. 1–161.

At the growth stage of BBCH 49 when the last treatment is performed, leaves of lettuces are already formed, and the typical leaf mass is reached. Notably, *Trichoderma atroviride* strain AT10 is known to produce two peptaibols and it has the capacity to produce 6-pentyl-2*H*-pyran-2-one (6-pentyl-2-pyrone) and a conidial pigment (see Section 1); however, it was not investigated whether these non-viable residues would occur in lettuce following applications in line with the representative use. The toxicological relevance of potentially formed metabolites for humans has been assessed and for some of them (e.g. peptaibols) adverse health effects cannot be excluded (see Section 2).

It is not demonstrated for the representative use on lettuce for *Trichoderma atroviride* strain AT10 and its metabolites that these are not to be expected at harvest.

More specifically, potentially present metabolites of concern, in particular for open leaf lettuce varieties, may concentrate in the lettuce. It cannot be concluded that non-viable residues, and also viable residues of *Trichoderma atroviride* strain AT10 which could potentially form metabolites while on the lettuces, would be reduced to levels below potential health concern by dietary intake. This results in a data gap for qualitative and quantitative information on the occurrence of metabolites of potential health concern linked to the representative use of *Trichoderma atroviride* strain AT10 on lettuce and which can subsequently be present at harvest under conditions reflecting the representative use. Consequently, the consumer risk assessment cannot be finalised (see Section 8.1). While noting that the specificity of open leaf lettuce varieties was not discussed during the peer review, the RMS is of the opinion that considering the method of application (drip irrigation), a distinction between open and closed lettuce varieties should not be relevant.

With regard to the five assessment criteria according to Commission guidance SANCO/11188/2013 rev. 2 (European Commission, 2015) for potential inclusion of an active substance in Annex IV of Regulation (EC) No 396/2005, none of the three criteria relevant for microorganisms (having no identified hazardous properties (criterion 3); natural exposure is higher than the one linked to the use as plant protection product (criterion 4) or consumer exposure is not expected (criterion 5)) were considered to be met for *Trichoderma atroviride* strain AT10 for the following reasons:

- *Trichoderma atroviride* strain AT10 can form metabolites (e.g. peptaibols) for which potential health concern cannot be excluded (see Sections 1 and 2);
- It is unknown if *Trichoderma atroviride* strain AT10 used as plant protection product would lead to a significant increase of background levels on the edible commodity compared to those naturally occurring;
- Consumer exposure to *Trichoderma atroviride* strain AT10 and its metabolites can be expected for the representative use on lettuce, i.e. field use by drip irrigation on lettuce: up to five applications ($1 \times (5 \times 10^{11})$ CFU/ha followed by $4 \times (2.5 \times 10^{11})$ CFU/ha) BBCH 10 up to a BBCH of 49.

Considering that none of the criteria laid down in the guidance are fulfilled, further risk management considerations are required to decide whether *Trichoderma atroviride* strain AT10 can be included into Annex IV of Regulation (EC) No 396/2005.

4. Environmental fate and behaviour

No specific information has been provided in relation to potential interference of *Trichoderma atroviride* strain AT10 with the analytical systems for the control of the quality of drinking water provided for in Directive 98/83/EC[4] (see specific Annex VI decision-making criteria in Part II of Commission Regulation (EU) No 546/2011[5]). However, as these methods require pathogenic bacteria to be identified and confirmed as absent, it was considered unlikely that filamentous fungi or their conidia would interfere with methodologies used for such determinations.

Being a mitotic asexual fungus (no sexual recombination or meiosis having been observed in its life cycle), in which plasmids are absent from the cell cytoplasm (only mitochondrial plasmids are known), *Trichoderma atroviride* strain AT10 would not be expected to have the potential for transfer of genetic material to other organisms.

[4] Council Directive 98/83/EC of 3 November 1998 on the quality of water intended for human consumption. OJ L 330, 5.12.1998, p. 32–54.

[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.

