EFSA Journal

CONCLUSION ON PESTICIDES PEER REVIEW

APPROVED: 16 December 2019

doi: 10.2903/j.efsa.2020.5985

Peer review of the pesticide risk assessment of the active substance benalaxyl

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Abstract

The conclusions of EFSA following the peer review of the initial risk assessments carried out by the competent authorities of the rapporteur Member State Romania and co-rapporteur Member State Portugal for the pesticide active substance benalaxyl 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 benalaxyl as a fungicide on tomatoes, flowers and ornamentals (field and protected use) and in grapes, onion and potato (field use). The reliable end points, appropriate for use in regulatory risk assessment, are presented. Missing information identified as being required by the regulatory framework is listed. Concerns are identified.

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

Requestor: European Commission

Question number: EFSA-Q-2017-00678

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Suggested citation: EFSA (European Food Safety Authority), Anastassiadou M, Arena M, Auteri D, Brancato A, Bura L, Carrasco Cabrera L, Chaideftou E, Chiusolo A, Court Marques D, Crivellente F, De Lentdecker C, Egsmose M, Fait G, Greco L, Ippolito A, Istace F, Jarrah S, Kardassi D, Leuschner R, Lostia A, Lythgo C, Magrans O, Mangas I, Miron I, Molnar T, Padovani L, Parra Morte JM, Pedersen R, Reich H, Santos M, Serafimova R, Sharp R, Stanek A, Sturma J, Szentes C, Terron A, Tiramani M, Vagenende B and Villamar-Bouza L, 2020. Conclusion on the peer review of the peer review of the pesticide risk assessment of the active substance benalaxyl. EFSA Journal 2020;18(1):5985, 32 pp. https://doi.org/10.2903/j.efsa.2020.5985

ISSN: 1831-4732

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

Summary

Commission Implementing Regulation (EU) No 844/2012, as amended by Commission Implementing Regulation (EU) No 2018/1659 (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. Benalaxyl 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), Romania, and co-rapporteur Member State (co-RMS), Portugal, received an application from FMC Chemical sprl for the renewal of approval of the active substance benalaxyl. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicant, the co-RMS (Portugal), the European Commission and the European Food Safety Authority (EFSA) about the admissibility.

The RMS provided its initial evaluation of the dossier on benalaxyl in the renewal assessment report (RAR), which was first received by EFSA on 12 October 2016. In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicant FMC Chemical sprl, for comments on 15 November 2016. 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 26 January 2017.

Following the kick-off teleconference between EFSA, RMS, co-RMS and European Commission held on 10 March 2017, in view of the nature and extent of revisions needed, the RMS, in agreement with the co-RMS, EFSA and European Commission, has decided to withdraw the RAR of benalaxyl and consequently the peer review was stopped. A new, updated version of the RAR was produced and resubmitted by the RMS on 20 October 2017. Subsequently, the peer review was recommenced and a new commenting period was launched with Member States, EFSA, the applicant and the general public. EFSA collated and forwarded all comments received to the European Commission on 19 March 2017.

Following consideration of the comments received on the updated 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, environmental fate and behaviour and ecotoxicology.

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

The conclusions laid down in this report were reached on the basis of the evaluation of the representative uses of benalaxyl as a fungicide on tomatoes, flowers and ornamentals (field and protected use) and in grapes, onion and potato (field use), as proposed by the applicant. Full details of the representative uses can be found in Appendix A of this report.

The use of benalaxyl according to the representative uses proposed at the European Union (EU) level results in a sufficient fungicidal efficacy against the target organisms.

A data gap has been identified as regards the search of the scientific peer-reviewed open literature on the active substance and its relevant metabolites.

In the section identity, physical/chemical properties, analytical methods, data gaps were identified for information on the identity of a polymeric co-formulant and for demonstration of the efficiency of the extraction procedure used in the monitoring methods for dry, high acid and high oil content commodities.

In the section on mammalian toxicology, the residue definition for human biomonitoring could not be finalised. Data gaps were also identified for further assessment of the toxicological relevance of the impurities and for an assessment of the toxicological profile of metabolites.

In the area of residues, the consumer dietary risk assessment could not be concluded since the risk assessment residue definition for fruit crops could not be finalised, residue definitions for root crops and rotational crops remain open and the livestock exposure assessment could not be conducted. The consumer exposure assessment through drinking water with regard to groundwater metabolites M2, F4-acetyl, F7 and F8 and to the unknown nature of residues that might be present in drinking water, consequent to water treatment processes could also not be finalised. It is also acknowledged that the representative formulation contains 2 active substances, benalaxyl and mancozeb, but the combined consumer dietary exposure assessment considering both active substances could not be conducted.

With respect to fate and behaviour in the environment, data gaps were identified concerning the stereoselective degradation of benalaxyl isomers as well as for adsorption/desorption data for

benalaxyl and the lysimeter metabolite F7. The groundwater simulations provided for the lysimeter metabolite F4-acetyl were considered provisional and further identification data are needed to address its toxicological relevance. New PEC GW calculations using agreed formation fractions and adsorption end points are also required. With the available information, a critical area of concern with respect to groundwater contamination by relevant metabolites has been identified. Appropriate 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 or groundwater are abstracted for drinking water is not available, leading to the consumer risk assessment not being finalised.

A critical area of concern was identified as regards the long-term risk to birds and secondary poisoning of earthworm-eating birds. The risk from secondary poisoning of fish-eating birds and mammals could not be finalised due to lack of a valid bioconcentration factor (BCF) estimate. A data gap was identified for a risk assessment to birds and mammals from metabolites. Risk mitigation is needed for aquatic organisms. A high risk to honey bees cannot be excluded for the representative uses evaluated. A high risk is indicated for non-target arthropods for all representative uses, leading to a critical area of concern. The risk from metabolite M1 to earthworms remains unresolved (data gap). In addition, a data gap was identified on the toxicity to earthworms for the active substance when formulated.

Based on the available information on humans and non-target organisms, the assessment of the endocrine disrupting potential of benalaxyl could not be finalised.

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Background

Commission Implementing Regulation (EU) No 844/2012[1], as amended by Commission Implementing Regulation (EU) No 2018/1659[2] (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[3]. 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).

Furthermore, in accordance with Article 13(3a), where the information available in the dossier is not sufficient to conclude the assessment on whether the approval criteria for endocrine disruption are met, additional information can be requested to be submitted in a period of minimum 3 months, not exceeding 30 months, depending on the type of information requested.

In accordance with Article 1 of the Regulation, the RMS Romania and co-RMS Portugal received an application from FMC Chemical sprl for the renewal of approval of the active substance benalaxyl. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicant, the co-RMS (Portugal), the European Commission and EFSA about the admissibility.

The RMS provided its initial evaluation of the dossier on benalaxyl in the RAR, which was first received by EFSA on 12 October 2016 (Romania, 2016).

In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicant FMC Chemical sprl, for consultation and comments on 15 November 2016. 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 26 January 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 applicant was invited to respond to the comments in column 3 of the reporting table. The comments and the applicant's response were evaluated by the RMS in column 3.

The need for expert consultation and the necessity for additional information to be submitted by the applicant in accordance with Article 13(3) of the Regulation as well as the way forward for the active substance were considered in a telephone conference between EFSA, the RMS, co-RMS and the European Commission on 10 March 2017.

In view of the large number of comments and outstanding issues requiring the complete revision of the RAR, the RMS, in agreement with the co-RMS, EFSA and the European Commission, has decided to withdraw the RAR of benalaxyl and consequently the peer review was stopped. A new, updated version of the RAR was produced and resubmitted by the RMS on 20 October 2017 (Romania, 2017). Subsequently, the peer review was recommenced and a new commenting period was launched on 16 January 2018 with Member States, EFSA, the applicant and the general public. EFSA collated and forwarded all comments received to the European Commission on 19 March 2017.

On the basis of the comments received, the applicant's response to the comments and the RMS's evaluation thereof, it was concluded in a teleconference between EFSA and the RMS held on 30 May 2018 that additional information should be requested from the applicant, and that EFSA should conduct an expert consultation in the areas of mammalian toxicology, residues, environmental fate and behaviour and ecotoxicology.

[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] Commission Implementing Regulation (EU) No 2018/1659 of 7 November 2018 amending Implementing Regulation (EU) No 844/2012 in view of the scientific criteria for the determination of endocrine disrupting properties introduced by Regulation (EU) 2018/605.

[3] 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.

In addition, following a consultation with Member States at the Pesticide Peer Review Experts' Meeting PREV 05 (joint Mammalian toxicology – Ecotoxicology meeting) in May 2019, it was considered necessary to request additional information in accordance with Commission Implementing Regulation (EU) No 2018/1659, to be able to conclude whether the approval criteria for endocrine disruption in line with the scientific criteria for the determination of endocrine disrupting properties, as laid down in Commission Regulation (EU) 2018/605[4], are met. Following the request, however, the applicant informed EFSA that they will not perform any of the requested studies. Subsequently, as a follow-up, the applicant was given the opportunity to submit, within a period of 3 months, any additional information to address the approval criteria set out in point 3.6.5 and/or point 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605, and/or documentary evidence demonstrating that the conditions for the application of the derogation under Art. 4(7) of Regulation (EC) No 1107/2009 are met. The applicant has confirmed that they will not submit any additional information therefore EFSA proceeded with the peer review.

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

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

A consultation on the conclusions arising from the peer review of the risk assessment took place with Member States via a written procedure in January – February 2019.

In addition, a targeted written consultation with Member States took place in October–November 2019 subsequent to the completion of the peer review of the updated endocrine assessment conducted by EFSA in line with the new scientific criteria for the determination of endocrine disrupting properties, as laid down in Commission Regulation (EU) 2018/605.

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 benalaxyl as a fungicide on tomatoes, flowers and ornamentals (field and protected use) and in grapes, onion and potato (field use), as proposed by the applicant. In accordance with Article 12(2) of Regulation (EC) No 1107/2009, risk mitigation options identified in the RAR and considered during the peer review are presented in the conclusion. 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, 2019a), 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 initial RAR;
- the comments received on the updated RAR;
- the reporting tables (8 March 2017 and 30 May 2018);
- the evaluation tables (27 February 2019 and 25 October 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 (Romania, 2018), as well as the peer review report and the EFSA addendum on endocrine assessment (EFSA, 2019b), all these 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 European Union for which the applicant has not demonstrated that it has regulatory access to the information on which this conclusion report is based.

[4] 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.

