CONCLUSION ON PESTICIDES PEER REVIEW

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Peer review of the pesticide risk assessment of the active substance aqueous extract from the germinated seeds of sweet *Lupinus albus*

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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, the Netherlands, for the pesticide active substance aqueous extract from the germinated seeds of sweet *Lupinus albus* 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 uses of the aqueous extract from the germinated seeds of sweet *Lupinus albus* as a fungicide on strawberry and tomatoes (field use and greenhouse application). 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 were not identified.

Keywords: Aqueous extract from the germinated seeds of sweet *Lupinus albus*, sweet lupin, peer review, risk assessment, pesticide, fungicide

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Summary

Aqueous extract from the germinated seeds of sweet *Lupinus albus* 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), the Netherlands, received an application from CEV SA on 7 June 2016 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 18 January 2017.

An initial evaluation of the dossier on the active substance aqueous extract from the germinated seeds of sweet *Lupinus albus* (formerly: Sweet Lupin (seeds), *Lupinus albus* L., germ., ext.) 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 uses of aqueous extract from the germinated seeds of sweet *Lupinus albus*, according to the representative uses as a fungicide on field and protected strawberry and tomatoes, as proposed at EU level, result in a sufficient fungicidal efficacy against the target organisms.

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 and technical properties of the aqueous extract from the germinated seeds of sweet *Lupinus albus* or the representative formulation.

In the area of mammalian toxicology and non-dietary exposure, critical areas of concern or issues that could not be finalised were not identified.

An MRL application for inclusion of the active substance in Annex IV of Regulation (EC) No 396/2005 has been submitted. The aqueous extract from the germinated seeds of sweet *Lupinus albus* is proposed to be included in Annex IV of Regulation (EC) No 396/2005 on the basis of expert judgement, although the criteria for the inclusion in the Annex IV of Regulation (EC) No 396/2005 are not met.

The data available on environmental fate and behaviour are sufficient to carry out the required environmental exposure assessments at EU level.

In the area of ecotoxicology, low risk to birds and mammals, aquatic organisms, non-target arthropods, earthworms and soil microorganisms, non-target terrestrial plants and sewage treatment organisms is concluded for all the representative uses. Critical areas of concern or issues that could not be finalised were not identified.

The aqueous extract from the germinated seeds of sweet *Lupinus albus* does not meet the criteria for endocrine disruption for humans and non-target organisms according to points 3.6.5 and 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605.

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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).

Aqueous extract from the germinated seeds of sweet *Lupinus albus* is a new active substance for which, in accordance with Article 7 of the Regulation, the RMS, the Netherlands (hereinafter referred to as the 'RMS'), received an application from CEV SA on 7 June 2016 for approval of the active substance sweet lupin (seeds), *Lupinus albus* L., germ., ext. This name was changed during the evaluation procedure to aqueous extract from the germinated seeds of sweet *Lupinus albus*. 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 18 January 2017.

The RMS provided its initial evaluation of the dossier on the active substance aqueous extract from the germinated seeds of sweet *Lupinus albus* in the DAR, which was received by EFSA on 1 April 2019 (The Netherlands, 2019). The peer review was initiated on 30 April 2019 by dispatching the DAR to the Member States and the applicant, CEV SA, 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 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 applicant in accordance with Article 12(3) of the Regulation were considered in a telephone conference between EFSA and the RMS on 5 September 2019. On the basis of the comments received, the applicant's response to the comments and the RMS's evaluation thereof, it was concluded that additional information should be requested from the applicant, and that EFSA should conduct an expert consultation in the areas of mammalian toxicology and ecotoxicology.

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

The conclusions arising from the consideration by EFSA, and as appropriate by the RMS, of the points identified in the evaluation table, together with the outcome of the expert consultation where this 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 the active substance aqueous extract from the germinated seeds of sweet *Lupinus albus* 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 proposal for inclusion of the substance in Annex IV of Regulation (EC) No 396/2005 took place with Member States via a written procedure in May–June 2020.

[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.

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 uses of the aqueous extract from the germinated seeds of sweet *Lupinus albus*, as a fungicide on strawberry and tomatoes (field use and greenhouse application) 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.

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.

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

- the comments received on the DAR;
- the reporting table (10 September 2019);
- the evaluation table (15 June 2020);
- the report(s) of the scientific consultation with Member State experts (where relevant);
- the comments received on the assessment of the additional information (where relevant);
- the comments received on the draft EFSA conclusion.

Given the importance of the DAR including its revisions (The Netherlands, 2020) and the peer review report, both documents are considered as background documents to this conclusion.