4.1. Fate and behaviour in the environment of the microorganism

No specific studies on the **persistence and multiplication in soil** of *Trichoderma atroviride* strain AT10 were provided. However, a weight of evidence approach based on the open literature on *Trichoderma species* and *Trichoderma atroviride* was provided and considered sufficient to conclude that *Trichoderma atroviride* strain AT10 will respect the uniform principles criterion of not being expected to persist in soil in concentrations considerably higher than the natural background levels, taking into account repeated applications over the years. Predicted environmental concentrations (PEC) in soil have been calculated (see Appendix A).

With respect to the **persistence and multiplication in water,** published peer-reviewed literature studies in the dossier indicated that *Trichoderma species* are able to survive in aquatic environments under favourable conditions. Even though germination and population growth are likely to be prevented due to the relatively low availability of nutrients in most natural surface water systems, no information to support the viability/population dynamics of *Trichoderma atroviride* strain AT10 in natural water and sediment systems is available; therefore, a data gap has been identified (see Section 9). Due to the method of application assessed via drip irrigation, the *Trichoderma atroviride* strain AT10 applied has not the potential to reach surface water via spray drift. Furthermore, it is likely that exposure via lateral subsurface flow or drainage via field drains will be negligible, as available literature data indicated that *Trichoderma atroviride* strain AT10 did not percolate through soil at significant levels and had restricted potential to grow except in the topsoil layers (though it might be expected that mycelial growth occurs in the rhizosphere). Therefore, PEC in surface water have not been calculated for the assessed representative use by drip irrigation.

Published peer-reviewed literature studies in the dossier indicate that *Trichoderma species* have been isolated from the **air** both indoors and outdoors. The genera appear to occur naturally in the air, though the concentrations detected were usually low compared to other fungal genera.

No specific studies on the **mobility** of *Trichoderma atroviride* strain AT10 are available. However, a weight of evidence approach based on the open literature on *Trichoderma species* and *Trichoderma atroviride* indicated that *Trichoderma atroviride* strain AT10 had restricted potential to grow except in the topsoil layers. Horizontal spread over the soil and to above ground plant parts was indicated to occur but to a limited extent.

4.2. Fate and behaviour in the environment of any relevant metabolite formed by the microorganism under relevant environmental conditions

Certain *Trichoderma* species are able to produce a lot of different metabolites such as polyketides, sesquiterpenes (including the mycotoxin group of trichothecenes), viridofungins and peptaibols. Some of these are inhibitory to fungi or bacteria; others have proven toxicity to mammals.

A data gap is identified since it is not known to what extent *Trichoderma atroviride* strain AT10 will produce any metabolites (which may include peptaibols such as a 19-mer atroviridin-like peptaibol and a short peptaibol like compound, and 6-pentyl-2*H*-pyran-2-one (6-pentyl-2-pyrone)) following the application once the conidia reach soil. These compounds are also present in low levels in the product. It is not clear if such metabolites might fulfil the criteria according to Part B section 7 (iv) of Commission Regulation (EU) No 283/2013[6] namely:

- the relevant metabolite is stable outside the microorganism;
- a toxic effect of the relevant metabolite is independent of the presence of the microorganism;
- the relevant metabolite is expected to occur in the environment in concentrations considerably higher than under natural conditions.

Therefore, data on the potential for *Trichoderma atroviride* strain AT10 to produce metabolites in relation to these criteria are necessary to assess if the further data requirements and the corresponding risk assessment according to Commission Regulation (EU) No 283/2013, part A, Section 7 (standard data requirements and assessment mandatory for chemical plant protection active substances) are triggered. Consequently, this resulted in a data gap and assessment that could not be

[6] Commission Regulation (EU) 283/2013 of 1 March 2013 setting out the data requirements for active substances in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market. OJ L 93, 3.4.2013, p. 1-84.

finalised (see Section 8.1). *Trichoderma atroviride* strain AT10 has the capacity to produce a conidial pigment (see Section 1); however, once the conidia germinate the pigment it is not expected to be in the environment.