The active substance and the formulated product

Benalaxyl is the ISO common name for methyl *N*-(phenylacetyl)-*N*-(2,6-xylyl)-DL-alaninate (IUPAC). The active substance is a racemate. A peer review on the R-isomer (benalaxyl-M) has already been completed, leading to the EFSA Conclusion issued in 2013 (EFSA, 2013a).

The representative formulated product for the evaluation was 'Galben M', a wettable powder (WP) containing 80 g/kg benalaxyl and 650 g/kg mancozeb.

The representative uses evaluated were foliar spray applications for the control of a range of fungal pests in tomatoes, flowers and ornamentals (field and protected use) and in grapes, onion and potato (field use). Full details of the Good Agricultural Practices (GAPs) can be found in the list of end points in Appendix A.

Based on the available data, it can be concluded that the use of benalaxyl results in a sufficient fungicidal efficacy against the target organisms according to the representative uses proposed at EU level, following the guidance document SANCO/2012/11251-rev. 4 (European Commission, 2014).

A literature review report was available in the dossier but was not properly assessed and summarised in the RAR. Therefore, a formal data gap is identified for a detailed and transparent assessment (including search methodology) to be reported following the Guidance of EFSA (2011). The literature search should also be performed following the recommendations of the ECHA/EFSA Guidance (2018) for the hazard identification of endocrine disrupting properties. In addition, a data gap has been identified for an updated scientific literature search to further investigate the stereoselective metabolism and degradation of benalaxyl isomers.[5]

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).

The proposed specification for benalaxyl is based on batch data from industrial plant production. The proposed minimum purity of the technical material is 960 g/kg. It should be noted that the evaluation of the toxicological relevance of the impurities is not finalised (see Section 2). The batches used in the (eco)toxicological assessment support the proposed renewal specification, but not the original reference specification (see Sections 2 and 5). As a consequence, an update of the reference specification is recommended. There is no FAO specification available for benalaxyl.

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 benalaxyl or the representative formulations. However, a data gap for information on the identity of a polymeric co-formulant was identified. The main data regarding the identity of benalaxyl 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. Methods of analysis are available for the determination of the active substance in the technical material, in the representative formulation and for the determination of the respective impurities in the technical material.

Benalaxyl residues (sum of constituent isomers) can be monitored in food and feed of plant origin by the QuEChERS method using liquid chromatography with tandem mass spectrometry (LC–MS/MS) with limit of quantification (LOQ) of 0.01 mg/kg in all commodity groups. However, it should be noted that the extraction procedure used was verified for high water content commodities only, therefore a data gap for extraction efficiency for the other commodity groups was identified. QuEChERS method using LC–MS/MS with a LOQ of 0.01 mg/kg can be used for determination of benalaxyl residues (sum of constituent isomers) in animal products. It should be noted that residue definition for monitoring in food of animal origin is not concluded (see Section 3) and as a consequence new monitoring methods might be required if other components will be included in the residue definition.

Benalaxyl residues (sum of constituent isomers) in soil, drinking and surface water can be monitored by LC–MS/MS with LOQs 5 μg/kg, 0.1 μg/L and 0.5 μg/L, respectively. Appropriate high-

[5] For further details see Evaluation Table open points 2.7, 3.11, 4.43 and 5.37 (EFSA, 2019a).

performance liquid chromatography with tandem mass spectrometry HPLC–MS/MS method exists for monitoring benalaxyl residues (sum of constituent isomers) in air with a LOQ of 1.08 μg/m^3.

The LC–MS/MS method can be used for monitoring of benalaxyl residues in body fluids (urine and plasma) with a LOQ of 0.05 mg/L. Benalaxyl residues in tissues can be determined by using the monitoring methods for residues in food of animal origin. It should be noted that the residue definition for body fluids and tissues is not concluded (see Section 2); as a consequence, new analytical methods might be required if some of the metabolites are considered more suitable for monitoring.

2. Mammalian toxicity

The following guidance documents were used for this conclusion: European Commission (2003, 2012), EFSA PPR Panel (2012), EFSA (2014) and ECHA (2017).

Benalaxyl was discussed at the Pesticides Peer Review Experts' Meeting 182 in September 2018.

The test material used in the toxicity studies is representative of the technical specification proposed for the renewal but not of the original technical specification. Considering both technical specifications, the toxicological relevance of the impurities has not been sufficiently assessed to be concluded upon (data gap).

With regard to the bridging of toxicological properties between benalaxyl and benalaxyl-M, the experts considered the pattern of effects and no observed adverse effect levels (NOAELs) in the available studies with both benalaxyl and benalaxyl-M and concluded that the two compounds are of similar toxicity. Benalaxyl is rapidly and extensively absorbed and excreted after oral administration, mainly via faeces (with extensive bile excretion) and also via urine (limited). Widely distributed within the body and extensively metabolised (mainly by oxidation), there is no accumulation after repeat-dose administration. In an *in vitro* comparative metabolism study with human, rat and dog hepatocytes the metabolic profiles were qualitatively similar and no major unique metabolite was observed in human hepatocytes. Since metabolites were not analysed in the bile excretion study, it cannot be concluded that those found in the faeces at levels higher than 10% are major rat metabolites. On the basis of the available data, no residue definition for human biomonitoring (body fluids and tissues) can be defined (data gap and issue not finalised).

In the **acute toxicity** studies, the results did not trigger any classification (except for the acute neurotoxicity study, see below), and benalaxyl was neither irritant (skin or eye) nor skin sensitising. Since the compound does not absorb electromagnetic radiation in the range of 290–700 nm, further investigation of the phototoxicity and photomutagenicity potential is not required.

In **short-term** dietary studies, the liver was the target organ in all species (rat, mouse and dog), with increased weight accompanied or not by changes in clinical chemistry parameters and histopathological findings. The relevant NOAEL of 6.5 mg/kg body weight (bw) per day was identified in the 1-year dog study, where effects were also observed in the testis (atrophy of the seminiferous tubules).

Benalaxyl is considered unlikely to be genotoxic on the basis of the available *in vitro* and *in vivo* **genotoxicity** studies.[6]

In the **long-term** rat study, systemic effects included heart weight changes accompanied by effects on clinical chemistry parameters (lactate dehydrogenase (LDH) and potassium) with a NOAEL of 4.42 mg/kg bw per day, whereas an increased incidence of astrocytomas (0, 1, 1, 2 in the different dose groups in males), a rare tumour for which no historical control data from the performing laboratory were available, triggered a carcinogenic NOAEL of 4.42 mg/kg bw per day. While this was not concluded for the harmonised classification[7] or during the first peer review of the study for benalaxyl-M (EFSA, 2013a), the experts considered that the criteria for classification according to Regulation (EC) No 1272/2008[8] (ECHA, 2017) may be met for classification as Carcinogen category 2 based on the finding of astrocytomas. In the long-term mouse study, taking into account the low survival at the two high dose levels, only a systemic lowest observable adverse effect level (LOAEL) of 42.9 mg/kg bw per day could be established on the basis of amyloidosis findings in the liver (and multiple tissues in males)[9]; urinary

[6] See Expert consultation point 2.2 in the Meeting Report from the Pesticides Peer Review Experts' Meeting 182 (EFSA, 2019a).

[7] 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, 1–1355. It is noted that this harmonised classification has been transferred from agreements under previous Directive 67/548/EEC.

[8] 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, 1–1355.

[9] See Expert consultation point 2.3 in the Meeting Report from the Pesticides Peer Review Experts' Meeting 182 (EFSA, 2019a).

bladder tumours (submucosal mesenchymal tumours) observed at the high dose (559 mg/kg bw per day, three incidences, above the maximum tolerated dose).

In the **reproductive toxicity studies**, fertility and overall reproductive performance were not impaired. In the multigeneration rat study, the parental NOAEL was 7.9 mg/kg bw per day based on increased liver weight in females; the offspring NOAEL was 66.57 mg/kg bw per day based on decreased pup body weight during lactation and increased liver weight; the reproductive NOAEL is 275 mg/kg bw per day (highest dose tested). In the teratogenicity studies, incomplete cranial ossification was observed in rat fetuses, with a developmental NOAEL of 150 mg/kg bw per day, while maternal body weight changes led to a maternal NOAEL of 150 mg/kg bw per day. In rabbit fetuses, the developmental NOAEL was 5 mg/kg bw per day based on retarded growth (reduced weight and retarded skeletal development), while the maternal NOAEL was 5 mg/kg bw per day based on body weight changes.[10]

In the acute **neurotoxicity** studies with benalaxyl, all animals in the 2,000 mg/kg bw dose group died after a few hours (and the peer review agreed that the criteria for classification according to Regulation (EC) No 1272/2008 may be met for the category Acute Tox 4) with a NOAEL of 50 mg/kg bw per day based on clinical signs in females but no specific neurotoxicity findings. After repeated administration, the NOAEL for neurotoxic effects was 677 mg/kg bw per day (highest dose level). Adverse effects on the immune system were not observed in the available toxicity studies.

The groundwater **metabolites M1** and **M2** were not acutely toxic by oral administration, they can be concluded as unlikely to be genotoxic, and no adverse effect was observed in the 90-day rat studies up to the highest dose tested (923 and 819 mg/kg bw per day, respectively), demonstrating a lower toxicity than benalaxyl. An acceptable daily intake (ADI) of 0.9 mg/kg bw per day has been derived for M1. The groundwater **metabolites F4-acetyl** and **F7/F8** were not acutely toxic by oral administration, concluded as unlikely to be genotoxic, and no adverse effect was observed in the 28-day rat studies up to the highest dose tested (820 and 776 mg/kg bw per day, respectively). It is noted that the identity of F4-acetyl should be clarified (see Section 4) to confirm the reliability of the available toxicological data (see data gap in Section 4). It was also concluded that the groundwater **metabolite M9** is unlikely to be genotoxic. It is noted that the metabolites detected in groundwater (M2, M9, F4-acetyl and F7/F8) should be considered toxicologically relevant according to the guidance document (European Commission, 2003) pending ECHA's decision on the carcinogenic potential of benalaxyl. In the meanwhile, a data gap is set for further assessment of the carcinogenic potential of the metabolites. It is noted that reference values for some of these metabolites have been discussed and agreed by the experts, should the carcinogenic potential of these metabolites be resolved/ clarified.[11]

No toxicological data were available for the metabolites **GX5a/GX5b isomers**, **GX5c** and their glucoside conjugates and for **benalaxyl acid, 2-benzoic acid** (data gap), see also Section 3.