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 active substance and the formulated product

The active substance aqueous extract from the germinated seeds of sweet *Lupinus albus* is considered by the International Organization for Standardization not to require a common name. It is an extract from sweet lupin, its main component, the BLAD protein (not ISO 1750), is registered at GenBank at NCBI with accession number DQ142920.1 (*Lupinus albus* BLAD mRNA, partial cds). The original name used for the active substance was 'sweet lupin (seeds), *Lupinus albus* L., germ., ext.'. This name was changed during the evaluation procedure based on the proposal of the European Chemicals Agency (ECHA), who received a submission for harmonised classification for the same substance.

The representative formulated product for the evaluation was 'Problad Plus', a soluble concentrate (SL) containing 1,000 g/kg aqueous extract from the germinated seeds of sweet *Lupinus albus*, corresponding to a nominal content of 200 g/kg BLAD protein. An FAO specification does not exist for this product.

The representative uses evaluated comprise spray applications against foliar fungi in field cultivation of strawberry and tomatoes in the Southern and Central European zones and spray applications in protected strawberry and tomatoes in the EU. Full details of the GAP can be found in the list of end points in Appendix A.

Data were submitted to conclude that the uses of aqueous extract from the germinated seeds of sweet *Lupinus albus* according to the representative uses proposed at EU level result in a sufficient fungicidal efficacy, following the guidance document SANCO/10054/2013-rev. 3 (European Commission, 2013).

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: European Commission, 2000a,b, 2010, 2012, 2013.

The active substance aqueous extract from the germinated seeds of sweet *Lupinus albus* is considered a UVCB substance (Substance of Unknown or Variable composition, Complex reaction product or Biological material). The lead component BLAD ('Banda de *Lupinus albus* doce') is a naturally occurring seed storage protein in germinated sweet lupins; it is a 210 kDa glyco-oligomer containing mainly a polypeptide of β-conglutin.

The technical material is only a hypothetical stage in the continuous production process of the end use product. As a consequence, the specification is given only for the formulation 'Problad Plus". The specification is based on pilot scale production. The extract has a declared purity of 1,000 g/kg. The content of the lead component BLAD is between 195 and 210 g/kg (the minimum content of BLAD is 330 g/kg on dry weight basis). Quinolizidine alkaloids (QAs; lupanine, 13α-OH-lupanine, 13α-angeloyloxylupanine, lupinine, albine, angustofoline, 13α-tigloyloxylupanine, α-isolupanine, tetrahydrohombifoline, multiflorine, sparteine) were considered as relevant compounds that need to be specified (see Section 2). As a consequence, a data gap was identified for five-batch data of the quinolizidine alkaloids and a corresponding specification.

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 and technical properties of the representative formulation. It should be noted that label instructions are needed concerning the measures to address foaming and stability of dilutions of the formulation.

Acceptable method was available for the determination of the BLAD in the representative formulation. A data gap was identified for an analytical method for the determination of total quinolizidine alkaloids in the product. It should be noted that an analytical method exists for the determination of the lupanine content in the representative formulation.

Since residue definitions were not defined in any compartments, methods for post-authorisation control and monitoring purposes are not required.

2. Mammalian toxicity

The toxicological profile of the active substance aqueous extract from the germinated seeds of sweet *Lupinus albus* was discussed at the Pesticides Peer Review Experts' Teleconference 25 (March 2020) and assessed based on the following guidance documents: European Commission (2003, 2012, 2014a), EFSA PPR Panel (2012), EFSA (2014) and ECHA (2017a).

The active substance is considered as a botanical active substance as defined in SANCO/11470/2012 – rev.8 (European Commission, 2014a). The toxicological profile of the active substance was assessed based on toxicity studies that were representative of the proposed technical specification for the active substance. The experts agreed that total quinolizidine alkaloids (QAs) are considered relevant components given their neurotoxic potential (EFSA CONTAM Panel, 2019). The provisional maximum content for total QAs[3] (see confidential information in DAR Volume 4, April 2020) was calculated considering the content of lupanine in the five-batch analysis and with the assumption that lupanine is around 70% of total QAs[4] since method(s) of analysis for total QAs are not yet available (see data gap in Section 1). The provisional maximum content of total QAs in the specification is acceptable from the toxicological point of view (see confidential information in DAR Volume 4, April 2020). However, further refinement is needed since EFSA considered that the 11 QAs which are considered most relevant with respect to occurrence in lupin species for human and animal consumption in Europe (lupanine, 13α-OH-lupanine, 13α-angeloyloxylupanine, lupinine, albine, angustofoline, 13α-tigloyloxylupanine, α-isolupanine, tetrahydrohombifoline, multiflorine, sparteine) (EFSA CONTAM Panel, 2019) should be measured (see data gap in Section 1).