5. Ecotoxicology

Insufficient data were available to address infectivity and pathogenicity to **birds** from the representative use of *Trichoderma atroviride* strain AT10. A non-published and non-GLP study was available on the effect of environmental parameters (temperature and pH) on the mycelial growth of *Trichoderma atroviride* strain AT10. The study indicated limited growth of the strain at the body temperature of birds. Information was not provided if the study was performed at a recognised testing facility, for which reason the study was not considered further. Consequently, a data gap leading to an assessment not finalised was identified for the potential infectivity and pathogenicity of *Trichoderma atroviride* strain AT10 to **birds** (see Sections 9 and 8.1, relevant for the representative use). Information to assess potential risk from *Trichoderma atroviride* strain AT10 to vertebrates with lower body temperatures e.g. amphibians and reptiles were not available.

As concluded in Section 2, sufficient information is available to finalise the assessment for infectivity and pathogenicity of *Trichoderma atroviride* strain AT10 in **mammals**. A low risk to wild mammals was concluded (relevant for the representative use).

Adequate data were available for freshwater invertebrates and algae with *Trichoderma atroviride* strain AT10 resulting in a low risk from the representative use. Insufficient data were available for fish and aquatic plants from the representative use of *Trichoderma atroviride* strain AT10. Overall, low risk was concluded for **aquatic organisms** (fish, freshwater invertebrates, algae and aquatic plants) from *Trichoderma atroviride* strain AT10 as the exposure from the representative use by drip irrigation was assessed to be marginal (see Section 4).

Acute oral and contact toxicity studies for **honeybees** with *Trichoderma atroviride* strain AT10 were available. Laboratory studies with foliar species of **non-target arthropods** (*Typhlodromus pyri* and *Aphidius rhopalosiphi and Poecilus cupreus*) exposed to *Trichoderma atroviride* strain AT10 were available. These studies on honeybees and non-target arthropods indicated low effects except for the study with *Aphidius rhopalosiphi,* where a statistically significant difference between the control and treated groups was observed for adults after 8-day exposure. In the study with *Aphidius rhopalosiphi,* performed at a higher application rate than the rate for the representative use, a non-statistically significant reduction in reproduction was observed. In the studies on honeybees and non-target arthropods, potential infectivity and pathogenicity were not reported. Due to the biology and behaviour of honeybees and non-target foliar arthropods, the exposure to these organisms from the intended use is expected to be low. Therefore, low risk is concluded for honeybees and non-target foliar arthropods from the representative use by drip irrigation as exposure is assessed to be low. A data gap leading to an assessment not finalised was identified for the potential infectivity and pathogenicity of *Trichoderma atroviride* strain AT10 to soil-dwelling non-target arthropods for the representative use (see Section 8.1).

Insufficient data were available to address toxicity, infectivity and pathogenicity to **earthworms** and other **soil macroorganisms** from the representative use of *Trichoderma atroviride* strain AT10. In addition, insufficient data were available for assessing the potential effects of *Trichoderma atroviride* strain AT10 on **soil microorganisms**. This resulted in a data gap and assessment not finalised for earthworms, other soil macro- and microorganisms for the representative use (see Section 8.1).

The risk assessment for **toxins/secondary metabolites** (see Section 4.2) could not be finalised for terrestrial non-target organisms (birds, wild mammals, non-target arthropods in soil, earthworms, other soil macro- and soil microorganisms) and aquatic organisms (fish, freshwater invertebrates, algae and aquatic plants) for the representative use. Toxicity data were not available for toxins/ secondary metabolites to perform a hazard characterisation (resulting in a data gap and issue not finalised, see Section 8.1).[7] Due to the biology and behaviour of honeybees and non-target foliar arthropods, the exposure of metabolites to these organisms from the intended use is expected to be marginal and low risk is concluded.

[7] For freshwater invertebrates, data on acute toxicity of the peptaibols (alamethicin and paracelsin) from a published paper was available indicating low risk when comparing with the concentrations of peptaibols in the formulated product. However, limited details on identity of the peptaibols measured in the formulated product and/or *in situ* after application were available (see Section 1), resulting in the risk assessment for aquatic invertebrates from these peptaibols (alamethicin and paracelsin) not finalised (relevant for the representative use).

