Peer review of the pesticide risk assessment of the active substance clodinafop (variant evaluated clodinafop-propargyl)

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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, Greece, and co-rapporteur Member State, Germany, for the pesticide active substance clodinafop-propargyl 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 clodinafop-propargyl as a herbicide on wheat, rye and triticale. 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. The European Commission mandated EFSA to reconsider the acceptable operator exposure level (AOEL) setting and to update the non-dietary exposure assessment if needed.

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Keywords: clodinafop-propargyl, clodinafop, peer review, risk assessment, pesticide, herbicide

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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. Clodinafop 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), Greece, and co-rapporteur Member State (co-RMS), Germany, received an application from Syngenta Crop Protection AG and ADAMA-Agan Ltd. for the renewal of approval of the active substance clodinafop. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicants, the co-RMS (Germany), the European Commission and the European Food Safety Authority (EFSA) about the admissibility.

The RMS provided its initial evaluation of the dossier on clodinafop-propargyl in the renewal assessment report (RAR), which was received by EFSA on 20 June 2017. In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicants, Syngenta Crop Protection AG and ADAMA-Agan Ltd., for comments on 4 October 2017. 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 7 December 2017.

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, residues and ecotoxicology.

In accordance with Article 13(1) of the Regulation, EFSA should adopt a conclusion on whether clodinafop-propargyl 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.

With a mandate of 18 July 2019, the European Commission asked EFSA to reconsider the setting of the AOEL in a peer review and to update the EFSA conclusion in relation to the non-dietary exposure risk assessment accordingly if needed.

The conclusions laid down in this report were reached on the basis of the evaluation of the representative uses of clodinafop-propargyl as a herbicide on wheat, rye and triticale, as proposed by the applicants. Full details of the representative uses can be found in Appendix A of this report.

The use of clodinafop-propargyl according to the representative uses proposed at the European Union (EU) level results in a sufficient herbicidal efficacy against the target weeds.

A data gap was identified for a detailed evaluation of the search of the scientific peer-reviewed open literature on the active substance and its relevant metabolites dealing with side effects on health. In the section identity, physical/chemical properties, analytical methods data gaps were identified for additional validation information for the analytical method used in support of the developmental toxicity study in rat (key study to derive the acute reference dose (ARfD) and acute acceptable operator exposure level (AAOEL)) and for the method used in the residue trials for esters and conjugates of clodinafop, for data demonstrating applicability of the existing monitoring method for food/feed of plant origin and for animal products for analysing esters and conjugates or a new monitoring method applicable for all components of the residue definition.

Regarding the mammalian toxicology area, data gaps were identified to address the toxicological relevance of the individual impurities in comparison with the toxicity profile of the active substance and to address the phototoxicity and photomutagenicity potential of the substance, although it is acknowledged that there is currently no validated test guideline for ultraviolet B (UVB) absorbers such as clodinafop-propargyl. Clodinafop-propargyl is proposed to be classified as carcinogenic but not as toxic for reproduction category 2, on this basis, the conditions of the interim provisions of Annex II, Point 3.6.5 of Regulation (EC) No 1107/2009 concerning human health for the consideration of endocrine-disrupting (ED) properties are not met. From a scientific perspective, an endocrine-mediated mode of action cannot be excluded based on adverse effects on endocrine organs observed in the apical studies. Toxicological information is needed on the relative toxicity of the R- and S-enantiomers and possible preferential metabolism or degradation from the R to the S enantiomers in animals, plants and the environment and on the safener used in combination with clodinafop-propargyl, cloquintocet-mexyl.

In the section of residues, the finalisation of the consumer dietary risk assessment is pending clarification of several data gaps. Some of them may significantly impact the risk assessment outcome (e.g. ultimate confirmation of freezer storage stability of residues and suitability of the analytical
method to validate the residue concentrations used in the assessment, finalisation of assessment of residue transfer in animal commodities, currently not considered in the intake assessment, not even at limit of quantification (LOQ) level, impact of potential change of the isomer composition in the terminal residues in cereal commodities).

The data available on environmental fate and behaviour are sufficient to carry out the required environmental exposure assessments at the EU level for the representative uses assessed, with the exception that the regulatory dossier does not provide information on the environmental behaviour of the R isomer of clodinafop-propargyl and its metabolite CGA 193469 that was eligible to be considered by the regulatory framework. It is not known if any enantioselective transformation in the environmental compartments occurs.

In the area of ecotoxicology, a data gap and a critical area of concern were identified to address the risk to mammals. Additional data gaps were identified to address the risk for aquatic organisms, for birds and mammals from exposure to metabolites and for bees. Furthermore, a data gap was identified to confirm the compliance of the different batches used in the ecotoxicological tests with the technical specification.
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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 an additional 3 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, Greece, and co-RMS, Germany, received an application from Syngenta Crop Protection AG and ADAMA-Agan Ltd. for the renewal of approval of the active substance clodinafop. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicants, the co-RMS (Germany), the European Commission and EFSA about the admissibility.

The RMS provided its initial evaluation of the dossier on clodinafop-propargyl in the RAR, which was received by EFSA on 20 June 2017 (Greece, 2017).

In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicants, Syngenta Crop Protection AG and ADAMA-Agan, Ltd., for consultation and comments on 4 October 2017. 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 7 December 2017. At the same time, the collated comments were forwarded to the RMS for compilation and evaluation in the format of a reporting table. The applicants were invited to respond to the comments in column 3 of the reporting table. The comments and the applicants’ 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 applicants in accordance with Article 13(3) of the Regulation were considered in a telephone conference between EFSA and the RMS on 2 February 2018. On the basis of the comments received, the applicants’ 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, residues 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.

With a mandate of 18 July 2019, the European Commission asked EFSA to reconsider the setting of the AOEL in a peer review and to update the EFSA conclusion in relation to the non-dietary exposure risk assessment accordingly if needed. The peer review initiated with the acceptance of the mandate on 30 September 2019. The RMS, Greece, provided an update of the relevant parts of the RAR. An expert meeting for the section on mammalian toxicology was organised.

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 final consultation on the conclusions arising from the peer review of the risk assessment took place with Member States via a written procedure in September 2018.

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\(^1\) 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.
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 clodinafop-propargyl as a herbicide on wheat, rye and triticale, as proposed by the applicants. 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, 2018), 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 (2 February 2018);
- the evaluation tables (27 September 2018 and 10 December 2019);
- the reports 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.

Given the importance of the RAR, including its revisions (Greece, 2018, 2019), 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

Clodinafop is the ISO common name for (R)-2-[4-(5-chloro-3-fluoro-2-pyridyloxy)phenoxy]propionic acid (IUPAC). The substance evaluated, clodinafop-propargyl, a derivative of clodinafop, is the modified ISO common name for prop-2-ynyl (R)-2-[4-(5-chloro-3-fluoro-2-pyridyloxy)phenoxy] propionate (IUPAC).

The representative formulated product for the evaluation was 'A7957E', an emulsifiable concentrate (EC) containing 100 g/L clodinafop-propargyl and 25 g/L cloquintocet-mexyl (as a safener).