Specific toxicokinetics studies have not been conducted. As the active substance contains the naturally occurring polypeptide component, BLAD, the protein will be broken down, enter the amino acid pool and

[3] The maximum content of total quinolizidine alkaloids is still open, but it is not expected to be of toxicological concern given the provisional estimates as given in the DAR Volume 4, April 2020.

[4] See experts' consultation point 2.6 from the Pesticides Peer Review Experts' Teleconference 25 (March 2020) (EFSA, 2020).

will be consumed into normal catabolic processes. Considering the nature of the active substance, a residue definition for body fluids and tissues is not necessary. For the risk assessment, an oral absorption of 100% is assumed. In the acute toxicity studies, the active substance has low acute toxicity when administered orally, dermally or by inhalation to rats. It is not a skin or eye irritant. A phototoxicity and photogenotoxicity test is not required for the active substance. In the 90-day oral rat toxicity study, a no observed adverse effect level (NOAEL) of 500 mg/kg body weight (bw) per day was set by the majority of experts based on vacuolation in brain and spinal cord in one female at 1,000 mg/kg bw per day. The RMS did not agree. In the 22-day dermal rat toxicity study, an NOAEL of 300 mg/kg bw per day was set based on increased adrenal weight. The active substance is unlikely to be genotoxic *in vivo*. Further toxicological studies (i.e. carcinogenicity or reproductive toxicity) were not available and were considered unnecessary by the majority of the experts; there were no indications of any link to carcinogenicity or reproductive toxicity from the active substance in the public literature.

The experts agreed that the active substance should not be considered a skin sensitiser according to the results of the Buehler test. The applicant provided some evidence that the active substance may not be a food allergen; however, lupins and lupin products, from which the active substance is derived, have been included in the group of allergens which must appear in the labelling of foodstuffs in Regulation (EU) No 1169/2011[5]. On this basis, medical treatment should be proposed by the applicant leading to a data gap. In addition, the applicant should further address the relevance of existing findings/case reports on *L. albus* intoxication in humans for the active substance as described by the EFSA CONTAM Panel, 2019.

The **agreed acceptable daily intake** (ADI) and **systemic acceptable operator exposure level** (AOEL) are 5 mg/kg bw per day, on the basis of the relevant short-term NOAEL of 500 mg/kg bw per day in the 90-day study in rats based on vacuolation in brain and spinal cord in one female at 1,000 mg/kg bw per day. An uncertainty factor (UF) of 100 was applied. Given the nature of the active substance and considering that there were no indications of any link to carcinogenicity or reproductive toxicity of the active substance in the public literature, an additional UF was not considered necessary despite the limited data package available. A correction factor for oral absorption/systemic bioavailability is not needed to derive the AOEL. The experts agreed that an **acute reference dose** (ARfD) or **acute acceptable operator exposure level** (AAOEL) was not needed for the active substance.

The RMS estimated **non-dietary exposure** (i.e. operator, worker, bystander and resident exposure estimates) considering a default dermal absorption value of 25% for the concentrate and the dilution as input values. Considering the representative uses as a fungicide in strawberry and tomato (outdoor and indoor uses), the maximum estimated operator exposure was below the AOEL (59% of the AOEL) without the use of personal protective equipment (PPE) during mixing and loading and application according to the Dutch Model (indoor uses). Worker exposure was below the AOEL without the use of PPE (maximum 96% of the AOEL, strawberry (outdoor/indoor uses)). Resident exposure was below the AOEL (maximum 13% of the AOEL; child resident, tomato (outdoor use)). Bystander was not calculated because an acute AOEL (AAOEL) was not required for the active substance.

3. Residues

The assessment in the residue section is based on the following guidance documents: OECD (2009, 2011), European Commission (2011) and JMPR (2004, 2007).

No standard studies according to EU/OECD guidance documents and EU data requirements have been submitted to address the metabolic behaviour of aqueous extract from the germinated seeds of sweet *Lupinus albus*, for the representative uses.

In two supportive studies conducted at 0.5 N rate, the fate of aqueous extract from the germinated seeds of sweet *Lupinus albus*, when applied to grape leaves and tomatoes was investigated and provided evidence that the lead component BLAD, which forms 20% w/w of the formulation 'Problad Plus" is degraded 18 h after application and no longer detectable in the investigated tissues.