6. Overview of the risk assessment of the organism or metabolite 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)	Ecotoxicology
Trichoderma atroviride strain AT10	A data gap leading to an assessment not finalised was identified for earthworms, other non-target soil macro- and microorganisms for the representative use.
Toxins/secondary metabolites (which may include peptaibols and 6-pentyl-2*H*-pyran-2-one (6-pentyl-2-pyrone))	A data gap leading to an assessment not finalised was identified for earthworms, other non-target soil macro- and microorganisms for the representative use.

Table 2: Groundwater[(a)]

Compound (name and/or code)	> 0.1 µg/L at 1 m depth for the representative use[(b)] Step 2	Biological (pesticidal) activity/ relevance Step 3a.	Hazard identified Steps 3b. and 3c.	Consumer RA triggered Steps 4 and 5	Human health relevance
Toxins/secondary metabolites (which may include peptaibols, and 6-pentyl-2*H*-pyran-2-one (6-pentyl-2-pyrone))	Data gap	Open	Open	Open	Open

(a): Assessment according to European Commission guidance of the relevance of groundwater metabolites (2003).
(b): FOCUS scenarios or relevant lysimeter.

Table 3: Surface water and sediment

Compound (name and/or code)	Ecotoxicology
Trichoderma atroviride strain AT10	Low risk to aquatic organisms from *Trichoderma atroviride* strain AT10 for the representative use.
Toxins/secondary metabolites (which may include peptaibols, and 6-pentyl-2*H*-pyran-2-one (6-pentyl-2-pyrone))	A data gap leading to an assessment not finalised for aquatic organisms was identified for the representative use.

Table 4: Air

Compound (name and/or code)	Toxicology
Trichoderma atroviride strain AT10	$LC_{50} \geq 1.13 \times 10^7$ CFU/ animal (corresponding to 3.4×10^7 CFU/kg bw)
Toxins/secondary metabolites (which may include peptaibols and 6-pentyl-2*H*-pyran-2-one (6-pentyl-2-pyrone))	Data gap and risk assessment not finalised from non-dietary exposure of operators, workers, residents and/ or bystanders due to lack of identification/quantification and toxicological assessment.

7. Particular conditions proposed to be taken into account by risk managers

Risk mitigation measures (RMMs) identified following consideration of Member State (MS) and/or applicant's proposal(s) during the peer review, if any, are presented in this section. These measures applicable for human health and/or the environment leading to a reduction of exposure levels of operators, workers, bystanders/residents, environmental compartments and/or non-target organisms for the representative uses are listed below. The list may also cover any RMMs as appropriate, leading to an acceptable level of risks for the respective non-target organisms.

It is noted that final decisions on the need of RMMs to ensure the safe use of the plant protection product containing the concerned active substance will be taken by risk managers during the decision-making phase. Consideration of the validity and appropriateness of the RMMs remains the responsibility of MSs at product authorisation, taking into account their specific agricultural, plant health and environmental conditions at national level.

Table 5: Risk mitigation measures proposed for the representative use assessed

Representative use	**Lettuce**
	Drip irrigation
Operator risk	Use of PPE/RPE might be considered to reduce dermal and inhalation exposure (for the sensitisation potential)
Worker exposure	Use of PPE/RPE might be considered to reduce dermal and inhalation exposure (for the sensitisation potential)

8. Concerns and related data gaps

8.1. 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 one or more of 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[5] 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).

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.

The following issues or assessments that could not be finalised have been identified, together with the reasons including the associated data gaps where relevant, which are reported directly under the specific issue to which they are related:

1) The non-dietary risk assessment for workers and residents potentially exposed to **peptaibols** cannot be finalised (see Section 2) considering the identified data gaps:
   a) To decide on the relevance of the peptaibols found in the product, the determination of their identity is required (relevant for the representative use, see Section 1).
   b) Pending identification and quantification of secondary metabolites produced *in situ* (see Section 4), further toxicological data/information might be needed to finalise the risk assessment (relevant for the representative use, see Section 2).
2) The non-dietary risk assessment for operators, workers, residents and bystanders potentially exposed to 6-pentyl-2*H*-pyran-2-one (6-pentyl-2-pyrone) by inhalation cannot be finalised (see Section 2) considering the identified data gaps:
   a) Quantification of 6-pentyl-2*H*-pyran-2-one (6-pentyl-2-pyrone) in the MPCA is required (relevant for the representative use, see Section 1).
   b) Pending quantification of the secondary metabolite 6-pentyl-2-pyrone both in the product (see Section 1) and produced *in situ* (see Section 4), further toxicological data/ information might be needed to finalise the risk assessment (relevant for the representative use, see Section 2).
3) The dietary consumer risk assessment cannot be finalised considering the identified data gap (see Section 3):
   a) Further information on qualitative and quantitative occurrence of metabolites of potential health concern (e.g. peptaibols) linked to the representative use of *Trichoderma atroviride* strain AT10 on lettuce and which can be present at harvest is required (relevant for the representative use, see Section 3).