The representative uses evaluated were foliar spray application for post-emergence control of grasses such as Avena spp., Phalaris spp., Poa trivialis, Alopecurus spp. and Lolium spp. in wheat (soft and durum), rye and triticale. Full details of the good agricultural practices (GAPs) can be found in the list of end points in Appendix A.

Data were submitted to conclude that the uses of clodinafop-propargyl according to the representative uses proposed at EU level result in a sufficient herbicidal efficacy against the target grasses, following the guidance document SANCO/2012/11251-rev. 4 (European Commission, 2014b).

A data gap has been identified for a detailed evaluation of the search of the scientific peer-reviewed open literature on the active substance and its relevant metabolites, dealing with side effects on health, 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, 2011a).

Clodinafop-propargyl consists of a single enantiomer (R-isomer). A data gap and an issue that could not be finalised have been identified for addressing the relative toxicity and possible preferential metabolism or degradation of the R and S enantiomers of clodinafop-propargyl and its metabolite CGA 193469 present in animals, plants and the environment.

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) and SANCO/825/00-rev. 8.1 (European Commission, 2010).
The proposed specification for clodinafop-propargyl is based on batch data from industrial plants and quality control data. The proposed minimum purity of the technical material is 950 g/kg. It should be noted that evaluation of the toxicological relevance of the impurities is not finalised (see Section 2). The applicants and RMS have proposed to maintain the current reference specification with minimum purity of the technical material 950 g/kg. However, it should be noted that based on the data submitted for the renewal, a higher minimum purity of the technical material could be set (960 g/kg) for the Syngenta source. The batches used in the toxicological assessment do not support the original reference specification (either from the Syngenta or Adama sources) but support the newly proposed specification from the Syngenta source (see Section 2, see also open point 0.1 in the evaluation table Section 1). The information provided is insufficient to confirm the compliance of batches used in the ecotoxicity tests with any of the specifications (See Section 5). An FAO specification under the new procedure 683.225/TC (May 2008) exists with min 960 g/kg clodinafop-propargyl content, belonging to the material of Syngenta Crop Protection AG.

It should be noted that all data evaluated for the renewal belong to the derivative clodinafop-propargyl. 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 clodinafop-propargyl or the representative formulation. The main data regarding the identity of clodinafop-propargyl 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, except for the method used in the developmental toxicity study in rat (see also Section 2) and for the method used in the residue trials for esters and conjugates of clodinafop (see also Section 3). Methods of analysis are available for the determination of the active substance in the technical material and in the representative formulation and for the determination of the respective impurities in the technical material.

A quick, easy, cheap, effective and safe method (QuEChERS) using liquid chromatography with tandem mass spectrometry (LC-MS/MS) exists for monitoring of clodinafop, its S-isomer and their salts residues (expressed as clodinafop) in food and feed of plant origin with a limit of quantification (LOQ) of 0.01 mg/kg in each commodity group. However, the residue definition in food/feed of plant origin was concluded as ‘clodinafop, its S-isomer, their salts, esters and conjugates, expressed as clodinafop’ and therefore a data gap for data demonstrating applicability of the existing method for esters and conjugates or a new monitoring method applicable for all components of the residue definition was identified. Residues of clodinafop, its S-isomer and their salts (expressed as clodinafop) in food of animal origin can be determined by QuEChERS method using LC-MS/MS with LOQ of 0.01 mg/kg in all animal matrices (including blood). However, the residue definition in animal products was concluded as ‘clodinafop, its S-isomer, their salts, esters and conjugates, expressed as clodinafop’, therefore a data gap for data demonstrating applicability of the existing method for esters and conjugates or a new monitoring method applicable for all components of the residue definition was identified.

‘Clodinafop and its S-isomer’ can be monitored in soil by LC-MS/MS with an LOQ of 0.0005 mg/kg. Appropriate LC-MS/MS method exists for monitoring of components of the residue definition ‘clodinafop and its S-isomer’ in water with an LOQ of 0.05 µg/L. However, it should be noted that the residue definition in water is not finalised (see Section 5) and new monitoring methods might be required if new components have to be included. ‘Clodinafop-propargyl and its S-isomer’ in air can be monitored by LC-MS/MS with an LOQ of 0.78 µg/m³.

‘Clodinafop and its S-isomer’ in body fluids and tissues can be determined by using the monitoring methods for residues in food of animal origin (tissues and blood).

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), Guidance on dermal absorption (EFSA PPR Panel, 2012), Guidance on operators, workers, residents and bystanders exposure (EFSA, 2014) and Guidance on the Application of the CLP Criteria (ECHA, 2017).

Clodinafop-propargyl was discussed at the Pesticides Peer Review Teleconference 179 in May 2018 and Teleconference 200 in October 2018. Following the mandate from the European Commission to reconsider the AOEL setting and the update of the non-dietary exposure risk assessment accordingly if needed, the substance was re-discussed during the Pesticides Peer Review Experts’ Meeting 18 in November 2019.
The current technical specifications (either from Syngenta or ADAMA sources) are not supported by the toxicological assessment due to two impurities in each specification that were not sufficiently tested and for which the assessment of the toxicological relevance was not sufficiently substantiated (data gap). However, the newly proposed technical specification from the Syngenta source is supported since it was comparable to the material used in the testing that was used to derive the toxicological reference values, complemented with genotoxicity tests. However, the toxicological relevance of the individual impurities has not been fully addressed in comparison with the toxicity profile of the parent compound, the quantitative structure-activity relationship (QSAR) analysis provided was of low reliability overall and no considerations have been provided on the potential impact of the structural differences of the impurities in comparison with the parent (data gap). The analytical methods used in the toxicological studies were considered fit-for-purpose for most relevant studies, except for the developmental toxicity study in rat (data gap), this was considered an issue that could not be finalised since the study was used to derive the acute reference dose (ARfD) and acute acceptable operator exposure Level (AAOEL).

The oral absorption of clodinafop-propargyl is not complete (around 70%\(^3\) oral absorption was used to derive the acceptable operator exposure level (AOEL) and AAOEL; this value is considered appropriate independently of the addition or not of safener cloquintocet-mexyl to the formulation. The active substance is widely distributed, showing potential for accumulation in fat, extensively metabolised (major metabolites being clodinafop and its conjugates) and eliminated, mainly via urine. A residue definition for body fluids and tissues was established as ‘clodinafop and its S-isomer’. Male rats presented a higher area under the blood concentration/time curve (AUC) and slower elimination rate in comparison with female rats and presented higher sensitivity to clodinafop-propargyl administration over the whole toxicological dossier. No unique human metabolites were seen in an in vitro comparative metabolism study with rat and human liver microsomes.

In the acute toxicity studies, clodinafop-propargyl presented low to moderate acute toxicity when administered by the oral, dermal or inhalation routes. No skin or eye irritation was attributed to the active substance, but potential for skin sensitisation was observed. The resulting classification with the harmonised classification according to Regulation (EC) No 1272/2008\(^4\). Clodinafop-propargyl is negative following in vitro phototoxicity testing; however, the test is not considered appropriate to investigate ultraviolet B (UVB) absorbers such as clodinafop-propargyl. It should, however, be noted that no validated method is currently available to properly investigate UVB absorber chemicals and this applies to both phototoxicity and photomutagenicity endpoints (data gap).