Supervised residue trials with strawberries, tomatoes and grapes were performed in the US according to the proposed GAPs. As the analytical method provides only semiquantitative results and

[5] Regulation (EU) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers, amending Regulations (EC) No 1924/2006 and (EC) No 1925/2006 of the European Parliament and of the Council, and repealing Commission Directive 87/250/EEC, Council Directive 90/496/EEC, Commission Directive 1999/10/EC, Directive 2000/13/EC of the European Parliament and of the Council, Commission Directives 2002/67/EC and 2008/5/EC and Commission Regulation (EC). OJ L 304, 22.11.2011, p. 18–6.

information on the storage stability of BLAD was not available, these trials were considered only supportive.

The aqueous extract from the germinated seeds of sweet *Lupinus albus* is proposed for inclusion in Annex IV of Regulation (EC) No 396/2005 provided that the outstanding issues regarding quinolizidine alkaloids (QAs) are cleared (see Section 2). Although none of the five criteria listed in the guidance document on criteria for the inclusion of active substances into Annex IV of Regulation (EC) No 396/2005 (European Commission, 2015) are met, the proposal is supported on the basis of expert judgement as outlined in the Evaluation table (Open point 3.3; EFSA, 2020).

A residue definition is not meaningful as the major compound is a naturally occurring seed storage protein which was shown to be degraded when applied according to the representative uses and cannot not be regarded unique, nor would be any other compound of the aqueous extract from the germinated seeds of sweet *Lupinus albus* be a good marker for the residue definition for enforcement.

Therefore, in this specific case, further data on plant metabolism, residue trials for the representative uses, storage stability as well as residue definitions are not required.

It is also acknowledged that an ADI of 5 mg/kg bw per day has been proposed, but a consumer risk assessment is not deemed necessary for the reasons given above.

However, given that the allergenic potential has not be fully addressed by the applicant and lupins and lupin products, from which the active substance is derived, have been included in the group of allergens which must appear in the labelling of foodstuffs as well considering that the proposed foliar application might lead to residues of lupin allergens on or in foodstuffs, a potential risk for vulnerable consumer groups due to the allergenic properties can not be excluded.

Literature search was conducted for both the aqueous extract from the seeds of sweet *Lupinus albus* and the quinolizidine alkaloids.

Residues in pollen and honey bee products were not investigated and based on the above given reasons further information is not necessary; but not on grounds that the application is conducted after the flowering which is according to the GAP not correct.

3.1. Maximum residue levels

The aqueous extract from the germinated seeds of sweet *Lupinus albus* is, on the basis of expert judgement, proposed to be included in Annex IV of Regulation (EC) No 396/2005 provided that the outstanding issues regarding quinolizidine alkaloids (QAs) are cleared (see Section 2), although the criteria for the inclusion in the Annex IV of Regulation (EC) No 396/2005 are not met.

4. Environmental fate and behaviour

Aqueous extract from the germinated seeds of sweet *Lupinus albus* consists of many different components; the main one is the protein BLAD which represents 20% of the formulated product 'Problad Plus'. Protein BLAD is not isolated during the preparation of the product, and therefore, the majority of the studies were carried out using the formulated product 'Problad Plus'.

The rates of degradation in the soil and surface water and sediment were estimated based on ready biodegradability tests and ECHA Guidance (2017b). Aqueous extract from the germinated seeds of sweet *Lupinus albus* and its major component protein BLAD were demonstrated to be readily biodegradable. Since in ECHA (2017b), the relevant reference temperature for degradation is 12°C, in the present assessment data were normalised to 20°C as this is the reference temperature used by the relevant calculation tools used for active substances in plant protection product exposure assessments.

Aqueous extract from the germinated seeds of sweet *Lupinus albus* exhibited moderate to high persistence in soil considering the ECHA Guidance (2017b).

Experimental studies were not available for the determination of the mobility of aqueous extract from the germinated seeds of sweet *Lupinus albus* in soil. However, QSAR estimations of adsorption were made for protein BLAD and the relevant impurity lupanine. Protein BLAD was indicated to exhibit immobility in soil, while lupanine was indicated to exhibit moderate to low mobility in soil.

In natural sediment water systems, protein BLAD was considered to exhibit low persistence considering the ECHA Guidance (2017b).

The necessary surface water and sediment exposure assessments (predicted environmental concentrations (PEC) calculations) were carried out for the formulated product 'Problad Plus', using the FOCUS (FOCUS, 2001) step 1 and step 2 approach (version 3.2 of the Steps 1–2 in FOCUS calculator).

The surface water and sediment exposure assessments for the representative protected uses were considered covered by the available calculations for the field uses.

