CONCLUSION ON PESTICIDES PEER REVIEW

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Peer review of the pesticide risk assessment of the active substance metalaxyl-M (amendment of approval conditions)

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Abstract

The conclusions of the EFSA following the peer review of the initial risk assessments carried out by the competent authorities of the rapporteur Member State, Belgium, and co-rapporteur Member State, Greece, for the pesticide active substance metalaxyl-M are reported. The context of the peer review was that required by Regulation (EC) No 1107/2009 of the European Parliament and of the Council. The conclusions were reached on the basis of the evaluation of the representative uses for the amendment to the conditions of approval of metalaxyl-M as a fungicide seed treatment for sunflower and spinach seeds intended to be sown in field and on the basis of data submitted to update the specified level of an impurity in the technical active substance. The reliable endpoints, appropriate for use in regulatory risk assessment are presented. Missing information identified as being required by the regulatory framework is listed. Concerns are reported where identified.

Keywords: metalaxyl-M, peer review, risk assessment, pesticide, fungicide

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Summary

Regulation (EC) No 1107/2009 of the European Parliament and of the Council lays down, *inter alia*, the detailed rules as regards the procedure for the assessment of applications for amendment to the conditions of approval of active substances.

Metalaxyl-M was renewed on 01 June 2020 by Commission Implementing Regulation (EU) 2020/617, following a peer review of the risk assessment as set out in the EFSA Conclusion on metalaxyl-M, approved on 19 January 2015. It was a specific provision of the approval that, when used for seed treatment, only the treatment of seeds intended to be sown in greenhouses may be authorised. In accordance with Article 7 of the Regulation, the rapporteur Member State (RMS) Belgium received an application from Syngenta Crop Protection AG on 17 June 2020 for an amendment to the conditions of approval of the active substance metalaxyl-M to lift the restriction and to allow uses to be authorised as a seed treatment where treated seed may also be sown outside in fields, and to update the specified level of an impurity in the technical active substance.

An initial evaluation of the dossier on metalaxyl-M was provided by the RMS in a revised renewal assessment report (RAR), and subsequently, a peer review of the pesticide risk assessment on the RMS evaluation was conducted by EFSA in accordance with Article 12 of Regulation (EC) No 1107/2009. The following conclusions are derived.

The uses of metalaxyl-M according to the representative uses as a fungicide on sunflower and spinach (seed treatment), as proposed at EU level result in a sufficient fungicidal efficacy against the targets *Plasmopara halstedii*, *Peronospora* spp. and *Pythium* spp.

The data provided with the current assessment do not change the conclusions reached during the previous peer review with respect to the **identity, physical and chemical properties** of the active substance and the formulation for representative uses, and analytical methods. However, based on the current toxicological assessment, an updated specified level was proposed for an impurity in the technical active substance.

In the **mammalian toxicology** section, the newly submitted data for one metabolite and one impurity did not impact on the conclusions of the renewal assessment including toxicological reference values and risk assessment for operators, workers, residents and bystanders.

In the **residue** section, no new studies were submitted under the current procedure; thus, the conclusions reached during the previous peer review for the consumer risk assessment are still valid. However, following the submission of new data in the environmental fate section, an update on the consumer risk assessment via the consumption of drinking water was triggered resulting in the consumer risk assessment being not finalised.

The data available on **environmental fate and behaviour** are sufficient to carry out the required environmental exposure assessments at EU level for the representative uses except information to address the effect of water treatments processes on the nature of the residues that might be present in surface water and groundwater, when surface water or groundwater is abstracted for drinking water purposes was not available.

In the area of **ecotoxicology**, a high acute and long-term risk was identified for birds and wild mammals.

Endocrine-disrupting properties were not discussed in this conclusion being dealt as part of the legally binding requirement established in the renewal of the approval of metalaxyl-M (confirmatory information under Commission Implementing Regulation (EU) 2020/617).

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Background

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

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

Metalaxyl-M is a substance covered by the second stage of the renewal programme (AIR II) in accordance with Regulation (EU) No 1141/2010[2] and was renewed on 01 June 2020 by Commission Implementing Regulation (EU) 2020/617,[3] following a peer review of the risk assessment as set out in the EFSA Conclusion on metalaxyl-M, approved on 19 January 2015 (EFSA, 2015). It was a specific provision of the approval that, when used for seed treatment, only the treatment of seeds intended to be sown in greenhouses may be authorised. In accordance with Article 7 of Regulation (EC) No 1107/2009, Belgium (hereinafter referred to as the rapporteur Member State, 'RMS') subsequently received an application from Syngenta Crop Protection AG on 17 June 2020 for amendment to the conditions of approval of the active substance metalaxyl-M to lift the restriction and allow uses to be authorised as a fungicide for seed treatment where seeds are sown outside in fields. The representative uses applied for were for sunflower and spinach seeds and included an extended use pattern covering lower application rates for spinach seed treatment than those had been assessed previously (EFSA, 2015).

The RMS provided its initial evaluation of the dossier on metalaxyl-M in the form of a revised renewal assessment report (RAR), which was received by EFSA on 09 March 2021 (Belgium, 2021). The peer review was initiated on 08 April 2021 by dispatching the revised RAR to Member States and the applicant, Syngenta Crop Protection AG, for consultation and comments. EFSA also provided comments. In addition, EFSA conducted a public consultation on the revised RAR. The comments received were collated by EFSA and forwarded to the RMS for compilation and evaluation in the format of a reporting table. The applicant was invited to respond to the comments in column 3 of the reporting table. The comments and the applicant response were evaluated by the RMS in column 3.