Following short- and long-term administration in rats and dogs, clodinafop-propargyl is showing target organ toxicity in the liver and blood; harmonised classification as STOT RE 2 (specific target organ toxicity – repeated exposure), H373 ‘may cause damage to organs’ is based on haematological changes indicative of anaemia. The critical No Observed Adverse Effect Level (NOAEL) after short-term exposure was agreed by the majority of experts during the pesticides peer review experts’ meeting 18\(^5\) at 0.92 mg/kg body weight (bw) per day (instead of 0.13 mg/kg bw per day previously concluded\(^6\)) from the 90-day toxicity study in rats, based on liver effects and haematological and clinical chemistry changes observed at 8.24 mg/kg bw per day; these effects were also observed in additional studies included in the data set. Isolated changes in the mammary gland (mammary gland carcinoma) were considered not treatment related and incidental in their nature, lacking a biological plausible link with treatment (i.e. individual occurrence in two tested groups (low mid-dose and high dose), observed in a study of short duration, only occurring during recovery period, not reproduced in the second short-term study available or the long-term study at similar doses, and not concomitant effect in the mammary gland in the treatment groups indicative of pre-neoplastic changes or any target organ pathology). Upon long-term exposure, the critical NOAEL was 0.03 mg/kg bw per day in male rats based on prostate carcinomas observed at the lowest observed adverse effect level (LOAEL) of 0.32 mg/kg bw per day. A higher incidence over controls for additional tumours, namely ovary adenomas and mammary gland carcinomas (the treatment relationship was discussed during the pesticides peer review experts’ meeting 18\(^5\) and considered questionable), were seen at the highest

\(^3\) The previously set oral absorption value was 75% (EFSA, 2005; European Commission, 2006).
\(^4\) Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. OJ L 353, 31.12.2008, p. 1–1355.
\(^5\) See Report of the Pesticides Peer Review Meeting 18 (4-8 November 2019), Experts’ Consultation 2.1.
\(^6\) See Reports of the Pesticides Peer Review TC 179 and TC 200, Experts’ Consultation 2.3.
Annex VI of Regulation (EC) No 1272/2008 where classification is not included (1st Adaptation to Technical Progress (ATP) to the CLP Regulation). No genotoxicity in vivo of clodinafop-propargyl classification with regard to the human health entry in Annex VI of Regulation (EC) No 1272/2008 where classification and labelling for carcinogenicity was not included (1st Adaptation to Technical Progress (ATP) to the CLP Regulation). No genotoxic potential is attributed to clodinafop-propargyl in vivo.

No adverse effects were observed on reproduction and fertility endpoints. Offspring's toxicity (lower pup weight, delayed physical development and pelvis dilatation) as well as developmental effects (delayed or absent ossification and bilateral ureteral torsion) were observed at parental toxic dose levels in rats with an NOAEL of 5 mg/kg bw per day. Potential neurotoxicity (increased incidence over controls of demyelination upon acute exposure) and immunotoxicity (changes in spleen and thymus weights and atrophy) were observed at high doses eliciting clinical signs of general toxicity. Clodinafop-propargyl is proposed to be classified as carcinogenic but not as toxic for reproduction category 2, on this basis, the conditions of the interim provisions of Annex II, Point 3.6.5 of Regulation (EC) No 1107/2009 concerning human health for the consideration of endocrine-disrupting (ED) properties are not met. However, an endocrine-mediated mode of action cannot be excluded considering the apical effects observed in the toxicity studies: decreased testes weights, adenohypophysis cystic dilation and increased ovary weights in rats; testicular tubular atrophy, decreased spermatogenesis and increased adrenal weights in male mice. A number of level 2-5 tests from the OECD Conceptual Framework (OECD, 2012) are available from the open literature but the mode of action should be further investigated, for instance with an Hershberger assay (data gap and issue not finalised).

The acceptable daily intake (ADI) of clodinafop-propargyl is 0.0003 mg/kg bw per day based on the NOAEL of 0.03 mg/kg bw per day for prostate carcinomas in the 2-year rat study and applying an uncertainty factor (UF) of 100. The AOEL was agreed by the majority of experts during the pesticides peer review experts' meeting 18 based on the revised NOAEL of 0.92 mg/kg bw per day for liver effects and haematological and clinical chemistry changes from the 90-day rat study, applying an UF of 100 and a correction for limited oral absorption of 70%. The ARfD is 0.05 mg/kg bw based on the developmental toxicity study in rats with a developmental NOAEL of 5 mg/kg bw per day supported by the offspring's NOAEL of 3.4 mg/kg bw from the 2-generation reproduction toxicity study and applying an UF 100. The AAOEL is 0.035 mg/kg bw on the same basis as the ARfD, applying a correction factor of 70% for limited oral absorption.

Regarding the representative formulation, 'Topik 100 EC' ('A7957E'), an emulsifiable concentrate containing 100 g clodinafop-propargyl/L, dermal absorption was established at 2% for the concentrated formulation, 33% for an in-use spray dilution of 0.6 g/L and 40% for a spray dilution of 0.2 g/L based on in vitro dermal absorption study with human skin. For the representative uses in cereals, the estimated operator exposure exceeds the AOEL according to the UK POEM (358% of the AOEL), even with the use of personal protective equipment (PPE), such as gloves during mixing, loading and application in addition to standard workwear (long-sleeved shirt and long trousers). According to the German model and the EFSA calculator, the estimated operator exposure remains below the (A)AOEL assuming that PPE is used, such as workwear during mixing, loading and application, as well as protective gloves during mixing and loading operations. The estimated worker exposure does not exceed the AOEL according to the EUROPOEM II model when workwear is used but without additional PPE Bystander and resident's exposure does not exceed the (A)AOEL according to the EFSA calculator, if a buffer zone of at least 5 m is established to protect the residential children.

Clodinafop-propargyl consists of a single enantiomer (R-isomer). The relative toxicity between the R- and S-isomers, as well as any metabolism or degradation shift of the R- to the S-enantiomer in...
animals, plants and the environment were not investigated. It is therefore unknown whether a possible shift to a potentially more toxic enantiomer would result in an increased risk, in particular for workers and residents (data gap and issue that could not be finalised, see also Sections 3, 4 and 5).

Clodinafop-propargyl is used in combination with the safener cloquintocet-mexyl (ratio 4:1) and short-term toxicity studies were submitted on the mixture. Studies on the safener alone exist, but the applicant provided only a summary of these studies. Since the two substances have a different toxicity profile (urinary bladder being the target organ of the safener), a toxicological data package is also needed for the safener11 (data gap and issue not finalised).

3. Residues

The assessment in the residue section is based on the OECD guidance document on overview of residue chemistry studies (OECD, 2009), the OECD publication on maximum residue level (MRL) calculations (OECD, 2011), the European Commission guideline document on MRL setting (European Commission, 2011) and the Joint Meeting on Pesticide Residues (JMPR) recommendations on livestock burden calculations (JMPR, 2004, 2007).