The **ADI** for benalaxyl is 0.04 mg/kg bw per day based on the 2-year rat study (as in the original peer review (European Commission, 2004) and the EFSA conclusion for benalaxyl-M (EFSA, 2013a)). The acute reference dose (**ARfD**) is 0.5 mg/kg bw based on the acute rat neurotoxicity study (no ARfD was set during the original peer review (European Commission, 2004) and the EFSA conclusion (EFSA, 2013a)). The acceptable operator exposure level (**AOEL**) is 0.05 mg/kg bw per day based on the rat 2-generation study, supported by the rabbit developmental study (an AOEL of 0.06 mg/kg bw per day was proposed during the original peer review (European Commission, 2004) and the EFSA conclusion (EFSA, 2013a), based on the 90-day rat study for which a higher NOAEL was agreed during the renewal assessment). The acute acceptable operator exposure level (**AAOEL**) is 0.5 mg/kg bw based on the rat acute neurotoxicity study. All reference values were derived with a standard uncertainty factor of 100 (and no correction for oral absorption for the AOEL and AAOEL).

Based on an *in vitro* study with human skin, the dermal absorption values for benalaxyl in the product 'Galben M' were 0.7% for the concentrate, 6% for the 1 g/L dilution and 18% for the 0.2 g/L dilution.

For the use on grapevines, the operator exposure estimates are below the AOEL for the tractor-mounted application with the use of gloves, and for hand-held application without the use of personal protective equipment (PPE), both according to the German model (and also according to the EFSA model (EFSA, 2014), without use of PPE for the tractor-mounted and with use of PPE for the hand-held application). For the field use on tomatoes (covering also potatoes and onions), the operator

[10] See Expert consultation point 2.4 in the Meeting Report from the Pesticides Peer Review Experts' Meeting 182 (EFSA, 2019a).
[11] See Expert consultation point 2.7 in the Meeting Report from the Pesticides Peer Review Experts' Meeting 182 (EFSA, 2019a).

exposure estimates are below the AOEL without the use of PPE according to the German and EFSA models, but PPE are required with the UK POEM. For the field use on ornamentals, the operator exposure estimates are below the AOEL without the use of PPE according to the German, UK POEM and EFSA models. For the protected uses on ornamentals and tomatoes, the operator exposure estimates are below the AOEL with the use of PPE with the Dutch Greenhouse Model for hand-held spraying. For all uses, bystander and resident exposure estimates are below the AOEL with the German approach[12] and EFSA model (EFSA, 2014); and worker exposure estimates are below the AOEL when using protective gloves in the EUROPOEM model (see also Appendix A for further details).

As the representative formulation contains two active substances, benalaxyl and mancozeb, a combined exposure assessment has been performed, taking into account the sum of the exposure estimates (expressed as % of the respective AOELs). For the operators and workers, for all representative uses a total exposure level below 100% is estimated in at least one of the models when appropriate PPE is used. For the residents and bystanders, the total exposure is also below 100% (see also Appendix A for further details).

3. Residues

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

Benalaxyl was discussed at the Pesticides Peer Review Experts' Meeting 184 in September 2018.

The metabolism of benalaxyl in plants was investigated upon foliar treatment in fruit crops (grapes, tomatoes) and in the leaves of grape vines, tomatoes, tobacco and potatoes with benalaxyl labelled in the [^{14}C-phenyl] ring. Plant metabolism was also studied in root crops (potatoes) but this study could not be relied upon since no metabolites' identification was attempted in potato tubers in view of the very low recovered total radioactive residues (< 0.01 mg/kg). All these studies from the 1980s were not suitable as guideline-compliant metabolism studies in view of numerous identified shortcomings and were therefore considered as supportive data only. The predominant compound of the terminal residues was the parent benalaxyl in grapes (52–98% total radioactive residue (TRR)) and in leaves of grapevines, tobacco and potatoes (from 20% to 44.7% TRR). The tentatively identified metabolites resulted mainly from the hydroxylation of the phenyl ring (GX5c) or of the lateral side chain of the phenyl ring of the parent structure (GX5a/GX5b isomers), with subsequent successive conjugation steps with several molecules of glucose and malonic acid increasing with time. These glucoside and malonic acid glucoside conjugates were found at significant proportions in grapes fruit and leaves (25% and 63.4% TRR, respectively), tomato fruits and leaves (14.6% TRR and up to 40.6% TRR, respectively), tobacco leaves (20.3% TRR) and potato leaves (19.5% TRR). From a more recent metabolism study on tomato, a more comprehensive metabolic pattern of benalaxyl could be depicted with the parent compound being predominant in tomato fruit and green plant parts (33% and 45% TRR, respectively), while the metabolite 'benalaxyl acid, 2-benzoic acid' occurred at a level of 15% TRR in fruit. It is however highlighted that the glucoside conjugates and malonic acid glucoside conjugates of compounds GX5a/GX5b isomers and GX5c tentatively identified in the studies from the 1980s were not recovered in the more recent tomato metabolism study. While upon enantiomer-specific analysis of residues of benalaxyl in tomato fruit and green plant parts no significant change in the isomer ratios was observed within 90 days after treatment, there is indication from the scientific peer-reviewed open literature that significant stereo-selective degradation of benalaxyl can occur in several crops (fruit crops, leafy crops and root crops) with an enrichment of the benalaxyl *R*-isomer (benalaxyl-M) residues in these crops. However, it was concluded that benalaxyl and benalaxyl-M are of similar toxicity (see Section 2). Based on the available data on fruit crops, the **plant residue definition for monitoring** is set as '**benalaxyl (sum of constituent isomers)'**. For **risk assessment,** in view of the discrepancies observed between the studies on fruit crops from the 1980's and the new metabolism study on tomato related to the presence of conjugates, the residue definition for fruit crops is provisionally set as **'benalaxyl (sum of constituent isomers), 2-hydroxy methyl benalaxyl (GX5a/GX5b isomers), 3-hydroxy benalaxyl (GX5c) and their conjugates and benalaxyl acid, 2-benzoic acid'**. In order to finalise the proposed residue definition for the risk assessment, sufficient field residue trials compliant with the representative uses on grapes and tomatoes and analysing for all compounds included in this proposal should be

[12] The Martin et al. (2008) approach is not scientifically supported any longer, considering the limited data included for 3-dimensional exposure to spray drift and the lack of exposure estimate to vapour for low volatility compounds. Accordingly, the predictions are considered underestimated and should be given only for informative purpose.

submitted (data gap). The toxicity of GX5a/GX5b isomers, GX5c and their glucoside conjugates and of benalaxyl acid, 2-benzoic acid should also be addressed (see data gap in Section 2). The proposed residue definitions are limited to fruit crops only following foliar treatment as the metabolic pattern of benalaxyl could not be elucidated in root crops. A new metabolism study in root crops compliant with the representative uses on potatoes and onions is therefore required (data gap).

A confined rotational crop metabolism study conducted at representative intervals after bare soil application of benalaxyl at 960 g a.s./ha in lettuce, wheat and radish demonstrated a steady decline of the total residue levels in all the edible parts of the rotational crops over time. The parent benalaxyl was detected in wheat hay and straw only but at a low level (< 10% TRR), while a preferential soil uptake of major soil metabolites M1 and M2 was observed mainly in immature lettuce (11.3–12.8% TRR), wheat straw (12.7% TRR for M2 only), radish root (16.3-19.3% TRR) and in radish tops (18.6–25.3% TRR) at the 30-day plant-back interval (PBI). Despite the shortcomings, i.e. underdosed study considering the maximum plateau concentration of benalaxyl in soil and the low rate of metabolites' identification throughout the rotational crops (15% TRR in wheat straw, 25% TRR in immature lettuce, 36% TRR in radish roots, 45% TRR in radish tops), the unidentified radioactive fractions were shown to be constituted of numerous minor components and a significant fraction of the radioactive residues was incorporated into the natural constituents of the plants, mainly in wheat crop parts (23% to 45% TRR). Currently, a specific residue definition for rotational crops is not proposed as compounds M1 and M2 were concluded to be of lower toxicity compared to benalaxyl (see Section 2). However, and having regard to the low to high persistence of the soil metabolite M9 (see Section 4), confined rotational crops metabolism data addressing the fate of this compound in leafy, small grains cereal and root crops at the different PBIs should be provided (data gap). The need to set residue definitions for rotational crops should be reconsidered accordingly.

Benalaxyl was shown to be stable under frozen conditions for up to 36 months in grapes, tomatoes and potatoes. It is noted that according to the current guidelines storage stability data on a commodity representative of the bulb vegetables are also required in order to support the representative use on onions (data gap).

For the determination of benalaxyl (sum of isomers) residues, 7 and 5 residue trials on grapes compliant, respectively, with the NEU and SEU GAPs were submitted. 1 and 3 residue trials on grapes are therefore requested to complete the northern European Union (NEU) and southern European Union (SEU) residue data sets, respectively (data gap). Sufficient GAP-compliant residue trials on tomatoes were provided. All these trials were supported by acceptable storage stability data and validated analytical methods. The validity of the residue trials reported in support of the representative uses on onions and potatoes and analysing for benalaxyl residues only cannot currently be assessed as residue definitions for root crops could not be derived. Sufficient NEU and SEU GAP-compliant residue trials on these crops in accordance with the residue definitions set in root crops, once agreed, are required (data gap). For the time being, only provisional maximum residue level (MRLs) for grapes and tomatoes are proposed pending upon the finalisation of the risk assessment residue definition for fruit crops.

In a hydrolysis study simulating standard food processing conditions, benalaxyl was found to be hydrolytically stable under pasteurisation, baking/brewing/boiling and sterilisation. However, and pending upon finalisation of the residue definition for risk assessment in fruit crops and agreed residue definitions in root crops, it cannot be excluded that further data addressing the nature of residues at processing of all compounds included in the residue definition might be needed. The residue definition for risk assessment in processed commodities is set provisionally as benalaxyl (sum of constituent isomers) only.

Currently, in the absence of an agreed plant residue definition for risk assessment for potatoes, it is not possible to calculate the total livestock dietary burden and to assess the potential for the occurrence of significant residues in food of animal origin. Metabolism studies in laying hens and lactating goats conducted with ^{14}C-benalaxyl were submitted but were not guideline compliant in terms of metabolites' identification in all livestock matrices. Benalaxyl was extensively metabolised and was hardly detected in liver only (< 1% TRR). Compound 'G6' was recovered in egg yolk at 20.5% TRR, while compounds 'G8' and 'G14' under their conjugated form accounted for respectively 21.3% TRR and 15% TRR in kidney. These compounds occurred at much lower levels in liver (< 10% TRR, each). The remaining radioactivity was constituted of unknown fractions and no metabolites' identification was conducted in muscle, fat or milk. Whether studies with benalaxyl alone are fully adequate to set monitoring and risk assessment residue definitions for livestock is pending upon the finalisation of the assessment of the pertinent residues in potatoes as a primary crop and in rotational crops, once the residue definitions for risk assessment in root crops and in rotational crops are

finalised (see data gaps in Section 8). Whether or not a metabolism study in fish is necessary or can be waived is also pending upon finalisation of the residue definition for risk assessment for potatoes.