The necessary groundwater exposure assessments were appropriately carried out using FOCUS (European Commission, 2014b) 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 the indicator compounds of the aqueous extract from the germinated seeds of sweet *Lupinus albus* 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 some information to address the effect of water treatment processes on the nature of the residues that might be present in surface water, when surface water is abstracted for drinking water. The information justifying the dilution factors proposed between small water bodies and large ones where drinking water abstraction would take place was considered inappropriate. However, considering the indicated high adsorption characteristics of the indicator components of the active substance, it can be qualitatively assessed that at the point of abstraction of surface water for drinking water, concentrations would be expected to be below 0.1 μg/L (the drinking water limit). Consequently, abstracted surface water is unlikely to contain residues that might be changed by water treatment purposes.

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

5. Ecotoxicology

The risk assessment was based on the following documents: European Commission (2002a,b, 2014a), SETAC (2001), EFSA (2009, 2013) and EFSA PPR Panel (2013). Some specific aspects related to the environmental risk assessment of aqueous extract from the germinated seeds of sweet *Lupinus albus* were discussed in the Pesticide Peer Review Experts' Teleconference 25 in March 2020.

The information to support the compliance of the batches used in the ecotoxicological studies with the technical specification was considered sufficient.

Acute oral toxicity data were available for wild **mammals** with the representative formulation 'Problad Plus'. No acute toxicity data for **birds** were available. Instead, the acute risk was assessed by considering the available information from the literature and the very high margin of safety obtained in the acute risk assessment for mammals. Based on the available information and risk assessments, a low acute risk to birds and mammals was concluded for all the representative spray uses. Appropriate long-term oral end points were not available for either birds or wild mammals. However, due to the nature of the active substance and its lead component (BLAD protein), the specific mode of action and ready biodegradability of the BLAD protein (see Section 4), the provision of long-term studies was not required and a low long-term risk to both birds and mammals was concluded for the representative uses. The risk from secondary poisoning of earthworm-eating birds and mammals was considered low for all the representative uses. Considering the characteristics of the active substance, bioaccumulation in fish is not expected; therefore, a quantitative risk assessment from exposure via secondary poisoning of fish-eating birds and mammals was considered unnecessary. A low risk to birds and mammals from consumption of contaminated water was concluded for all the representative uses. Relevant plant metabolites were not identified; therefore, exposure to plant metabolites has not been considered further.

Acute data for assessing the oral toxicity of the representative formulation were available for **fish** (the rainbow trout, *Oncorhynchus mykiss*), **aquatic invertebrates** (the water flea *Daphnia magna*) and two green **algae** (*Desmodesmus subspicatus* and *Raphidocelis subcapitata*). Chronic toxicity data were available for *Daphnia* and the representative formulation. Chronic end points for other aquatic organisms were not provided. Based on the available tier 1 data and the characteristics of the active substance, low risk to fish, aquatic invertebrates and algae was concluded for all the representative uses by using FOCUS Step 1–2 exposure estimates. Relevant aquatic metabolites were not identified; therefore, exposure to aquatic metabolites has not been considered further.

Appropriate acute and chronic toxicity data on honey **bees** were available for the formulated product. In addition, studies investigating the chronic oral toxicity of 'Problad Plus' to honey bee larvae were available. The risk assessment performed in line with the EFSA bee guidance document (EFSA, 2013) showed a low acute risk to honey bees from contact and oral exposure for all the representative uses (the same conclusion would be reached by applying the guidance document on terrestrial ecotoxicology (European Commission, 2002a)). The risk to honeybee larvae was assessed as low for all uses evaluated. A high chronic risk was indicated in the screening step for all uses. The tier 1 chronic

risk assessment resulted in a low risk for the use in tomatoes and in a high risk from exposure to residues from pollen and nectar in the treated crop in strawberries. However, considering the nature of the substance and the foliar degradation of its lead component following application (see Section 3), the chronic risk to honey bees in the treated crop scenario can also be considered as low for the uses in strawberries. The risk from exposure to contaminated surface water was not assessed (data gap). An assessment of accumulative effects was not available. No data were available on sublethal effects, e.g. hypopharyngeal glands (data gap). Toxicity data and risk assessment were not provided for bumblebees or solitary bees.

Tier 1 and extended laboratory toxicity tests on the **non-target arthropods**, the parasitic wasp *Aphidius rhopalosiphi* and the predatory mite *Typhlodromus pyri*, were available with the representative formulation. In addition, an extended laboratory test on the green lacewing *Chrysoperla carnea* with the representative formulation was submitted. Based on the available data and risk assessment, a low in-field and off-field risk to non-target arthropods was concluded for all the representative uses.