4) Satisfactory information was not available on the production of toxins/secondary metabolites (see Section 4.2) and their levels present in the environment after application including potential for exposure to groundwater and their potential toxicity in order to conclude on the risk assessment for non-target terrestrial organisms (birds, wild mammals, non-target soil arthropods, earthworms, other soil macro- and microorganisms) and non-target aquatic organisms (fish, freshwater invertebrates, algae and aquatic plants other than algae) leading to an assessment not finalised (relevant for the representative use; see Sections 4.2 and 5) considering the identified data gap:

   a) Pending further investigations on the production of toxins/secondary metabolites (see Section 4.2) and their levels present in the environment after application, further considerations will have to be given to their potential toxicity in order to conclude on the risk assessment for terrestrial non-target organisms (birds, wild mammals, non-target soil arthropods, earthworms, other soil macro- and microorganisms) and aquatic organisms (fish, freshwater invertebrates, algae and aquatic plants other than algae) and on the groundwater exposure assessment (relevant for the representative use; see Sections 4.2 and 5).[8,9]

5) Satisfactory information was not available for the potential infectivity, pathogenicity and adverse effects to non-target terrestrial organisms (birds, non-target soil arthropods, earthworms and other soil macro- and microorganisms) from *Trichoderma atroviride* strain AT10 for the assessment of the representative use by drip irrigation, leading to an assessment not finalised (see Section 5) considering the identified data gap:

   a) Data and information for the assessment of the potential infectivity and pathogenicity to non-target terrestrial organisms (birds, non-target soil arthropods, earthworms and other soil macro- and microorganisms) from *Trichoderma atroviride* strain AT10 (relevant for the representative use, see Section 5).

8.2. 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.

The following critical areas of concern are identified, together with any associated data gaps, where relevant, which are reported directly under the specific critical area of concern to which they are related:

Critical areas of concern were not identified.

[8] For freshwater invertebrates, data on acute toxicity of the peptaibols (alamethicin, and paracelsin) from a published paper was available indicating low risk when comparing with the concentrations of peptaibols in the formulated product. However, limited details on identity of the peptaibols measured in the formulated product and/or *in situ* after application were available (see section 1), resulting in the risk assessment for aquatic invertebrates from these peptaibols (alamethicin and paracelsin) not finalised (relevant for the representative use).

[9] For honeybees and non-target foliar arthropods, exposure from toxins/secondary metabolites is assessed to be low and low risk is concluded for the representative use.

8.3. Overview of the concerns identified for each representative use considered (Table 6)

(If a particular condition proposed to be taken into account to manage an identified risk, as listed in Section 7, has been evaluated as being effective, then 'risk identified' is not indicated in Table 6.)

Table 6: Overview of concerns reflecting the issues not finalised, critical areas of concerns and the risks identified that may be applicable for some but not for all uses or risk assessment scenarios

Representative use		Lettuce
		Drip irrigation
Operator risk	Risk identified	
	Assessment not finalised	X[2]
Worker risk	Risk identified	
	Assessment not finalised	X[1], X[2]
Resident/bystander risk	Risk identified	
	Assessment not finalised	X[1] X[2]
Consumer risk	Risk identified	
	Assessment not finalised	X[3]
Risk to wild non-target terrestrial vertebrates	Risk identified	
	Assessment not finalised	X[4,5]
Risk to wild non-target terrestrial organisms other than vertebrates	Risk identified	
	Assessment not finalised	X[4,5]
Risk to aquatic organisms	Risk identified	
	Assessment not finalised	X[4]
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	X[4]

The superscript numbers relate to the numbered points indicated in Section 8.1.
(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).