Clodinafop-propargyl was discussed at the Pesticide Peer Review meeting 180 (June 2018).

Information on possible isomerisation of clodinafop-propargyl (R-isomer) is not available as isomer-specific analysis was not conducted in the tests and studies in the residue section. All residues referred to as clodinafop-propargyl and clodinafop in this section could therefore contain the mixture of the R- and S-enantiomer in any possible ratio.

The metabolism of clodinafop in wheat was investigated in five different studies on wheat. These studies have been conducted with the variant clodinafop-propargyl (R-isomer) and with the racemic mixture containing also the S-isomer and were characterised by different experimental designs with a subset of studies also including application of the safener. Despite deficiencies identified in the individual studies, the data set altogether is sufficient to address the metabolism of clodinafop in cereal crops with and without safener.

The impact of the presence of a safener on the metabolic pattern of clodinafop was negligible as the same metabolites were identified in the studies with and without safener. Metabolism in the presence of the safener appeared to be slightly faster than without the safener only during the very first days after application.

Clodinafop-propargyl, clodinafop, metabolites CGA 193468 (M1), CGA 144462 (M3), CGA 214111 (M4) and II2 were identified in forage, fodder and grain. The presence of significant proportions (compared to occurrence of free residues) of clodinafop, M1, M3, II2 and CGA 302371 following enzymatic or acid hydrolysis indicated their presence also as conjugates. A pyridinyl label-specific metabolite, CGA 302371, was detected mainly in leafy plant parts (forage/fodder and straw, 6–17% total radioactive residue (TRR)). Across all studies, proportions of individual components of the TRR in the different commodities varied. In mature wheat grain and straw, clodinafop-propargyl was recovered, if at all, as a minor residue (<10% TRR). Clodinafop accounted for up to 21% TRR in grain. In forage, II2 and clodinafop occurred at levels up to 17% TRR.

The residue definition for monitoring and risk assessment in plants is proposed as the ‘sum of clodinafop, its S-isomer, their salts, esters and conjugates, expressed as clodinafop’. This residue definition is restricted to cereals. The impact on the possible isomerisation of the R-isomer on the consumer risk assessment cannot be currently addressed based on the residue data. A data gap is therefore set to address the potential formation of S-isomers in plants and animals by further data which leads to an issue that could not be finalised.

In a confined rotational crop study in spinach, radish and wheat with clodinafop-propargyl at the recommended rate, uptake of residues by the crops was very low. TRRs in the crops declined with increasing plant back interval (PBI) (32 days and 126 days) and were always <0.01 mg/kg in spinach, radish and wheat grain, while slightly higher residues were found in wheat straw and wheat chaff but those did not exceed 0.02 mg/kg. As for the low residues identification significant residues of clodinafop or its soil metabolites in plants via uptake from soil are not expected provided the representative GAP is adhered to. Further investigation of residues in rotational crops is currently not triggered.

11 The RMS considered that there is no need to investigate the toxicity profile of the safener (no data gap needed) since the NOAEL values of clodinafop in the short-term rat and dog studies do not change in the presence of the safener at 4:1 ratio; see Report Pesticides Peer Review TC 179, Expert’s consultation 2.2.
In the goat metabolism study with clodinafop-propargyl, clodinafop was predominant in kidney (up to 57% TRR), liver (up to 46% TRR), muscle (up to 21% TRR) and fat (up to 10 31% TRR). In the hen metabolism study, an additional compound CGA 214111 (free and conjugated) was present at the same level as clodinafop in hen liver (12% TRR). Based on the available data, the residue definition for monitoring and risk assessment in animal products is proposed as the ‘sum of clodinafop, its S-isomer, their salts, esters and conjugates, expressed as clodinafop’.

Data gaps were set to address nature and magnitude of potential residues in fish.

The dietary burden calculation, conducted with provisional input values, exceeded the trigger for some species of ruminant and poultry. Based on a provisional assessment using the metabolism studies, residues > 0.005 mg/kg are not expected in animal matrices and feeding studies with ruminant and poultry may be waived provided the feeding rates (mg/kg bw) in the metabolism studies are clarified (data gap) and reliable input values for feed items are provided and a reassessment does not lead to altered estimations of the potential residue transfer in animal matrices.

A sufficient number of residue trials in wheat are available to assess residues that could occur upon application of clodinafop-propargyl to according to the GAP in NEU and SEU. Provided that storage stability for all analytes and over the entire relevant periods of freezer storage of the samples can be demonstrated in grain and straw (data gaps), and the applicability of the analytical method used in the residue trials for esters and conjugates of clodinafop is demonstrated (data gap), the trials would be sufficient to derive risk assessment input values and to extrapolate to rye and triticale in order to address all requested representative uses.

A data gap was identified to further address residue levels in pollen and in bee products for human consumption resulting from residues taken up by honeybees from crops at blossom.

The RMS voiced concerns that by the applied analytical methods in the residue trials (varying of limits of quantification (LOQs) from 0.01 to 0.1 mg/kg) potential residues > 0.01 mg/kg in grain could have been censored. As residues could concentrate in cereal processed commodities and in view of the very low ADI and critical risk assessment outcome (see below), further investigation of the impact of processing on cereal commodities might be warranted (data gap for a standard hydrolysis study simulating food processing conditions).

Chronic and acute consumer dietary intake assessments were provisionally performed by the RMS for wheat and rye, using the revision 2 of the EFSA PRIMo (Pesticide Residue Intake Model). The calculated theoretical maximum daily intake (TMDI) with the tentatively derived MRL of 0.1 mg/kg exceeds for several European diets the ADI. Based on the STMR value (0.02 mg/kg) derived from the wheat trials, the highest long-term dietary intake from wheat and rye accounted for 66% of the ADI (DK Child). The international estimated short-term intake (IESTI) reaches a maximum of 1.4% of the ARfD (wheat).

It is noted that the finalisation of the consumer dietary risk assessment is pending clarification of several data gaps. Some of them may significantly impact the risk assessment outcome (e.g. ultimate confirmation of freezer storage stability of residues and suitability of the analytical method to validate the residue concentrations used in the assessment, finalisation of assessment of residue transfer in animal commodities, currently not considered in the consumer intake assessment, not even at LOQ level, impact of potential change of the isomer composition in the terminal residues in cereal commodities).

An update of the consumer risk assessment that was conducted in the review of MRLs according to Article 12 of Regulation (EC) No 396/2005 (EFSA, 2011b) has been performed using the lower ADI of 0.0003 mg/kg bw per day established during the peer review. The updated consumer risk assessment resulted in an estimated chronic consumer exposure corresponding to 66% ADI at the maximum (DK, child). It is noted that the Art. 12 MRL review used the recommended MRL of 0.02* mg/kg for wheat and rye grain, while a higher MRL of 0.1* mg/kg for these commodities is tentatively derived as outcome of the peer review. Furthermore, an amendment of the plant residue definitions was proposed in order to additionally consider residues of clodinafop present in form of ester or conjugates for risk assessment and monitoring as the data subjected to the peer review supported this decision. Residue definitions for animal commodities were established, that had not been derived under the Art. 12 MRL review.