Since all the crops under consideration show attractiveness to bees for pollen and/or nectar collection and treatment can take place at flowering, the presence of residues of benalaxyl and its metabolites in pollen and bee products cannot be concluded and further information is requested (data gap).

The consumer dietary intake calculation cannot be conducted considering the outstanding data to finalise the risk assessment residue definition for fruit crops and to set residue definitions for root crops and for rotational crops. Furthermore, the livestock exposure assessment could not be conducted. In addition, should the classification as 'Carcinogen category 2' be confirmed for benalaxyl, the need for a complete toxicological assessment of the groundwater metabolites M2, F4-acetyl, F7 and F8 will be reconsidered accordingly (see Section 2). Therefore and pending also on the finalisation of the predicted PEC groundwater levels for these metabolites (see Section 4), the consumer exposure with regard to residues of these compounds in groundwater used as drinking water cannot be assessed in accordance with the Guidance SANCO/221/2000-rev.10–final (European Commission, 2003). Finally, the consumer risk assessment is also not finalised with regard to the unknown nature of residues that might be present in drinking water, consequent to water treatment processes following abstraction of surface water that might contain benalaxyl and its metabolites (issue not finalised, see also Section 4). It is also acknowledged that the representative formulation contains 2 active substances, benalaxyl and mancozeb, but the combined consumer dietary exposure assessment towards both active substances could not be conducted in view of the data gaps identified for benalaxyl and the absence of data for mancozeb.

The toxicological reference values (ARfD) and the residue definition for risk assessment have been changed compared to those used in the review of the existing MRLs for benalaxyl (EFSA, 2013c). While the residue definitions for monitoring and risk assessment were derived for all categories of crops under the Article 12 MRL review, the residue definitions agreed in the framework of the renewal of the approval of benalaxyl are restricted to fruit crops and remain open for root crops. Based on the newly proposed ARfD of 0.5 mg/kg bw for benalaxyl and including the existing MRLs for benalaxyl, no acute intake concern was identified for the consumers for all the existing uses assessed under the Article 12 MRL review (IESTI: 9% of the ARfD, melon). The data gaps identified following the assessment of the existing uses under the Article 12 MRL review were not addressed based on the data that were submitted in the framework of the renewal of the approval of benalaxyl.

4. Environmental fate and behaviour

The fate and behaviour in the environment of benalaxyl was discussed in the Pesticides Peer Review Experts' teleconference 195 (September 2018). During the peer review, the applicant agreed with the 'risk envelope approach'[13] proposed by the RMS and that no separate assessment was performed for the protected crops.[14]

There is information on the route and rate of degradation of ^{14}C-labelled benalaxyl under dark aerobic conditions from 14 soils, five of those experiments are available in the submitted dossier. The major degradation metabolites were **M1** (max 4.5–45.2% applied radioactivity (AR)), **M2** (max 2.6–34.1% AR) and **M9** (max 2.8–10.1%). In these studies, benalaxyl exhibited moderate to high persistence. It is stated that the enantiomeric purity of the metabolites was specifically checked in the study and no racemisation of the chiral centre in the molecule was observed during the degradation process. However, details of the analysis and their results to substantiate this statement have not been provided, despite that they were specifically requested during the peer review. Therefore, a data gap has been identified for the applicant to provide further details on the chiral analysis performed in study Curtis-Jackson, P. (2015) presented in the RAR (Romania, 2018). In particular, it should be reported for which samples chiral analysis was performed and the enantiomer excesses observed (or the concentration measured for the individual enantiomers) for each of the chiral compounds analysed.

Mineralisation was low (0–17.1% at the end of the studies). At the end of the studies (117–133 days), unextractable residues amounted to 18.8–48.9% AR.

[13] For the concept of the 'risk envelope approach' please refer to the European Commission guidance document on the preparation and submission of dossiers for plant protection products according to the 'risk envelope approach'. SANCO/11244/2011 rev.5, 14 March 2011 (European Commission, 2011b).

[14] See Evaluation Table, open point 4.38 in EFSA (2019a).

The rate of degradation of metabolite M1 was investigated under dark aerobic conditions in three soils. This compound exhibits moderate to medium persistence in soil. The rate of degradation of the metabolite M2 was investigated under dark aerobic conditions in four soils. This compound exhibits medium to high persistence in soil. Information on the rate of degradation of the metabolite M9 under dark aerobic conditions is available in three soils from data presented in the EFSA conclusion for benalaxyl-M (EFSA, 2013a). In addition, the rate of degradation of the metabolite M9 was investigated under dark aerobic conditions in one experiment where benalaxyl was applied as parent compound and in other three soils in a study submitted within the benalaxyl dossier under examination. Metabolite M9 exhibits low to high persistence in soil under these conditions. It should be highlighted that the formation fractions proposed by the applicant for the metabolites were not agreed by the experts during the experts' consultation. The rate of degradation of benalaxyl metabolites found in lysimeter studies was investigated in soil under dark aerobic conditions for F4-acetyl (three soils), F7 (three soils) and F8 (three soils plus three additional soils from benalaxyl-M; EFSA, 2013a). Under these conditions, F4-acetyl exhibited moderate persistence in soil and F7 and F8 moderate to high persistence.

The route and rate of degradation of benalaxyl under dark anaerobic conditions was investigated in one study. The main metabolite under these conditions was M1 (50.73% at 203 days). The study gives indications that the degradation will be slower under anaerobic conditions. Anaerobic metabolism is not expected to be a major degradation route given the proposed representative uses.

No photolysis in soil study is available; however, taking into account the UV absorbance of benalaxyl, contribution of photolysis to the dissipation of benalaxyl in soil is not expected.

Bare soil field dissipation studies (1 site in Italy and 4 sites in Germany) are available. Benalaxyl metabolites M1 and M2 were found as major soil metabolites in these studies.

PEC in soil were calculated for the representative uses based on the worst-case field half-life for benalaxyl, assuming a 50% crop interception for ornamentals and 10% for onions. Relative maxima amounts of metabolites and worst-case laboratory half-lives were used in the calculation of PEC in soil of metabolites M1, M2 and M9.

Soil batch adsorption/desorption was investigated for benalaxyl and metabolites M1, M2, M9, F4-acetyl, F7 and F8. According to the results of these studies, it may be expected that benalaxyl will exhibit low to medium mobility, M1 low to high mobility in acidic soils and very high mobility in alkaline soils, M2 medium to high mobility in acidic soils and very high mobility in alkaline soils, M9 medium to high mobility, F4-acetyl and F7 very high mobility and F8 medium to very high mobility. Only experiments in two soils were considered fully reliable for benalaxyl. Therefore, a data gap for two additional experiments has been identified. Nevertheless, applying FOCUS rules, provisional groundwater exposure assessment can be carried out using the worst-case input parameter. Data for metabolite F7 were considered highly unreliable but indicative of the very high mobility of F7. A data gap is identified for reliable data on the adsorption/desorption of metabolite F7. Nevertheless, a worst-case exposure assessment can be performed assuming no adsorption ($K_{Foc} = 0$).

Column and aged column leaching studies are available. In the aged experiment, metabolites M1, M2 and M9 were found as the major radioactive components of the leachate.

A 2-year lysimeter study is available in the dossier. In this study, benalaxyl was applied at a rate of 4 $\times$ 240 g/ha to tomatoes during the first year. Soil metabolites M1 and M2 were identified in the lysimeter leachate at annual average levels of M1: 4.7 μg/L (first year) and 0.09–0.18 μg/L (second year) and M2: 5.11–8.22 μg/L (first year) and 2.72–3.6 μg/L (second year). Three new metabolites (F4-acetyl, F7 and F8), not previously identified in the soil aerobic degradation studies, were identified in the lysimeter leachate. All these metabolites exceed the trigger of 0.75 μg/L of annual average concentration in the leachate in the first year after application (the trigger of 0.1 μg/L is also exceeded in the second year). These metabolites were identified by LC–MS and their structures were confirmed by LC/NMR as further oxidation products of M1. The identity of the lysimeter metabolite named either F4 in the EFSA conclusion for benalaxyl-M (EFSA, 2013a) or F4-acetyl (benalaxyl dossier) is considered still open. EFSA considers the simulations provided for F4-acetyl as provisional, since the structure attributed to this lysimeter metabolite is still tentative. Further identification data are needed in order to address the toxicological relevance of this metabolite.

Benalaxyl may be considered stable to hydrolysis under environmental conditions. Photolysis in water is not expected because there is no adsorption at wavelengths above 290 nm. Benalaxyl is not readily biodegradable. No degradation of benalaxyl was observed in the aerobic mineralisation pelagic test in fresh water.

The degradation in water and sediment of benalaxyl, ^{14}C labelled in the aniline ring, was investigated under dark aerobic conditions at 20°C in one study with two systems. Benalaxyl was strongly adsorbed to the sediment (43–53% AR after 100 days). Benalaxyl is highly persistent in the whole system. The main metabolites identified were M1 and M9. Unextractable radioactivity reached maximum of 8.13% AR after 100 days (river aquatic sediment) and mineralisation was negligible in both systems.

The exposure to natural aquatic environment was assessed by calculation of PEC SW/sed values for benalaxyl and the metabolites M1, M2 and M9 for the representative uses proposed, with FOCUS SW models and scenarios. For the metabolites, FOCUS SW calculations up to step 2, while for benalaxyl FOCUS SW calculations up to step 4 were performed to consider potential mitigation measures of 10 or 20 m spray drift and vegetative buffer strip.