9. List of other outstanding issues

Remaining data gaps not leading to critical areas of concern or issues not finalised but considered necessary to comply with the data requirements, and which are relevant for some or all of the representative uses assessed at EU level. Although not critical, these data gaps may lead to uncertainties in the assessment and are considered relevant.

These data gaps refer only to the representative uses assessed and are listed in the order of the sections:

- A search of the scientific peer-reviewed open literature on the active substance and its relevant metabolites, dealing with side effects on human and animal health focusing on metabolites, as well as the environment to support the viability/population dynamics of *Trichoderma atroviride* strain AT10 in natural water and sediment systems, published within the 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 the representative use evaluated, see Section on 'The identity of the microorganism and the properties of the formulated product').

- Satisfactory information was not available to support the viability/population dynamics of *Trichoderma atroviride* strain AT10 in natural water and sediment systems (relevant for the representative use evaluated; see Sections 4 and 'The identity of the microorganism and the properties of the formulated product').
- Determination of the growth temperature range of the *Trichoderma atroviride* strain AT10 according to GLP or by a recognised testing facility (relevant for the representative use evaluated, see Section 1).

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Abbreviations

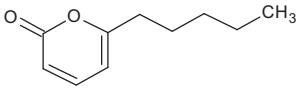
λ	Wavelength
ε	decadic molar extinction coefficient
µg	Microgram
µm	micrometer (micron)
AMA	Amphibian Metamorphosis Assay
a.s.	active substance
ADI	acceptable daily intake
AOEL	acceptable operator exposure level
ARfD	acute reference dose
bw	body weight
CABI	Centre for Agricultural Bioscience International

CFU	colony-forming units
cm	Centimetre
d	day
DAR	draft assessment report
DNA	deoxyribonucleic acid
EEC	European Economic Community
FAO	Food and Agriculture Organization of the United Nations
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
g	gram
GAP	Good Agricultural Practice
GPC	gel permeation chromatography
h	hour(s)
ha	hectare
HGPRT	hypoxanthine-guanine phosphoribosyl transferase
ISO	International Organization for Standardization
ITS	internal transcribed spacer
IUPAC	International Union of Pure and Applied Chemistry
iv	intravenous
kg	kilogram
L	litre
LC_{50}	lethal concentration, median
LOQ	limit of quantification
m	metre
M	mol
mg	milligram
mL	millilitre
mm	millimetre (also used for mean measured concentrations)
MPCA	active agent of the microbial pest control product
ng	nanogram
OECD	Organisation for Economic Co-operation and Development
Pa	pascal
pH	pH-value
PIE	potential inhalation exposure
pK_a	negative logarithm (to the base 10) of the dissociation constant
PKS	polyketide synthase
P_{ow}	partition coefficient between *n*-octanol and water
PPE	personal protective equipment
ppm	parts per million (10^{-6})
ppp	plant protection product
PT	proportion of diet obtained in the treated area
QSAR	quantitative structure–activity relationship
r^2	coefficient of determination
RPE	respiratory protective equipment
S	svedberg, S (10^{-13} s)
SD	standard deviation
SMILES	simplified molecular-input line-entry system
$t_{1/2}$	half-life (define method of estimation)
TBLASTN	translated nucleotide databases
tef1	translation elongation factor 1 α gene
WGS	whole genome sequencing
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.2022.7200

Appendix B – Used compound codes

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
6-pentyl-2*H*-pyran-2-one (6-pentyl-2-pyrone) (6-PP)	6-pentyl-2*H*-pyran-2-one O=C1C=CC=C(CCCCC)O1 MAUFTTLGOUBZNA-UHFFFAOYSA-N	

(a): The metabolite name in bold is the name used in the conclusion.
(b): ACD/Name 2020.2.1 ACD/Labs 2020 Release (File version N15E41, Build 116563, 15 June 2020).
(c): ACD/ChemSketch 2020.2.1 ACD/Labs 2020 Release (File version C25H41, Build 121153, 22 March 2021).