4. Environmental fate and behaviour

Satisfactory information was not provided to address the specific environmental behaviour of the R-isomer of clodinafop-propargyl and its metabolite CGA 193469, which contain chiral carbon atom.
Therefore, for those processes in which microbial metabolism is involved, some degree of enantioselective transformation cannot be excluded (data gap and issue that could not be finalised). 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, clodinafop-propargyl exhibited very low persistence, forming the major (> 10% applied radioactivity (AR)) metabolites CGA 193469 (clodinafop, max. 79.6% AR), CGA 193468 (max. 10.7% AR) and CGA 302371 (max. 22.5% AR), which exhibited low to moderate, very low and low persistence, respectively. Mineralisation of the phenyl and pyridinyl ring 14C radiolabels to carbon dioxide accounted for 35–66% AR and 34–41% AR after 84 days, respectively. The formation of unextractable residues for these radiolabels accounted for 33–54% AR after 84–365 days (phenyl radiolabel) and 50–58% AR after 84–365 days (pyridinyl radiolabel). In anaerobic soil incubations, clodinafop-propargyl was essentially stable. Clodinafop-propargyl exhibited medium to slight mobility in soil. CGA 193469 exhibited very high to high soil mobility, CGA 193468 exhibited medium to low soil mobility and CGA 302371 exhibited very high to high soil mobility. It was concluded that the adsorption of clodinafop-propargyl and its soil metabolites was not pH dependent. Field dissipation studies were carried out at four sites in Germany, two sites in Canada and one in France. None of these legacy studies was considered suitable for determination of persistence or modelling endpoints. However, the residue data in soil confirmed the very rapid degradation of clodinafop-propargyl to CGA 193469.

In non-aged column leaching studies performed with clodinafop-propargyl, most of the radioactivity found in the soil coarse was CGA 193469. However, neither clodinafop-propargyl nor CGA 193469 were detected in the soil segment of the aged column study. In 3 months field leaching study neither clodinafop-propargyl nor CGA 193469 was detected (limit of detection (LOD) = 0.05 μg/L) in samples collected from 50 cm or below; however, the study was not considered to represent a worst-case situation due to the low rainfall.

In laboratory incubations in dark aerobic natural sediment water systems, clodinafop-propargyl degraded very rapidly (max. 0.6% remaining after 1 day, forming the major metabolites CGA 193469 (max. ca. 93% AR in water and 30% AR in sediment), CGA 193468 (max. ca. 10% AR in sediment but only 1.7% AR in water) and CGA 302371 (max. ca. 46% AR in both water and sediment). The unextractable sediment fraction (not extracted by acetonitrile/water) was the major sink for both the phenyl and pyridinyl 14C radiolabels, accounting for 40–47% AR at study end (126–249 days). Mineralisation of this radiolabel accounted for 20–39% AR at the end of the study. In aqueous photochemical degradation studies clodinafop-propargyl degraded rapidly to CGA 193469 (max. 14.4% AR after 30 days) and SYN548912 (P5), a structural isomer of clodinafop-propargyl (max 28.9% AR after 4 days) and ‘U4’ (max 21.6% AR after ca. 10 days). It was concluded that photolysis may contribute to the environmental degradation of clodinafop-propargyl and CGA 193469 in water.

The necessary surface water and sediment exposure assessments (predicted environmental concentrations (PEC) calculations) were carried out for clodinafop-propargyl and the metabolites CGA 193469, CGA 193468, CGA 302371, SYN548912 (P5) and ‘U4’, using the FOCUS (FOCUS, 2001) step 1 and step 2 approach (version 3.2 of the Steps 1-2 in FOCUS calculator). The necessary groundwater exposure assessments were appropriately carried out using FOCUS (European Commission, 2014a) scenarios and the models PEARL 4.4.4, PELMO 5.5.3 and MACRO 5.5.4. The potential for groundwater exposure from the representative uses by clodinafop-propargyl and the metabolites CGA 193469, CGA 193468 and CGA 302371 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 provided appropriate information to address the effect of water treatments processes on the nature of the residues that might be present in surface water and groundwater, when surface water or groundwater are abstracted for drinking water. The conclusion of this consideration was that neither clodinafop-propargyl nor any of its degradation products that trigger assessment (CGA 193469, CGA 193468, CGA 302371, SYN548912 (P5) and ‘U4’) would be expected to undergo any substantial transformation due to oxidation at the disinfection stage of usual water treatment processes.

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

12 Simulations utilised the agreed Q10 of 2.58 (following EFSA, 2008) and Walker equation coefficient of 0.7.
5. Ecotoxicology

The risk assessment was based on the following documents: European Commission (2002a,b), SETAC (2001), EFSA (2009), EFSA PPR Panel (2013) and EFSA (2013).

Satisfactory information was not provided to address the environmental behaviour of the R-isomer of clodinafop-propargyl and its metabolite CGA193469 (see also Section 4). This adds uncertainty to the available aquatic and soil risk assessment. Therefore, a data gap was identified.

For clodinafop-propargyl, the available information was not sufficient to confirm the compliance of the batches used in the ecotoxicity tests with the technical specification (data gap).

Some aspects of the risk assessment of clodinafop-propargyl were discussed at the Pesticide Peer Review meeting 181 (June 2018).

A low acute and long-term dietary risk was concluded for birds at the screening step. For mammals, a low acute risk was concluded at the screening step. The long-term endpoint for wild mammals risk assessment was discussed at the Pesticides Peer Review meeting 181. The experts in the meeting agreed that an no observed effect concentration (NOEC) value of 3.4 mg a.s./kg bw per day (obtained from a two-generation rat study) should be used in the risk assessment. By following this approach, a high risk was concluded for large herbivorous mammal (TER = 4.8). Further refinements were not available; therefore, a data gap and a critical area of concern were identified to address the long-term risk to herbivorous mammals. Regarding the risk from secondary poisoning, a low risk was concluded for birds and mammals for clodinafop-propargyl. In the absence of a bioconcentration factor (BCF) value, a data gap was identified for addressing the risk of secondary poisoning for the metabolites CGA 193468 and SYN548912 (P5). The risk for birds and mammals from consumption of contaminated water was concluded as low. The available information was not sufficient to address the risk to birds and mammals for clodinafop-propargyl plant metabolites (data gap).

For aquatic organisms, valid acute and chronic toxicity data were available for clodinafop-propargyl for fish and aquatic invertebrates (including sediment dwellers). A low acute and long-term risk for fish and aquatic invertebrates (including sediment dwellers) was concluded. It is however noted that a study on a second algal species was not available. Additionally, there were uncertainties in the available toxicity study on macrophytes (Lemma gibba) and, based on the available information, concerns were raised during the peer review on whether other macrophyte species could be more sensitive than L. gibba (see Data requirement 5.6 in the evaluation table Section 5). As a consequence, data gaps for additional studies on algae and aquatic plants (i.e. other macrophyte species than L. gibba) were identified (issue that could not be finalised). Valid studies addressing the potential for the active substance of being more toxic when formulated with a safener were available for aquatic invertebrates only, but were not available for algae and aquatic plants. Considering that clodinafop-propargyl is a herbicide, a data gap was identified to address the potential of the active substance of being more toxic when formulated, in particular for algae and aquatic plants.