The potential for groundwater contamination was assessed based on the FOCUS GW scheme (PELMO 5.5.3, PEARL 4.4.4). The 20 years 80th percentile of the annual average concentration in the leachate at 1 m depth was calculated for benalaxyl and the soil metabolites M1, M2 and M9 and the lysimeter metabolites F4-acetyl, F7 and F8, when benalaxyl is applied according to the representative uses in grapevines, potatoes, onions, tomatoes and ornamentals. For the use in grapevines, the trigger of 0.1 μg/L is exceeded for the metabolites M2, F7 and F8 for all seven relevant scenarios and for metabolite F4-acetyl for five scenarios. For the use in onion, the trigger of 0.1 μg/L is exceeded for the metabolites M2, F7 and F8 for all six relevant scenarios, for metabolite F4-acetyl for five scenarios and for metabolite M9 for one scenario. For the use in tomato, the trigger of 0.1 μg/L is exceeded for the metabolite F7 for all five relevant scenarios, for the metabolites M2 and F8 for four scenarios and for metabolite F4-acetyl for three scenarios. For the use in potato, the trigger of 0.1 μg/L is exceeded for metabolite F7 for all nine relevant scenarios, for the metabolites M2 and F8 by eight scenarios and for metabolite F4-acetyl for seven scenarios. For the use in ornamentals, the trigger of 0.1 μg/L is exceeded for the metabolites M2, F4-acetyl, F7 and F8 for all seven relevant scenarios. For a number of uses and scenarios the metabolites M2, F7 and F8 exceed the level of 0.75 μg/L in the modelling exercise and the metabolites F4-acetyl, F7 and F8 in the lysimeter. Therefore, metabolites M2, F4-acetyl, F7 and F8 required the consideration of their effect on the consumer risk for assessing their relevance as potential groundwater pollutants (see Section 3). The formation fractions used in the simulations have been discussed during the peer review. The experts agreed that the data available do not allow obtaining robust formation fractions and that a default formation fraction of 0.69 should be used for the transformation of metabolite M1 to F4-acetyl, F7 and F8. Formation fraction of 0.65 should be used for the transformation of benalaxyl to M1 and a formation fraction of 0.39 for the transformation of benalaxyl to M9 and a formation fraction of 0.37 for the transformation of M9 to M2. In addition, the RMS was required to consolidate the end points of benalaxyl with those already agreed for benalaxyl-M. As a result, relatively more critical end points have been established for the adsorption in soil and pH dependence has been identified for the adsorption of some of them. However, these end points have not been used in the updated groundwater modelling. Therefore, a data gap for new PEC GW calculations using the agreed formation fractions and adsorption end points is identified. Nevertheless, the available calculations reported above can be used to identify main concerns with respect to leaching to groundwater, taking into account that a more worst-case picture may result from the updated calculations when available. A critical area of concern with respect to groundwater contamination by relevant metabolites has been identified.

The applicant did not provide appropriate 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 or groundwater are abstracted for drinking water. This has led to the identification of a data gap (see Section 7) and results in the consumer risk assessment not being finalised (see Section 9).

5. Ecotoxicology

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

Benalaxyl was discussed at the Pesticides Peer Review Experts' meeting 183 in September 2018.

It is noted that the uses on tomatoes and flowers/ornamentals include uses in greenhouses. From the available information it cannot be confirmed whether these uses are limited to permanent structures. Additionally, a specific risk assessment covering the use in permanent greenhouses was not provided and this was needed to draw a comprehensive conclusion for the risk assessment for aquatic

organisms. Therefore, the uses in greenhouse were considered as uses in low technology (non-permanent) structures as worst case assumption.

The batches used in ecotoxicological testing support the technical specification proposed for the renewal but not the original technical specification.

As reported in Sections 3 and 4, a stereoselective degradation of the residues of benalaxyl in the feed items and in the environmental compartments cannot be excluded. From the available information in the ecotoxicity data package the racemate (benalaxyl) and the single isomers presented similar toxicity.

The acute risk to **birds and mammals** from food items contaminated with benalaxyl was assessed as low for all uses evaluated. The long-term end point from the available bird reproduction study was discussed in the experts' meeting. The experts agreed on a NOAEL of 9 mg a.s./kg bw per day. A high long-term risk to birds was indicated in a tier 1 risk assessment based on the agreed end point for all uses evaluated (critical area of concern).

The long-term end point from the two-generation rat study was discussed. The experts agreed that the relevant NOAEL from the study is 52.96 mg/kg bw per day. The long-term risk to mammals was assessed as low for all uses with the exception of the use in flowers/ornamentals.

The risk from secondary poisoning for benalaxyl was assessed as high for earthworm-eating birds (critical area of concern) and assessed as low for earthworm-eating mammals for all representative uses.

The risk from secondary poisoning of fish-eating birds and mammals could not be finalised because a reliable bioconcentration factor (BCF) was not available for fish[15] (data gap and issue not finalised). Consideration to the stereoselective bioaccumulation should be given while addressing this point.

A risk assessment for birds and mammals for metabolites formed in food items was not provided (data gap).

The risk from uptake of benalaxyl via drinking water was assessed as low for birds and mammals.

The **aquatic** risk assessment for benalaxyl was driven by the chronic risk to daphnids. The following provides an overview on the risk assessment for the different uses:

Grapevine – the majority of FOCUS step 3 scenarios resulted in a low risk. Risk mitigation comparable to a 10 m no-spray buffer zone or a 10 m vegetated buffer strip is needed for the scenarios R1/stream, R2/stream, R3/stream, R4/stream and D6/ditch.

Tomatoes – half of the FOCUS step 3 scenarios resulted in a low risk. Risk mitigation comparable to a 10 m no-spray buffer zone or a 10 m vegetated buffer strip for run-off mitigation is needed for scenarios R3/stream and R4/stream.

Onion – less than half of the FOCUS step 3 scenarios resulted in a low risk. Risk mitigation comparable to a 10 m no-spray buffer zone or a 10 m vegetated buffer strip for run-off mitigation is needed for scenarios R1/stream, R3/stream and a 20 m no-spray buffer zone or a 20 m vegetated buffer strip for run-off mitigation is needed for scenario R4/stream. A high risk was indicated for scenario D6/ditch for the second crop. No FOCUS step 4 calculations were provided for this scenario. Therefore, it is unclear whether the risk for this scenario could be sufficiently mitigated with accepted risk mitigation methods.

Potatoes – more than half of the FOCUS step 3 scenarios resulted in a low risk. Risk mitigation comparable to a 10 m no-spray buffer zone or a 10 m vegetated buffer strip for run-off mitigation is needed for scenarios R1/stream and R3/stream. A high risk was indicated for scenario D6/ditch for the second crop. No FOCUS step 4 calculations were provided for this scenario. Therefore, it is unclear whether the risk for this scenario could be sufficiently mitigated with accepted risk mitigation methods.

Flowers/ornamentals – no full FOCUS step 3 scenario resulted in a low risk. Risk mitigation comparable to a 10 m no-spray buffer zone or a 10 m vegetated buffer strip for run-off mitigation is needed for scenarios D6 ditch, R1/stream, R2/stream, R3/stream, R4/stream.

The risk to sediment-dwelling organisms from exposure to benalaxyl was assessed as low.

The risk to aquatic organisms for metabolites M1, M2 and M9 was assessed as low.

The representative formulation 'Galben M', which contains 80 g benalaxyl/kg product and 650 g mancozeb, is significantly more toxic to aquatic organisms than the active substance benalaxyl alone. A risk assessment for the product for the combined exposure to these two active substances was provided based on spray drift entry into surface water, indicating a high risk to aquatic organisms. Risk mitigation comparable to a 10 m (tomatoes, onions, potatoes), 25 m (grapevine) and 30 m (flowers and ornamentals) no-spray buffer zone would be needed as a risk mitigation measure.

[15] See Expert consultation point 5.4 in the Meeting Report from the Pesticides Peer Review Experts' Meeting 183 (EFSA, 2019a).

A risk assessment performed in line with the EFSA bee guidance document (EFSA, 2013b) showed a low acute risk to **honey bees** from contact and oral exposure for all uses evaluated (the same conclusion would be reached by applying the guidance document on terrestrial ecotoxicology (European Commission, 2002). The risk to honey bee larvae was assessed as low for all representative uses.

A chronic high risk from exposure to residues from pollen and nectar in the treated crop was indicated in the screening step for all uses. The first-tier chronic risk assessment resulted in a low risk for the use in grapes. However, the first-tier risk assessment resulted in a high risk for the uses in ornamentals/flowers and onions. The chronic exposure toxicity ratio (ETR) values for the uses in potatoes and tomatoes are only slightly above the trigger and the chronic end points are greater than values. Therefore, the chronic risk to honey bees can be considered as low for exposure to residues in the treated crop for the uses in tomatoes and potatoes.

A high chronic risk to adult honey bees was concluded for the exposure to residues from pollen and nectar from flowering weeds in the field for all representative uses.

The chronic risk to honey bees for the scenarios adjacent crops, field margins and succeeding crops was assessed as low.

The risk from exposure to contaminated surface water was assessed as low. A correct risk assessment for exposure to puddle water based on concentrations in run-off water is missing (data gap). A risk assessment for exposure to guttation water and for exposure to metabolites formed in pollen and nectar is missing (data gap). An assessment of accumulative effects was not available. No data were available on sublethal effects, e.g. effects on hypopharyngeal gland (HPG) (data gap).

Acute oral and contact toxicity end points are available for bumble bees. A low acute risk from contact exposure was indicated for all uses evaluated. A high acute oral risk to bumblebees was indicated for the exposure to residues in the treated crops. The other exposure scenarios (adjacent fields, field margins, succeeding crops for all uses) and the weed scenario for grapes resulted in ETR values below the trigger, indicating a low risk. ETRs above the trigger were observed for the weeds scenario (ornamentals/flowers) or slightly above the trigger (onions, potato, tomato).

Chronic toxicity data for bumblebees and toxicity data for solitary bees were not available.

Overall, a low risk to honey bees cannot be concluded for all representative uses.

The first-tier assessment for **non-target arthropods** resulted in a high in-field and off-field risk for all evaluated uses. Modified exposure studies on natural substrate, 2-dimensional and 3-dimensional study design and aged residue studies were conducted. However, the in-field and off-field risk for predatory mites remains unresolved. A field study conducted with mites in grapevine did not cover the application interval and also other non-target arthropods (NTA) groups were not addressed. Overall, it is concluded that a high risk to non-target arthropods cannot be excluded for all representative uses (critical area of concern).

The risk to **earthworms** from exposure to benalaxyl and the soil metabolites M2 and M9 was assessed as low for all uses evaluated. The earthworm reproduction study with metabolite M1 was discussed by the experts. It was concluded that no reliable no observed effect concentration (NOEC) or EC_{10} can be derived from the study. The risk from metabolite M1 to earthworms remains unresolved for all the representative uses (data gap). It is noted that a study on the formulated product was not available for earthworms, therefore, it cannot be confirmed whether the active substance is not more toxic when formulated (data gap).

The risk to **soil macroorganisms other than earthworms** was assessed as low for exposure to the formulation 'Galben M' and metabolites M1, M2 and M9.