Chronic toxicity data with the formulated product were available for **earthworms**. No effects were observed in this study. Based on the risk assessment, a high chronic risk could not be excluded. However, taking into account the conservativeness in the PECsoil estimation and that the estimated toxicity exposure ratio (TER) value is close to the trigger, a low risk to earthworms is concluded for all the representative uses of 'Probad Plus'. Data on effects on **soil macroorganisms** other than earthworms were not required as a low risk to relevant non-target arthropod species was concluded at Tier 1. A low risk to **soil microorganisms** was concluded for all the representative uses.

A low risk to **non-target terrestrial plants** was concluded for all the representative uses. A study was not available for assessing the effects of 'Probad Plus' to organisms involved in **sewage treatment processes**; however, considering the ready biodegradability of the formulated product, a low risk was concluded.

6. Endocrine disruption properties

With regard to the assessment of the endocrine disruption potential of the aqueous extract from the germinated seeds of sweet *Lupinus albus* **for human health**, although a complete toxicological data package is not available to assess the endocrine-disrupting properties (see Section 2), further studies do not appear scientifically necessary considering that the active substance is of botanical nature, naturally occurring with a pesticide non-toxic mode of action specific to fungi only, the use of lupins in feed and food, the knowledge that the BLAD protein is biodegradable and that the available toxicity studies and public literature do not provide any major toxicological concern (see Section 2).

With regard to the assessment of the endocrine-disrupting potential of the aqueous extract from the germinated seeds of sweet *Lupinus albus* **for non-target organisms**, although no (eco)toxicological data are available to assess the endocrine-disrupting properties, this does not appear scientifically necessary as lupins may be part of the diet of poultry, fish in aquaculture and other terrestrial animals. Furthermore, in the environment, the active substance is constituted by water, proteins, carbohydrates and lipids.

Considering the above, it can be concluded that the aqueous extract from the germinated seeds of sweet *Lupinus albus* does not meet the criteria for endocrine disruption for humans and non-target organisms according to points 3.6.5 and 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605[6].

[6] Commission Regulation (EU) 2018/605 of 19 April 2018 amending Annex II to Regulation (EC) No 1107/2009 by setting out scientific criteria for the determination of endocrine disrupting properties. OJ L 101, 20.4.2018, p. 33–36.

7. 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
Aqueous extract from the germinated seeds of sweet *Lupinus albus*	Moderate to high persistence DT_{50} 14.1–141 days (normalised to 20°C)	Low risk

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
Aqueous extract from the germinated seeds of sweet *Lupinus albus*	–	–	Yes	Yes
Protein BLAD	Immobile K_{OC} 10,000 L/kg (estimated via QSAR)	No	Yes	Assessment not triggered
Lupanine	Moderate to low mobility K_{OC} 57.3–1287 L/kg (estimated via QSAR)	No	Unknown based on dossier information	Assessment not triggered

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

Table 3: Surface water and sediment

Compound (name and/or code)	Ecotoxicology
Aqueous extract from the germinated seeds of sweet *Lupinus albus*	Low risk

Table 4: Air

Compound (name and/or code)	Toxicology
Aqueous extract from the germinated seeds of sweet *Lupinus albus*	Low acute inhalation toxicity to rats

8. 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 the Regulation concerning information on potentially harmful effects).

- GLP five-batch data of the total quinolizidine alkaloids (lupanine, 13α-OH-lupanine, 13α-angeloyloxylupanine, lupinine, albine, angustofoline, 13α-tigloyloxylupanine, α-isolupanine, tetrahydrohombifoline, multiflorine, sparteine) and a corresponding specification (relevant for all representative uses evaluated; see Sections 1 and 2).
- Analytical method for the determination of total quinolizidine alkaloids in the product (relevant for all representative uses evaluated; see Sections 1 and 2).
- Medical treatment considering that lupins and lupin products, from which the active substance is derived, have been included in the group of allergens which must appear in the labelling of foodstuffs in Regulation (EU) No 1169/2011 (relevant for all representative uses evaluated; see Section 2).
- Assessment of the relevance of existing findings/case reports on *L. albus* intoxication in humans for the active substance (relevant for all representative uses evaluated; see Section 2).

- Risk from exposure of bees to contaminated surface water (relevant for all representative uses; see Section 5).
- Information to address the risk to bees from sublethal effects (e.g. HPG) (relevant for all representative uses; see Section 5).

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

- Label instructions are needed concerning the measures to address foaming and stability of dilutions of the formulation (see Section 1).

10. Concerns

10.1. 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 the Regulation and as set out in Commission Regulation (EU) No 546/2011[7] 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 the Regulation.

Issues that could not be finalised were not identified.

10.2. 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 the Regulation 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 the Regulation.