Valid toxicity data were available for fish (acute), aquatic invertebrates (acute) and algae for clodinafop and metabolites CGA 193468 and CGA 302371. Regarding the chronic risks of metabolites for fish and aquatic invertebrates, data were available only for clodinafop. For SYN548912 (P5) and U4, only data on aquatic plants were available. Based on the available data, a low risk was concluded for all pertinent surface water metabolites. However, considering the uncertainties on the most sensitive taxa for the primary producers for the parent, a data gap was identified for further information to address the risk for the pertinent surface water metabolites of clodinafop-propargyl and for further information to address the risk to aquatic organisms for clodinafop.

Suitable acute oral and contact toxicity studies on honeybees were available. Acute studies were available for both clodinafop-propargyl and the representative formulation (’A7957E’). It was however noted that only studies using the formulation ’A7957E’ were available for chronic toxicity testing on adults and larvae. Considering the similarity of the acute endpoints (oral and contact) of ’A7957E’ compared to acute endpoints of clodinafop-propargyl, this was considered acceptable for the risk assessment. The risk to bees has been assessed according to EPPO (2010) and European Commission (2002a). A low acute (oral and contact) risk for honeybees was concluded. The same conclusion was reached by performing a risk assessment according to EFSA (2013). A long-term risk assessment, a risk assessment for the metabolites and for consumption of contaminated water was performed according to EFSA (2013). The long-term risk to honeybee larvae and adults was assessed as low. The risk assessment for metabolites was performed considering that the metabolites are 10 times more...
toxic than the parent compound. By following this approach, a low acute and long-term risk was concluded. The risk for honeybees from consumption of contaminated water (surface water and guttation) was also concluded to be low. The presented assessment was not sufficient to address the risk to honeybees for exposure to contaminated puddle water (data gap). A suitable assessment for accumulative effects was not available. Information to address sublethai effects on honeybees (e.g. effects on HPG) was not available (data gap). No data were available on bumblebees and solitary bees.

Standard laboratory data for non-target arthropods were not available. Extended laboratory tests were available for the representative formulation 'A7957E'. The risk to both in- and off-field non-target arthropods for the use of clodinafop-propargyl was concluded to be low.

For earthworms, valid chronic studies were available with the representative formulation 'A7957E'. A low risk was concluded for clodinafop-propargyl and its metabolites for earthworms. A low risk has been concluded for soil macro-organisms other than earthworms for clodinafop-propargyl and its metabolites.

For soil microorganisms, a low risk was identified for clodinafop-propargyl and its metabolites (CGA 193468, CGA 302371, CGA 193469). A low risk for clodinafop-propargyl was also identified for non-target terrestrial plants and microorganisms involved in sewage treatment.

Pending on the data gap identified in Section 2 further data may be needed to address the potential endocrine-disrupting properties of clodinafop-propargyl for non-target organisms.
## 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 |
|----------------------------|-------------|---------------|
| Clodinafop-propargyl       | Very low persistence DT₅₀ < 1 day days (20°C pF₂ soil moisture) | Low risk to soil-dwelling organisms |
| CGA 193469                 | Low to moderate persistence Bi-phasic DT₅₀ 2.2–13.3 days (20–25°C, 40% MWHC or 75% FC soil moisture; DT₉₀ 27.6–112 days) | Low risk to soil-dwelling organisms |
| CGA 193468                 | Very low persistence Single first order and bi-phasic DT₅₀ 0.02–0.4 days (20°C pF₂ soil moisture; DT₉₀ 1.1–8.8 days) | Low risk to soil-dwelling organisms |
| CGA 302371                 | Low persistence Single first order and bi-phasic DT₅₀ 3.9–9.6 days (20°C pF₂ soil moisture; DT₉₀ 20.8–98.5 days) | Low risk to soil-dwelling 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 |
|-----------------------------|------------------|---------------------------------------------------|-------------------|------------------------|
| Clodinafop-propargyl        | Medium to slight mobility K₉₀ 252–2,364 mL/g | No | Yes | Yes |
| CGA 193469                  | Very high to high mobility K₉₀ 25.3–81.0 mL/g | No | No data, assessment not triggered | No data, assessment not triggered |
| CGA 193468                  | Medium to low mobility K₉₀ 238–630 mL/g | No | No data, assessment not triggered | No data, assessment not triggered |
| CGA 302371                  | Very high to high mobility K₉₀ 25.1–98.0 mL/g | No | No data, assessment not triggered | No data, assessment not triggered |

(a): FOCUS scenarios or relevant lysimeter.
Table 3: Surface water and sediment

| Compound (name and/or code) | Ecotoxicology                |
|-----------------------------|-------------------------------|
| Clodinafop-propargyl        | Data gap                      |
| CGA 193469                  | Data gap                      |
| CGA 193468                  | Data gap                      |
| CGA 302371                  | Data gap                      |
| SYN548912 (P5) (aqueous photolysis) | Data gap                |
| Compound 'U4' (aqueous photolysis) | Data gap                |

Table 4: Air

| Compound (name and/or code) | Toxicology                                                                 |
|-----------------------------|---------------------------------------------------------------------------|
| Clodinafop-propargyl        | Rat LC₅₀ inhalation > 2.3 mg/L air/4 h nose only, maximum attainable concentration (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).

- A detailed evaluation of the search of the scientific peer-reviewed open literature on the active substance and its relevant metabolites, dealing with side effects on human health, 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, 2011a; relevant for all representative uses evaluated; submission date proposed by the applicant: already submitted but detailed evaluation by RMS is missing).
- Clodinafop-propargyl consists of a single enantiomer (R-isomer). The relative toxicity between the R- and S-isomers, as well as a possible metabolism or degradation of the R- to the S-enantiomer of clodinafop-propargyl and its metabolite CGA 193469 in animals, plants and the environment needs to be investigated (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2, 3, 4 and 5).
- Data demonstrating applicability of the existing monitoring method for food/feed of plant origin and for animal products for analysing esters and conjugates or a new monitoring method applicable for all components of the residue definition (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 1).
- Additional validation information for the analytical method used in the developmental toxicity study in rats (key study in deriving the ARfD and AAOEL (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Sections 1 and 2).
- Data demonstrating the applicability of the analytical method used in the residue trials for esters and conjugates of clodinafop (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 1 and 3).
- Assessment of the toxicological relevance of the individual impurities in comparison with the toxicological profile of clodinafop-propargyl (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 1).
- Phototoxicity and photomutagenicity potential – being acknowledged that there is currently no validated test guideline to address these issues for UVB absorbers such as clodinafop-propargyl (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- An endocrine-mediated mode of action cannot be excluded considering the effects observed in the apical studies: decreased testes weights, adenohypophysis cystic dilatation and increased ovary weights in rats; testicular tubular atrophy, decreased spermatogenesis and increased adrenal weights in male mice, for which further data are needed to investigate the mode of action, for instance with an Hershberger assay (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- Toxicological data package on the safener cloquintocet-mexyl (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- Demonstration of integrity of the samples for all relevant analytes during freezer storage until analysis of the samples in the GAP compliant wheat residue trials (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).
- Storage stability study with clodinafop and SYN508109 in wheat grain and straw covering a period of 13–15 months (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown, however study currently in progress; see Section 3).
- Clarification of feeding rates in the animal metabolism studies expressed as mg/kg bw to conclude estimation of residue transfer in animal commodities (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).
- Information that enables an assessment of the nature and magnitude of residues with regard to fish. The applicant may provide a scientific case, considering the nature and magnitude of residues in potential feed items for fish, other data already available on fish (e.g. bioaccumulation tests) to justify that metabolism/feeding studies in fish are not necessary to
complete the risk assessment (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).