The risk to **soil microorganisms** (nitrogen transformation) was assessed as low for benalaxyl and metabolites M1, M2, M9 for all uses evaluated.

The risk to **non-target terrestrial plants** and **biological methods of sewage treatment** were assessed as low for all uses evaluated.

6. Endocrine disruption properties

The assessment of the endocrine disruption potential of benalaxyl according to the ECHA/EFSA Guidance (2018) was discussed at the Pesticides Peer Review Experts' Meeting PREV 05 (joint Mammalian toxicology – Ecotoxicology meeting) in May 2019, subsequent to the completion of the updated endocrine assessment conducted by EFSA in line with the new scientific criteria for the determination of endocrine disrupting properties, as laid down in Commission Regulation (EU) 2018/605.

In the experts' meeting, it was concluded that there is a need to request additional information in accordance with Commission Implementing Regulation (EU) No 2018/1659, to be able to conclude

whether the approval criteria for endocrine disruption in line with the scientific criteria for the determination of endocrine disrupting properties, as laid down in Commission Regulation (EU) 2018/605, are met.

As regards the assessment of the endocrine disruption potential of benalaxyl for **humans**, for the T-modality, minimal follicular cell hypertrophy was only observed in a 90-day rat study, while it was not reproducible in studies at higher dose levels and over longer duration in the same species and in studies performed in other species. Based on the available evidence, benalaxyl did not show a consistent pattern indicative of T-mediated adversity. Therefore, benalaxyl does not meet the ED criteria for the T-modality for humans.

Regarding oestrogen, androgen and steroidogenesis (EAS) modalities, no EAS-mediated adversity was observed, relevant for humans. However, EAS-mediated parameters were not sufficiently investigated (i.e. lack of OECD TG 416, version from 2001, or OECD TG 443) ruling out the possibility to exclude other potential EAS-mediated adverse effects.[16] The EAS-related endocrine activity was not sufficiently investigated either. Therefore, the following additional information was requested to be able to conclude whether the approval criteria for endocrine disruption are met:

- A study in line with OECD TG 455 (Stably Transfected Human Oestrogen Receptor-alpha Transcriptional Activation Assay (ER STTA assay));
- A study in line with OECD TG 440 (Uterotrophic assay) in case OECD TG 455 is negative;
- A study in line with OECD TG 456 (H295R Steroidogenesis Assay);
- A study in line with OPPTS 890.1200 (Aromatase assay);
- A study in line with OECD TG 458 (Stably Transfected Human Androgen Receptor Activation Assay (AR STTA assay));
- A study in line with OECD TG 441 (Hershberger Assay) in case OECD TG 456 and 458 and OPPTS 890.1200 are negative;

In case of positive result/s for at least one modality, additional testing would be needed:

- OECD TG 443 (with the inclusion of cohort 1B) or OECD TG 416 (according to the latest version from 2001).

The outcome of the assessment reported above for humans also applies to **wild mammals as non-target organisms**.

For non-target organisms other than mammals, a conclusion on the endocrine disruption potential of benalaxyl through the EATS-modalities could not be drawn since the endocrine activity/ endocrine adversity was not sufficiently investigated. In line with the assessment strategy proposed in the ECHA/EFSA Guidance (2018), level 3 tests are needed to complete the current data package, i.e.:

- a study in line with OECD TG 231 (Amphibian Metamorphosis Assay (AMA));
- a study in line with OECD TG 229 (Fish Short-Term Reproduction Assay (FSTRA)).

In case of positive result/s for at least one modality, additional testing would be needed:

- A study in line with OECD TG 241 (Larval Amphibian Growth and Development Test) and/or 240 (Medaka Extended One-Generation Reproduction Test).

Following the EFSA request for additional information the applicant confirmed that no additional studies will be performed. Therefore, currently, based on the available information on humans and non-target organisms, the assessment of the endocrine disrupting potential of benalaxyl 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, cannot be concluded (data gap and issue not finalised).

[16] Refer to point 2 of the 'Report Pesticide Peer Review 05_Mammalian toxicology – Ecotoxicology (joint session on ED) 05 benalaxyl' for more information (EFSA, 2019a).

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
Benalaxyl	Moderate to high (DT_{50} = 18.1–134 days)	The risk to earthworms, other soil macro-organisms and soil microorganisms was assessed as low. A data gap was identified for a study with the formulated active substance and earthworms
M1	Moderate to medium (DT_{50} = 49.7–88.7 days)	The risk to soil macro-organisms other than earthworms and soil microorganisms was assessed as low. A data gap was identified for addressing the risk to earthworms (no valid study with earthworms and metabolite M1 is available)
M2	Medium to high (DT_{50} = 68.4–132.49 days)	The risk to earthworms, other soil macroorganisms and soil microorganisms was assessed as low
M9	Low to high (DT_{50} = 4.8–337.4 days)	The risk to earthworms, other soil macro-organisms and soil micro-organisms was assessed as low

DT_{50}: period required for 50% dissipation (define method of estimation).

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
Benalaxyl	Low to medium (K_{FOC} = 453.9–598.4 mL/g)	FOCUS GW: No	Yes	Yes
M1	Low to high in acidic soils (K_{FOC} = 126–971 mL/g) and Very high alkaline soils (K_{FOC} = 10.15–16.40 mL/g)	FOCUS GW: No	No	Yes, should the peer review considerations be confirmed that criteria for classification of benalaxyl as Carcinogen category 2 may be metADI 0.9 mg/kg bw per day
M2	Medium to high in acidic soils (K_{FOC} = 85.19–440.83 mL/g) and Very high in alkaline soils (K_{FOC} = 8.43–6.28 mL/g)	FOCUS GW: Yes. Grapevines 7/7 scenarios, onion 6/6 scenarios, tomato 4/5 scenarios, potatoes 8/9 scenarios, ornamentals 7/7 scenarios	No	Yes, should the peer review considerations be confirmed that criteria for classification of benalaxyl as Carcinogen category 2 may be met
M9	Medium to high (K_{FOC} = 57–214 mL/g)	FOCUS GW: Yes. Onions 1/6	No	Yes, should the peer review considerations be confirmed that criteria for classification of benalaxyl as Carcinogen category 2 may be met

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
F4-acetyl (lysimeter metabolite, relevant for ground water assessment)	Very high (K_{FOC} = 13–36 mL/g)	FOCUS GW: Yes. Grapevines 5/7 scenarios, onion 5/6 scenarios, tomato 3/5 scenarios, potatoes 7/9 scenarios, ornamentals 7/7 scenarios	No	Yes, should the peer review considerations be confirmed that criteria for classification of benalaxyl as Carcinogen category 2 may be met
F7 (lysimeter metabolite, relevant for ground water assessment)	Very high (K_{FOC} = 0)[b]	FOCUS GW: Yes. Grapevines 7/7 scenarios, onion 6/6 scenarios, tomato 5/5 scenarios, potatoes 9/9 scenarios, ornamentals 7/7 scenarios	Screening for biological activity performed for a mixture of F7:F8 (1:3.8) showed no activity by the mixture	Yes, should the peer review considerations be confirmed that criteria for classification of benalaxyl as Carcinogen category 2 may be met
F8 (lysimeter metabolite, relevant for ground water assessment)	Medium to very high (K_{FOC} = 23.97–228.55 mL/g)	FOCUS GW: Yes. Grapevines 7/7 scenarios, onion 6/6 scenarios, tomato 4/5 scenarios, potatoes 8/9 scenarios, ornamentals 7/7 scenarios	Screening for biological activity performed for a mixture of F7:F8 (1:3.8) showed no activity by the mixture	Yes, should the peer review considerations be confirmed that criteria for classification of benalaxyl as Carcinogen category 2 may be met

K_{FOC}: Freundlich organic carbon adsorption coefficient; ADI: acceptable daily intake; bw: body weight; FOCUS: Forum for the Co-ordination of Pesticide Fate Models and their Use; GW: ground water.
(a): FOCUS scenarios or relevant lysimeter.
(b): Data gap identified for reliable adsorption/desorption data.

Table 3: Surface water and sediment

Compound (name and/or code)	Ecotoxicology
Benalaxyl	A low risk with risk mitigation measures, except for the D6 ditch scenario for the uses on potatoes and onions
M1	Low risk to aquatic organisms
M2	Low risk to aquatic organisms
M9	Low risk to aquatic organisms

Table 4: Air

Compound (name and/or code)	Toxicology
Benalaxyl	Rat LC_{50} > 4.2 mg/L (highest attainable concentration; nose-only, rat)

LC_{50}: lethal concentration, median.

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 Regulation (EC) No 1107/2009 concerning information on potentially harmful effects).

- An updated literature search and a detailed assessment of the scientific peer-reviewed open literature on the active substance and its relevant metabolites, dealing with side effects on health, the environment and non-target species to be conducted and reported in accordance with the EFSA guidance on the submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (EFSA, 2011). In particular, the stereoselective metabolism and degradation of benalaxyl isomers should be further investigated.[5] In addition, the literature search should also be performed following the recommendations of the ECHA/EFSA Guidance (2018) for the hazard identification of endocrine disrupting properties (relevant for the sections on mammalian toxicology, residues, environmental fate and behaviour and ecotoxicology; a report has been submitted by the applicant but was not (properly) evaluated by the RMS).
- Information on the identity of a polymeric co-formulant should be provided (relevant for all representative uses evaluated; see Section 1).
- Extraction efficiency of the procedures used in the monitoring methods for dry, high acid and high oil content commodities should be addressed (relevant for all representative uses evaluated; see Section 1).
- An assessment of the toxicological relevance of the impurities in the technical specification should be provided (relevant for all representative uses evaluated; see Section 2).
- Further assessment of the metabolites of benalaxyl to be included in the residue definition for human biomonitoring (present in significant amounts in body fluids and/or in tissues) (relevant for all representative uses evaluated; see Section 2).
- Further assessment of the toxicological profile of GX5a/GX5b isomers, GX5c and their glucoside conjugates and of benalaxyl acid, 2-benzoic acid is required (relevant for the uses on fruit crops; see Sections 2 and 3).
- The absence of carcinogenic potential of the metabolites found in groundwater should be demonstrated (relevant for all representative uses evaluated; see Section 2).
- A metabolism study in root crops and compliant with the representative uses on potatoes and onions is required (relevant for the uses in onions and potatoes, see Section 3).
- Sufficient field residue trials compliant with the representative uses on grapes and tomatoes and analysing for all compounds included in the provisional risk assessment residue definition for fruit crops are required (relevant for the uses in grapes and tomatoes, see Section 3).
- Having regard to the low to high persistence of the soil metabolite M9, confined rotational crops metabolism data addressing the fate of this compound in leafy, cereals small grains and root crops at the different PBIs are needed (relevant for the uses in tomatoes, onions, potatoes and flowers/ornamentals, see Section 3).
- Storage stability data on a commodity representative of the bulb vegetables crop category are required (relevant for the representative use in onions; see Section 3).
- Sufficient NEU and SEU GAP-compliant residue trials should be provided on onions and potatoes in accordance with the residue definitions in root crops, once agreed (relevant for the representative uses in onions and potatoes; see Section 3).
- 1 and 3 residue trials on grapes to complete the NEU and SEU residue data sets, respectively and analysing for benalaxyl residues are required (relevant for the representative use in grapes; see Section 3).
- Data on residues of benalaxyl and metabolites in pollen and bee products for human consumption resulting from residues taken up by honey bees from crops at blossom are required (relevant for all representative uses evaluated, it is acknowledged that no guidance/ test guideline is available for addressing this data requirement; see Section 3).
- Further details on the chiral analysis performed in study Curtis-Jackson, P. (2015) presented in the RAR (Romania, 2018) should be provided (relevant for all representative uses evaluated; see Section 4).