Critical areas of concern were not identified.

10.3. 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 9, has been evaluated as being effective, then 'risk identified' is not indicated in Table 5.)

[7] 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.

Table 5: Overview of concerns

Representative use		Strawberry (F)	Strawberry (G)	Tomato (F)	Tomato (G)
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[(a)]				
	Parametric value of 10 µg/L[(b)] breached				
	Assessment not finalised				

The superscript numbers relate to the numbered points indicated in Sections 10.1 and 10.2. Where there is no superscript number, see Sections 2–7 for further information.

(a): Based on classification made in the context of this evaluation procedure under Regulation (EC) No 1107/2009. It should be noted that harmonised classification and labelling is formally proposed and decided in accordance with Regulation (EC) No 1272/2008. Or it should be noted that the classification proposed in the context of this evaluation procedure under Regulation (EC) No 1107/2009 concurs with the harmonised classification and labelling in accordance with Regulation (EC) No 1272/2008.

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

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Abbreviations

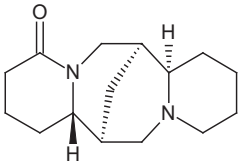
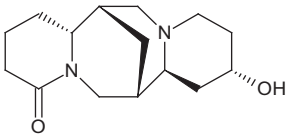
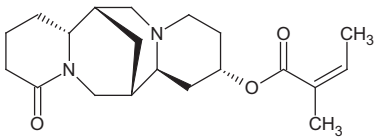
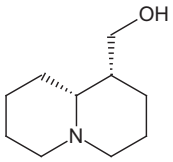
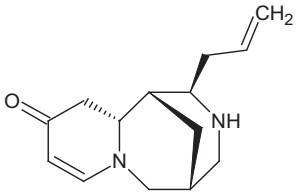
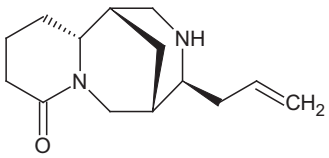
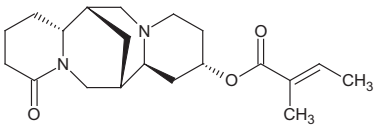
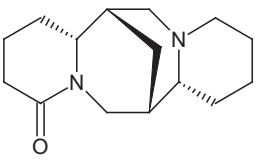
1/*n*	slope of Freundlich isotherm
λ	wavelength
ε	decadic molar extinction coefficient
a.s.	active substance
AAOEL	acute acceptable operator exposure level
ADE	actual dermal exposure
ADI	acceptable daily intake
AF	assessment factor
AOEL	acceptable operator exposure level
AOP	adverse outcome pathway
AP	alkaline phosphatase
AR	applied radioactivity
AR	androgen receptor
ARfD	acute reference dose
AST	aspartate aminotransferase (SGOT)
bw	body weight
CAS	Chemical Abstracts Service
CFU	colony-forming units
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)
EEC	European Economic Community
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EMDI	estimated maximum daily intake
ER_{50}	emergence rate/effective rate, median
ErC_{50}	effective concentration (growth rate)
ERO	ecological recovery option
ETO	ecological threshold option
ETR	exposure toxicity ratio
EU	European Union
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
GCPF	Global Crop Protection Federation (formerly known as International Group of National Associations of Manufacturers of Agrochemical Products GIFAP)
GGT	gamma glutamyl transferase
GM	geometric mean

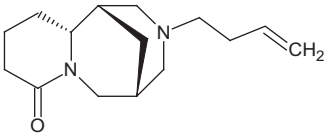
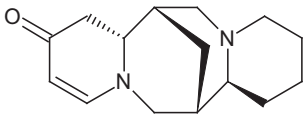
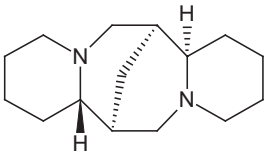
GS	growth stage
GSH	glutathione
Hb	haemoglobin
HQ	hazard quotient
HR	hazard rate
IEDI	international estimated daily intake
IESTI	international estimated short-term intake
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
iv	intravenous
JMPR	Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
LC	liquid chromatography
LC_{50}	lethal concentration, median
LC-MS	liquid chromatography–mass spectrometry
LC-MS-MS	liquid chromatography with tandem mass spectrometry
LD_{50}	lethal dose, medianaaa dosis letalis media
M/L	mixing and loading
MAF	multiple application factor
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
mm	millimetre (also used for mean measured concentrations)
MOA	mode of action
MRL	maximum residue level
MS	mass spectrometry
MSDS	material safety data sheet
MTD	maximum tolerated dose
MWHC	maximum water-holding capacity
NCBI	National Center for Biotechnology Information
NESTI	national estimated short-term intake
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NPD	nitrogen–phosphorus detector
OECD	Organisation for Economic Co-operation and Development
OM	organic matter content
Pa	pascal
PD	proportion of different food types
PEC	predicted environmental concentration
PEC_{soil}	predicted environmental concentration in soil
PHI	preharvest interval
PPE	personal protective equipment
ppm	parts per million (10^{-6})
SMILES	simplified molecular-input line-entry system
TER	toxicity exposure ratio
UV	ultraviolet
w/v	weight per unit volume
w/w	weight per unit weight
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.2020.6190