- A standard hydrolysis study to investigate the effect of processing on the nature of residues (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).

- Information against the data requirement on residue levels in pollen and in 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 complete list of codes and structures and full identity of the compounds referenced in the RAR Vol. 3 B.7 across the different residues studies (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).

- Further information to confirm the compliance of the batches used in the ecotoxicity tests with the technical specification (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).

- Further information to address the long-term risk to herbivorous mammals for the clodinafop-propargyl (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).

- Further information to address the risk to birds and mammals for clodinafop-propargyl plant metabolites (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).

- Further information to address the risk of secondary poisoning for the metabolites CGA 193468 and SYN548912 (P5) (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).

- Further information to address the risks on algae (second species) and aquatic plants for clodinafop-propargyl. Further information to address the risk to aquatic organisms for clodinafop and for the pertinent surface water metabolites of clodinafop-propargyl (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).

- Further data to address the potential for the active substance of being more toxic when formulated, in particular for algae and aquatic plants (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).

- Further assessment of sublethal effects (e.g. effects on HPG) and risk via exposure to puddle water for honeybees (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**

- Estimated operator exposure remains below the (A)AOEL assuming that workwear is used during mixing, loading and applications, as well as protective gloves during mixing and loading operations.

- A minimum buffer zone of 5 m has to be established to ensure that residential exposure (children) does not exceed the AOEL.

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 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).

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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) Clodinafop-propargyl consists of a single enantiomer (R-isomer). The relative toxicity between the R- and S-isomers, as well as a possible metabolism or degradation of the R- to the S-enantiomer in animals, plants and the environment were not investigated. It is therefore unknown whether a possible shift to a potentially more toxic enantiomer would result in an increased risk, in particular for consumers, workers and residents (see Sections 2, 3, 4 and 5).

2) No validated analytical methods were reported for the developmental toxicity study in rats (key study in deriving the ARfD and AAOEL); therefore, the reliability of the study is questioned and the developmental toxicity endpoint in rat could not be finalised (see Section 2).

3) Clodinafop-propargyl is proposed to be classified as carcinogenic but not as toxic for reproduction category 2, on this basis, the conditions of the interim provisions of Annex II, Point 3.6.5 of Regulation (EC) No 1107/2009 concerning human health for the consideration of endocrine-disrupting (ED) properties are not met. From a scientific perspective, an endocrine-mediated mode of action cannot be excluded considering the effects observed in the apical studies: decreased testes weights, adenohypophysis cystic dilation and increased ovary weights in rats; testicular tubular atrophy, decreased spermatogenesis and increased adrenal weights in male mice, for which further data are needed to investigate the mode of action, for instance with an Hershberger assay (see Section 2).

4) Clodinafop-propargyl is used in combination with the safener cloquintocet-mexyl; the toxicological profile of the safener has not been addressed and a toxicological data package is needed (see Section 2).

5) The consumer dietary risk assessment is not finalised pending clarification of several data gaps that may significantly impact the risk assessment outcome (see Section 3).

6) The aquatic risk assessment for clodinafop-propargyl for algae and macrophytes cannot be finalised considering the identified data gaps for studies on a second algal and macrophyte species, as required under the current legislation for active substances with a herbicidal mode of action (see Section 5).

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.

1) A high risk to large herbivorous mammals was concluded for the representative uses (see Section 5).

9.3. Overview of the concerns identified for each representative use considered

(If a particular condition proposed to be taken into account to manage an identified risk, as listed in Section 8, has been evaluated as being effective, then ‘risk identified’ is not indicated in Table 5.)
**Table 5:** Overview of concerns

| Representative use                                      | Wheat, rye, triticale |
|--------------------------------------------------------|-----------------------|
| **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 |
| **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 |
| **Risk to aquatic organisms**                          | Risk identified       |
|                                                        | Assessment not finalised |
| **Groundwater exposure to active substance**            | Legal parametric value breached |
|                                                        | Assessment not finalised |
| **Groundwater exposure to metabolites**                | Legal parametric value breached |
|                                                        | Parametric value of 10 µg/L<sup>a</sup> breached |
|                                                        | Assessment not finalised |

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

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**Abbreviations**

1/\(n\) slope of Freundlich isotherm  
\(\lambda\) wavelength  
\(\varepsilon\) decadic molar extinction coefficient  
a.s. active substance  
AAOEL acute acceptable operator exposure level  
ADE actual dermal exposure  
ADI acceptable daily intake  
AF assessment factor  
AOEL acceptable operator exposure level  
AOEL acute acceptable operator exposure level  
AP alkaline phosphatase  
AR applied radioactivity  
ARfD acute reference dose  
AST aspartate aminotransferase (SGOT)  
AUC area under the blood concentration/time curve  
AV avoidance factor  
BCF bioconcentration factor  
BREAM Bystander and Residential Exposure Assessment Model  
BUN blood urea nitrogen  
bw body weight  
CAS Chemical Abstracts Service  
CFU colony-forming units  
CI confidence interval  
CL confidence limits  
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)  
EC emulsifiable concentrate  
ECHA European Chemicals Agency  
EEC European Economic Community  
EUROPOEM European Predictive Operator Exposure Model  
f(twa) Time-weighted average factor  
FAO Food and Agriculture Organization of the United Nations  
FID flame ionisation detector  
FIR food intake rate  
FOB functional observation battery  
FOCUS Forum for the Co-ordination of Pesticide Fate Models and their Use  
GAP Good Agricultural Practice  
GC gas chromatography  
GM geometric mean  
GS growth stage  
HPLC high-pressure liquid chromatography or high-performance liquid chromatography  
HPLC-MS high-pressure liquid chromatography-mass spectrometry  
HPG hypopharyngeal glands  
HQ hazard quotient  
HR hazard rate  
IESTI international estimated short-term intake  
ISO International Organization for Standardization  
IUPAC International Union of Pure and Applied Chemistry  
iv intravenous
| Acronym   | Description                                                                 |
|-----------|-----------------------------------------------------------------------------|
| JMPR      | Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues) |
| K_FOC    | Freundlich organic carbon adsorption coefficient                          |
| LC        | liquid chromatography                                                      |
| LC_{50}   | lethal concentration, median                                               |
| LC-MS     | liquid chromatography–mass spectrometry                                   |
| LC-MS-MS  | liquid chromatography with tandem mass spectrometry                        |
| LOAEL     | Lowest observed adverse effect level                                       |
| LOD       | limit of detection                                                         |
| LOQ       | limit of quantification                                                    |
| M/L       | mixing and loading                                                         |
| mm        | millimetre (also used for mean measured concentrations)                    |
| MRL       | maximum residue level                                                      |
| MS        | mass spectrometry                                                          |
| MWHC      | maximum water-holding capacity                                              |
| NOAEL     | no observed adverse effect level                                            |
| NOEC      | no observed effect concentration                                            |
| NOEL      | no observed effect level                                                   |
| OECD      | Organisation for Economic Co-operation and Development                     |
| OM        | organic matter content                                                     |
| Pa        | pascal                                                                      |
| PD        | proportion of different food types                                          |
| PEC       | predicted environmental concentration                                       |
| PHI       | preharvest interval                                                        |
| PIE       | potential inhalation exposure                                               |
| P_{ow}    | partition coefficient between n-octanol and water                          |
| PPE       | personal protective equipment                                               |
| ppm       | parts per million (10^{-6})                                                |
| PT        | proportion of diet obtained in the treated area                            |
| PTT       | partial thromboplastin time                                                 |
| QSAR      | quantitative structure–activity relationship                              |
| r^2       | coefficient of determination                                               |
| RAR       | Renewal Assessment Report                                                   |
| REACH     | Registration, Evaluation, Authorisation of Chemicals Regulation             |
| SC        | suspension concentrate                                                     |
| SD        | standard deviation                                                         |
| SMILES    | simplified molecular-input line-entry system                              |
| STMR      | supervised trials median residue                                           |
| STOT-RE   | specific target organ toxicity – repeated exposure                         |
| t_{1/2}   | half-life (define method of estimation)                                    |
| TER       | toxicity exposure ratio                                                    |
| TER_A     | toxicity exposure ratio for acute exposure                                 |
| TK        | technical concentrate                                                      |
| TMDI      | theoretical maximum daily intake                                           |
| TRR       | total radioactive residue                                                   |
| TWA       | time-weighted average                                                      |
| UF        | uncertainty factor                                                         |
| UV        | ultraviolet                                                                |
| W/S       | water/sediment                                                             |
| w/v       | weight per unit volume                                                     |
| w/w       | weight per unit weight                                                     |
| WBC       | white blood cell                                                           |
| 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.2020.6151
## Appendix B – Used compound codes