- Further data and information are needed to demonstrate that residues of benalaxyl will have no immediate or delayed harmful effects on human health, including that of vulnerable groups, or animal health, . . .through drinking water (taking into account substances resulting from water treatment) (relevant to comply with the conditions of approval, not dependent of any specific use, see Section 4).
- Two additional batch adsorption/desorption experiments with benalaxyl are required (relevant for all representative uses evaluated; see Section 4).
- Reliable data on the adsorption/desorption of metabolite F7 in soil are required (relevant for all representative uses evaluated; see Section 4).
- Further identification data are needed in order to address the toxicological relevance of metabolite F4-acetyl (relevant for all representative uses evaluated; see Sections 2 and 4).
- New PEC GW calculations using agreed formation fractions and adsorption end points should be provided (relevant for all representative uses evaluated; see Section 4).
- A risk assessment for birds and mammals for metabolites formed in food items is required (relevant for all representative uses, see Section 5).
- A valid BCF estimate is required; consideration to the stereoselective bioaccumulation should be given while addressing this point (relevant for all representative uses evaluated, see Section 5).
- Further data are required to address the risk to honey bees from sublethal effects (e.g. effects on HPG), via exposure to guttation and puddle water, and via exposure to metabolites formed in pollen and nectar (relevant for all representative uses, see Section 5).
- Further information should be provided on the toxicity to earthworms for the active substance when formulated (relevant for all representative uses, see Section 5).
- A long-term study with earthworms and metabolite M1 is required (relevant for all representative uses, see Section 5).
- Further data to address the potential of benalaxyl for endocrine disruption (relevant for all representative uses, see Section 6).

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

- For the non-dietary exposure to benalaxyl, the use of personal protective equipment is required for operators (for tractor-mounted application in grapevines, for greenhouse application in tomatoes and ornamentals), and for workers (grapes, tomatoes and ornamentals, when estimations are done with EUROPOEM model) in order to have an exposure level below the AOEL (see Section 2 and details in Appendix A).
- For the combined exposure to benalaxyl and mancozeb, the total exposure level for operators and workers is below 100% for all representative uses in at least one of the models when appropriate PPE is used (see Section 2 and details in Appendix A).
- Risk mitigation comparable to a 10 m no-spray buffer zone or a 10 m vegetated buffer strip is needed for the scenarios R1/stream, R2/stream, R3/stream, R4/stream and D6/ditch for the use in grapevine (see Section 5).
- Risk mitigation comparable to a 10 m no-spray buffer zone or a 10 m vegetated buffer strip for run-off mitigation is needed for scenarios R3/stream and R4/stream for the use in tomatoes (see Section 5).
- Risk mitigation comparable to a 10 m no-spray buffer zone or a 10 m vegetated buffer strip for run-off mitigation is needed for scenarios R1/stream, R3/stream and a 20 m no-spray buffer zone or a 20 m vegetated buffer strip for run-off mitigation is needed for scenario R4/stream for the use in onions (see Section 5).
- Risk mitigation comparable to a 10 m no-spray buffer zone or a 10 m vegetated buffer strip for run-off mitigation is needed for scenarios R1/stream and R3 stream for the use in potatoes (see Section 5).
- Risk mitigation comparable to a 10 m no-spray buffer zone or a 10 m vegetated buffer strip for run-off mitigation is needed for scenarios D6 ditch, R1/stream, R2/stream, R3/stream, R4/stream for the use in flowers/ornamentals (see Section 5).

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 Regulation (EC) No 1107/2009 and as set out in Commission Regulation (EU) No 546/2011[17] and if the issue is of such importance that it could, when finalised, become a concern (which would also be listed as a critical area of concern if it is of relevance to all representative uses).

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

1) Residue definition for human biomonitoring (body fluids and tissues) could not be finalised (see Section 2).
2) The consumer dietary risk assessment could not be concluded since the risk assessment residue definition for fruit crops could not be finalised, residue definitions for root crops and rotational crops remain open and the livestock exposure assessment cannot be conducted (see Section 3).
3) The consumer risk assessment through drinking water is not finalised with regard to groundwater metabolites M2, F4-acetyl, F7 and F8 and the unknown nature of residues that might be present in drinking water, consequent to water treatment following abstraction of surface water that might contain the active substance and its metabolites (see Sections 2, 3 and 4).
4) The risk from secondary poisoning of fish-eating birds and mammals could not be finalised because no valid BCF estimate is available. A valid BCF estimate is also required for the B assessment of the PBT criteria (see Section 5).
5) Based on the available evidence, it was not possible to conclude whether benalaxyl has endocrine disrupting properties according to the scientific criteria for the determination of endocrine disrupting properties as set out in 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 (see Section 6).

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 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.

6) Potential groundwater contamination by relevant metabolites (see Sections 4 and 7).
7) High long-term risk to birds and earthworm-eating birds from secondary poisoning (see Section 5).
8) High long-term risk to non-target arthropods for all representative uses (see Section 5).

[17] 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.

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

In addition to the issues indicated in Table 5 below, the assessment of the endocrine disrupting properties of benalaxyl according to the scientific criteria for the determination of endocrine disrupting properties as set out in 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, could not be finalised.

Table 5: Overview of concerns

Representative use		Grapes	Tomato		Onion	Potato	Flowers and ornamentals	
			F	G			F	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	X[2.3]	X[2.3]	X[2.3]	X[2.3]	X[2.3]	X[2.3]	X[2.3]
Risk to wild non-target terrestrial vertebrates	Risk identified	X[7]	X[7]	X[7,(d)]	X[7]	X[7]	X[7]	X[7,(d)]
	Assessment not finalised	X[4]	X[4]	X[4,(d)]	X[4]	X[4]	X[4]	X[4,(d)]
Risk to wild non-target terrestrial organisms other than vertebrates	Risk identified	X[8]	X[8]	X[8,(d)]	X[8]	X[8]	X[8]	X[8,(d)]
	Assessment not finalised							
Risk to aquatic organisms	Risk identified				X[(c)]	X[(c)]		
	Assessment not finalised							
Groundwater exposure to active substance	Legal parametric value breached							
	Assessment not finalised							
Groundwater exposure to metabolites	Legal parametric value breached[(a)]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]
	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): When the consideration for classification made in the context of this evaluation under Regulation (EC) No 1107/2009 is confirmed under Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008.

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

(c): Only for D6 ditch scenario.

(d): For high technology permanent greenhouses, the risk is likely to be low.

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Abbreviations

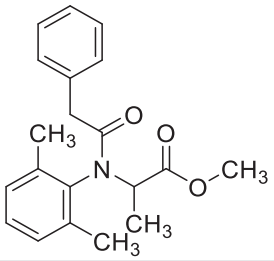
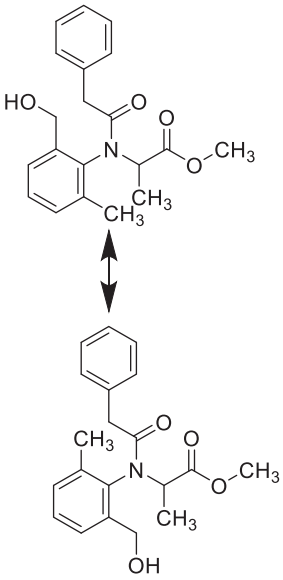
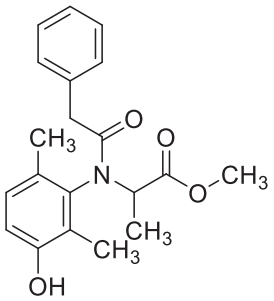
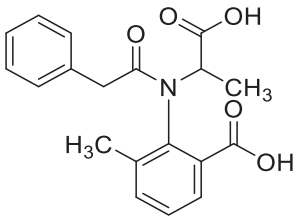
AAOEL	acute acceptable operator exposure level
ADI	acceptable daily intake
AMA	Amphibian Metamorphosis Assay
AOEL	acceptable operator exposure level
AR	applied radioactivity
AR STTA assay	Stably Transfected Human Androgen Receptor Activation Assay
ARfD	acute reference dose
BCF	bioconcentration factor
bw	body weight
DAR	draft assessment report
DT_{50}	period required for 50% dissipation (define method of estimation)
EAS	oestrogen, androgen and steroidogenesis modalities
EATS	oestrogen, androgen, thyroid and steroidogenesis modalities
EC_{10}	effective concentration, 10%
ECHA	European Chemicals Agency
EEC	European Economic Community
ER STTA assay	Stably Transfected Human Oestrogen Receptor-alpha Transcriptional Activation Assay
ETR	exposure toxicity ratio
FAO	Food and Agriculture Organization of the United Nations
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
FSTRA	Fish Short-Term Reproduction Assay
GAP	Good Agricultural Practice
HPLC–MS/MS	high-pressure liquid chromatography with tandem mass spectrometry
HPG	hypopharyngeal glands
IESTI	international estimated short-term intake
InChiKey	International Chemical Identifier Key
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
JMPR	Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
K_{Foc}	Freundlich organic carbon adsorption coefficient
LC_{50}	lethal concentration, median
LC–MS/MS	liquid chromatography with tandem mass spectrometry
LDH	lactate dehydrogenase
LOAEL	lowest observable adverse effect level