Appendix B – Used compound codes

Code/trivial name[a]	IUPAC name/SMILES notation/ InChiKey[b]	Structural formula[c]
lupanine	spartein-15-one O=C1CCC[C@@H]2N1C[C@@H]1C[C@H]2CN2CCCC[C@H]12 JYIJIIVLEOETIQ-FQUUOJAGSA-N	
13α-OH-lupanine	13α-hydroxyspartein-2-one O=C1CCC[C@H]2N1C[C@@H]1C[C@H]2CN2CC[C@H](O)C[C@@H]12 JVYKIBAJVKEZSQ-YHQUGGNUSA-N	
13α-angeloyloxylupanine	2-oxospartein-13α-yl (2*Z*)-2-methylbut-2-enoate C\C=C(\C)C(=O)O[C@@H]1C[C@H]2[C@@H]3CN4[C@H](CCCC4=O)[C@H](CN2CC1)C3 UPVPJQNTGLTBPC-CDTWXTRXSA-N	
lupinine	[(1*R*,9a*R*)-octahydro-2*H*-quinolizin-1-yl] methanol OC[C@@H]1CCCN2CCCC[C@H]12 HDVAWXXJVMJBAR-VHSXEESVSA-N	
albine	(1*S*,2*R*,5*R*,11a*R*)-2-(prop-2-en-1-yl)-1,2,3,4,5,6,11,11a-octahydro-10*H*-1,5-methanopyrido[1,2-a][1,5]diazocin-10-one O=C1C[C@@H]2[C@H]3C[C@H](CN[C@@H]3CC=C)CN2C=C1 QJVOZXGJOGJKPT-YXCITZCRSA-N	
angustofoline	(1*S*,4*S*,5*S*,11a*R*)-4-(prop-2-en-1-yl)decahydro-8*H*-1,5-methanopyrido[1,2-a][1,5]diazocin-8-one O=C1CCC[C@@H]2[C@@H]3CN[C@@H](CC=C)[C@H](CN21)C3 VTIPIBIDDZPDAV-ZDEQEGDKSA-N	
13α-tigloyloxylupanine	2-oxospartein-13α-yl (2*E*)-2-methylbut-2-enoate C\C=C(/C)C(=O)O[C@@H]1C[C@H]2[C@@H]3CN4[C@H](CCCC4=O)[C@H](CN2CC1)C3 UPVPJQNTGLTBPC-YDSNIZARSA-N	
α-isolupanine	11β-spartein-2-one O=C1CCC[C@H]2N1C[C@@H]1C[C@H]2CN2CCCC[C@H]12 JYIJIIVLEOETIQ-IGQOVBAYSA-N	

Code/trivial name[(a)]	IUPAC name/SMILES notation/ InChiKey[(b)]	Structural formula[(c)]
tetrahydrohombifoline	(1*S*,5*R*,11a*R*)-3-(but-3-en-1-yl)decahydro-8*H*-1,5-methanopyrido[1,2-a][1,5]diazocin-8-one O=C1CCC[C@H]2N1C[C@@H]1C[C@H]2CN(C1)CCC=C OKTIETCHYDTVGN-HZSPNIEDSA-N	
multiflorine	2,3-didehydrospartein-4-one O=C1C=CN2C[C@@H]3C[C@@H](CN4CCCC[C@@H]34)[C@H]2C1 HQSKZPOVBDNEGN-NZBPQXDJSA-N	
sparteine	sparteine C1CCCN2C[C@@H]3C[C@@H](CN4CCCC[C@H]43)[C@@H]12 SLRCCWJSBJZJBV-ZQDZILKHSA-N	

(a): The metabolite name in bold is the name used in the conclusion.
(b): ACD/Name 2019.1.1 ACD/Labs 2019 Release (File version N05E41, Build 110555, 18 July 2019).
(c): ACD/ChemSketch 2019.1.1 ACD/Labs 2019 Release (File version C05H41, Build 110712, 24 July 2019).