| Code/trivial name(a) | IUPAC name/SMILES notation/InChiKey(b) | Structural formula(b) |
|---------------------|--------------------------------------|-----------------------|
| **Clodinafop-**<br>propargyl | prop-2-ynyl (R)-2-[4-(5-chloro-3-fluoro-2-pyridyloxy)phenoxy]propanoate<br>\[\text{C}[\text{C}@@\text{H}]\text{(OC1=C=CC2(=NC(Cl)(=C=C2F))=C1=O)}\]<br>JBDHKLJNAIJC-LLVKDONJSA-N | ![prop-2-ynyl (R)-2-[4-(5-chloro-3-fluoro-2-pyridyloxy)phenoxy]propanoate](image1.png) |
| Clodinafop -<br>CGA 193469 | (R)-2-[4-(5-chloro-3-fluoro-2-pyridyloxy)phenoxy]propionic acid<br>\[\text{C}[\text{C}@@\text{H}]\text{(OC1=C=CC2(=NC(Cl)(=C=C2F))=C1=O)}\]<br>YUIKUTLBPMDDNQ-MRVPVSSYSA-N | ![Clodinafop - (R)-2-[4-(5-chloro-3-fluoro-2-pyridyloxy)phenoxy]propionic acid](image2.png) |
| **CGA 193468**<br>M1 | 4-((5-chloro-3-fluoropyridin-2-yl)oxy)phenol<br>\[\text{ClC(C=O)}\text{(C=CN=O)}\text{(OC1=C=CC2(=NC(Cl)(=C=C2F))=C1=O)}\]<br>QRDGJZIEMNJEKN-UHFFFAOYSA-N | ![4-((5-chloro-3-fluoropyridin-2-yl)oxy)phenol](image3.png) |
| **CGA 302371** | 5-chloro-3-fluoropyridin-2-ol<br>\[\text{ClC1}\text{(C=O)(F)}\text{=C1=O)}\]<br>AKLNMLGRGQMFY-UHFFFAOYSA-N | ![5-chloro-3-fluoropyridin-2-ol](image4.png) |
| **SYN 548912**<br>(P5) | prop-2-yn-1-yl 2-([5-(5-chloro-3-fluoropyridin-2-yl)oxy]-2-hydroxyphenyl)propanoate<br>\[\text{CC(C1=CC(OC2=NC(Cl)(=C=C2F))=C1=O)}\text{(OCC#C)=O)}\]<br>PJTPTGCPVRIXQS-UHFFFAOYSA-N | ![prop-2-yn-1-yl 2-([5-(5-chloro-3-fluoropyridin-2-yl)oxy]-2-hydroxyphenyl)propanoate](image5.png) |
| **U4 isomer 1** | 5-chloro-3-fluo-3-4-dihydropyridine-2,4-diol<br>\[\text{CIC(C(O)C1F)}\text{=C1=O)}\]<br>XWALIYBEZEHROZ-UHFFFAOYSA-N | ![5-chloro-3-fluo-3-4-dihydropyridine-2,4-diol](image6.png) |
| **U4 isomer 2** | 3-chloro-5-fluoro-2,3-dihydropyridine-2,6-diol<br>\[\text{CIC(C1F)}\text{C(O)N=C1O)}\]<br>CVALIKMIRHLPGQ-UHFFFAOYSA-N | ![3-chloro-5-fluoro-2,3-dihydropyridine-2,6-diol](image7.png) |
| **II2 (U7) - hydroxyl clodinafop acid** | (R)-2-[(6-chloro-3-fluoro-5-hydroxydpyridin-2-yl)oxy]propanoic acid<br>\[\text{C}[\text{C}@@\text{H}]\text{(OC1=C=CC2(=NC(Cl)(=C=C2F))=C1=O)}\]<br>YTPKMNHSJOCRVC-SSDOTTWSA-N | ![II2 (U7) - hydroxyl clodinafop acid](image8.png) |
| **CGA 214111** | (R)-2-[(4-hydroxyphenoxy)propanoic acid<br>\[\text{C}[\text{C}@@\text{H}]\text{(OC1=C=CC2(=NC(Cl)(=C=C2F))=C1=O)}\]<br>AQIHDXGKQHBNWX-ZCFIWBFSN-A | ![CGA 214111](image9.png) |
| Code/trivial name<sup>(a)</sup> | IUPAC name/SMILES notation/InChiKey<sup>(b)</sup> | Structural formula<sup>(b)</sup> |
|-------------------------------|---------------------------------|-------------------------------|
| **M3**<br>CGA 144462 | 2-(4-((5-chloro-3-fluoropyridin-2-yl)oxy)phenoxy) propanoic acid<br>CC(OC1=C-C(OC2=NC=C(O)C=C2F)C=C1)C(O)=O<br>YUIKUTLPMDDNQ-UHFFFAOYSA-N | ![Structural formula](image) |

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

<sup>(b)</sup> ChemBioDraw v.13.0.2.3021.