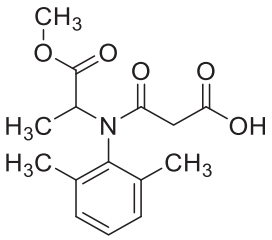
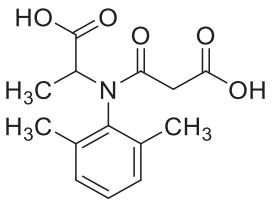
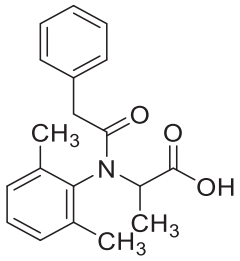
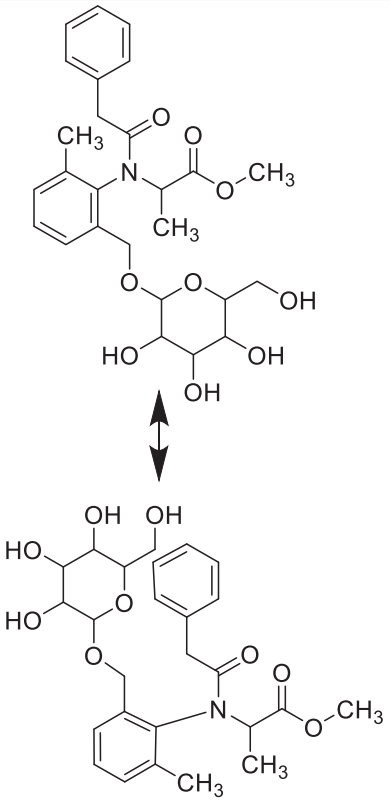
LOQ	limit of quantification
MRL	maximum residue level
NEU	northern European Union
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NTA	non-target arthropods
OECD	Organisation for Economic Co-operation and Development
PBT	persistent, bioaccumulative and toxic
PEC	predicted environmental concentration
PEC_{gw}	predicted environmental concentration in groundwater
PEC_{sed}	predicted environmental concentration in sediment
PEC_{soil}	predicted environmental concentration in soil
PEC_{sw}	predicted environmental concentration in surface water
RAR	Renewal Assessment Report
REACH	Registration, Evaluation, Authorisation of Chemicals Regulation
SEU	southern European Union
SMILES	simplified molecular-input line-entry system
TRR	total radioactive residue
WP	wettable powder
WHO	World Health Organization

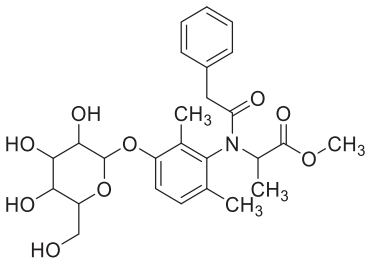
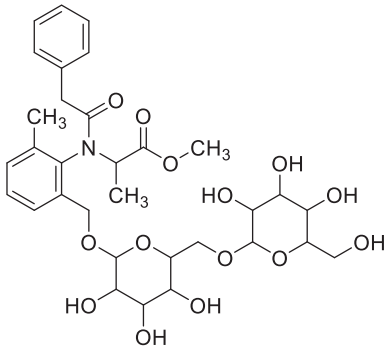
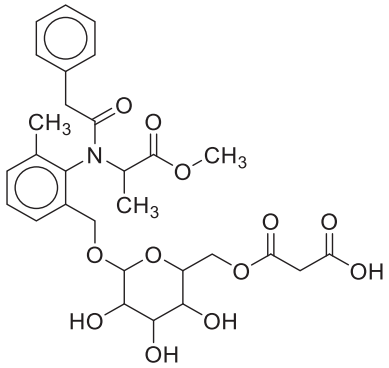
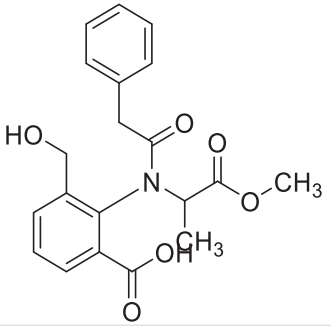
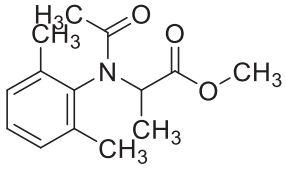
Appendix A – List of end points for the active substance and the representative formulation

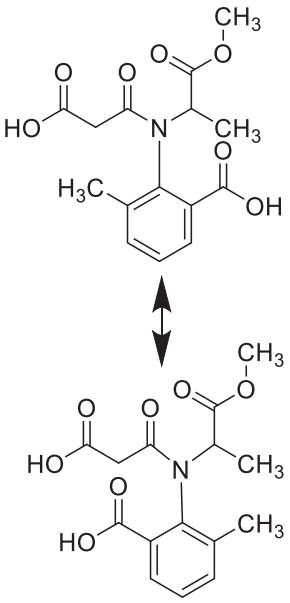
Appendix A can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2020.5985

Appendix B – Used compound codes

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[b]
benalaxyl	methyl *N*-(phenylacetyl)-*N*-(2,6-xylyl)-DL-alaninate CC1=C(N(C(CC2=CC=CC=C2)=O)C(C(OC)=O)C)C(C)=CC=C1 CJPQIRJHIZUAQP-UHFFFAOYSA-N	
GX5a/GX5b isomers, G8/G14 (2-hydroxy methyl benalaxyl)	methyl *N*-(2-(hydroxymethyl)-6-methylphenyl)-*N*-(2-phenylacetyl)alaninate CC(C(OC)=O)N(C(CC1=CC=CC=C1)=O)C2=C(C)C=CC=C2CO QHSRUJWLFUQNEB-UHFFFAOYSA-N	
GX5c (3-hydroxy benalaxyl)	methyl *N*-(3-hydroxy-2,6-dimethylphenyl)-*N*-(2-phenylacetyl) alaninate CC1=C(N(C(CC2=CC=CC=C2)=O)C(C(OC)=O)C)C(C)=CC=C1O VDALXZVEUBNREU-UHFFFAOYSA-N	
Benalaxyl acid, 2-benzoic acid	2-(*N*-(1-carboxyethyl)-2-phenylacetamido)-3-methylbenzoic acid CC(C(O)=O)N(C(CC1=CC=CC=C1)=O)C2=C(C)C=CC=C2C(O)=O SEHAWCUGAJCWKQ-UHFFFAOYSA-N	

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[b]
M1 (benalaxyl oxopropanoic acid)	3-((2,6-dimethylphenyl)(1-methoxy-1-oxopropan-2-yl) amino)-3-oxopropanoic acid O=C(O)CC(N(C1=C(C)C=CC=C1C)C(C)C(OC)=O)=O IRTDHGMDHHAJIE-UHFFFAOYSA-N	
M2	3-((1-carboxyethyl)(2,6-dimethylphenyl)amino)-3-oxopropanoic acid O=C(O)CC(N(C1=C(C)C=CC=C1C)C(C)C(O)=O)=O ZBHHMKQJXLOKMU-UHFFFAOYSA-N	
M9 (benalaxyl acid)	*N*-(2,6-dimethylphenyl)-*N*-(2-phenylacetyl)alanine CC1=C(C(C)=CC=C1)N(C(C)C(O)=O)C(CC2=CC=CC=C2)=O DXGQLQXGTYPVJL-UHFFFAOYSA-N	
GX1a/GX1b isomers (2-hydroxy methyl benalaxyl glucoside)	methyl *N*-(2-methyl-6-(((3,4,5-trihydroxy-6-(hydroxymethyl) tetrahydro-2*H*-pyran-2-yl)oxy)methyl)phenyl)-*N*-(2-phenylacetyl)alaninate O=C(C(N(c1c(C)cccc1COC2OC(C(C(C2O)O)O)CO)C (Cc3ccccc3)=O)C)OC JADCFAHBYNWZMK-UHFFFAOYSA-N	

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[b]
GX1c (glucoside conjugate of GX5c)	methyl *N*-(2,6-dimethyl-3-((3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)phenyl)-*N*-(2-phenylacetyl)alaninate CC1=C(C(C)=CC=C1OC2OC(CO)C(O)C(O)C2O)N(C(C)C(OC)=O)C(CC3=CC=CC=C3)=O CTLJUCPWBLZNRJ-UHFFFAOYSA-N	
GX6	methyl *N*-(2-methyl-6-(((3,4,5-trihydroxy-6-(((3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)methyl)tetrahydro-2*H*-pyran-2-yl)oxy)methyl)phenyl)-*N*-(2-phenylacetyl)alaninate CC(C(OC)=O)N(C1=C(COC2C(O)C(O)C(O)C(COC3C(O)C(O)C(O)C(CO)O3)O2)C=CC=C1C)C(CC4=CC=CC=C4)=O JQCOPNKVICZJMR-UHFFFAOYSA-N	
GX11	3-oxo-3-((3,4,5-trihydroxy-6-((2-(*N*-(1-methoxy-1-oxopropan-2-yl)-2-phenylacetamido)-3-methylbenzyl)oxy)tetrahydro-2*H*-pyran-2-yl)methoxy)propanoic acid O=C(C(N(c1c(C)cccc1COC2OC(C(C(C2O)O)O)COC(CC(O)=O)=O)C(Cc3ccccc3)=O)C)OC SZAOIOJGWIBWMQ-UHFFFAOYSA-N	
G6	3-(hydroxymethyl)-2-(*N*-(1-methoxy-1-oxopropan-2-yl)-2-phenylacetamido)benzoic acid CC(C(OC)=O)N(C(CC1=CC=CC=C1)=O)C2=C(CO)C=CC=C2C(O)=O AYFLTOWDPKZGKC-UHFFFAOYSA-N	
F4-acetyl*	methyl *N*-acetyl-*N*-(2,6-dimethylphenyl)alaninate CC(C(OC)=O)N(C1=C(C)C=CC=C1C)C(C)=O SQSRTKOJNAFFCW-UHFFFAOYSA-N	

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[b]
F7/F8	2-(2-carboxy-*N*-(1-methoxy-1-oxopropan-2-yl)acetamido)-3-methylbenzoic acid O=C(O)C1=CC=CC(C)=C1N(C(C)C(OC)=O)C(CC(O)=O)=O LOLLBQOBGKUVRA-UHFFFAOYSA-N	

IUPAC: International Union of Pure and Applied Chemistry; SMILES: simplified molecular-input line-entry system; InChiKey: International Chemical Identifier Key.
*: The structure attributed to this metabolite is considered tentative (see Section 4).
(a): The metabolite name in bold is the name used in the conclusion.
(b): ChemBioDraw v.13.0.2.3021.