The need for expert consultation and the necessity for additional information to be submitted by the applicant in accordance with Article 12(3) of the Regulation were considered in a telephone conference between EFSA and the RMS on 09 November 2021. On the basis of the comments received, the applicant's response to the comments and the RMS's evaluation thereof, it was concluded that additional information should be requested from the applicant and that EFSA should conduct an expert consultation in the areas of environmental fate and behaviour and ecotoxicology.

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

The conclusions arising from the consideration by EFSA, and as appropriate by the RMS, of the points identified in the evaluation table, together with the outcome of the expert consultation and the

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

[2] Commission Regulation (EU) No 1141/2010 of 7 December 2010 laying down the procedure for the renewal of the inclusion of a second group of active substances in Annex I to Council Directive 91/414/EEC and establishing the list of those substances. OJ L 322, 8.12.2011, pp. 10–19.

[3] Commission Implementing Regulation (EU) No 2020/617 of 5 May 2020 renewing the approval of the active substance metalaxyl-M, and restricting the use of seeds treated with plant protection products containing it, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market, and amending the Annex to Commission Implementing Regulation (EU) No 540/2011. OJ L 143, 6.5.2020, pp. 6–10.

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

In accordance with Article 12 of the Regulation, EFSA should adopt a conclusion on whether metalaxyl-M can be expected to meet the approval criteria provided for in Article 4 of the Regulation, taking into consideration recital (10) of the Regulation and in particular to amend the conditions of approval as a fungicide for seed treatment and allow uses to be authorised in fields. The representative uses applied for were for sunflower and spinach seeds treatment and included an extended use pattern covering lower application rates for spinach seed treatment than those had been assessed previously (EFSA, 2015).

A final consultation on the conclusions arising from the peer review of the risk assessment took place with Member States via a written procedure in July–August 2023.

This conclusion report summarises the outcome of the peer review of the risk assessment on the active substance and the formulation for representative uses evaluated on the basis of the representative uses of metalaxyl-M as a fungicide on sunflower and spinach (seed treatment) as proposed by the applicant. In accordance with Article 12(2) of Regulation (EC) No 1107/2009, risk mitigation options identified in the revised RAR and considered during the peer review, if any, are presented in the conclusion.

A list of the relevant end points for the active substance and the formulation is provided in Appendix B. In addition, the considerations as regards the cut-off criteria for metalaxyl-M according to Annex II of Regulation (EC) No 1107/2009 are summarised in Appendix A.

A key supporting document to this conclusion is the peer review report (EFSA, 2023), which is a compilation of the documentation developed to evaluate and address all issues raised in the peer review, from the initial commenting phase to the conclusion. The peer review report comprises the following documents, in which all views expressed during the course of the peer review, including minority views, where applicable, can be found:

the comments received on the RAR;
the reporting table (09 November 2021);
the evaluation table (15 September 2023);
the report(s) of the scientific consultation with Member State experts (where relevant);
the comments received on the assessment of the additional information (where relevant);
the comments received on the draft EFSA conclusion.

Given the importance of the RAR, including its revisions (Belgium, 2023), and the peer review report, both documents are considered as background documents to this conclusion and thus are made publicly available.

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

The active substance and the formulation(s) for representative uses

Metalaxyl-M is the ISO common name for methyl *N*-(2,6-dimethylphenyl)-*N*-(methoxyacetyl)-D-alaninate (IUPAC). Metalaxyl-M is a single enantiomer (R enantiomer) of the racemic mixture metalaxyl.

The formulated product for the representative uses for this evaluation was 'Apron XL' an emulsion for seed treatment (ES) containing 339 g/l metalaxyl-M.

The representative uses for this evaluation are fungicide seed treatments of spinach and sunflower seeds to be sown outside in fields as requested for the amendment to the approval conditions. Full details of the GAP (good agricultural practice) can be found in the list of end points in Appendix B.

The formulation 'Ridomil Gold MZ 68WG/Fubol Gold' water dispersible granules (WG) containing 38.8 g/kg metalaxyl-M and 640 g/kg mancozeb[4] included for the renewal of approval of the active substance (EFSA, 2015) which had representative uses of foliar spray applications to tomatoes and grapes was not part of the current evaluation.

[4] The active substance mancozeb is now not approved with the Commission Implementing Regulation (EU) 2020/2087 of 14 December 2020 concerning the non-renewal of the approval of the active substance mancozeb, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market, and amending the Annex to Commission Implementing Regulation (EU) No 540/2011.

Data were submitted to conclude that the uses of metalaxyl-M according to the representative uses proposed at EU level as seed treatments result in a sufficient fungicidal efficacy against the target diseases following the relevant guidance document (European Commission, 2014).

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 (2000, 2012).

Data submitted for the amendment of approval conditions do not change the minimum purity of 920 g/kg; the specification levels of the relevant impurities CGA72649 (2,6-dimethyl-phenylamine, 0.5 g/kg) and CGA363736 (4-methoxy-5-methyl-5H-[1,2]oxathiole 2,2-dioxide, 1 g/kg); and the specification levels of the significant impurities as proposed in the assessment previously conducted (EFSA, 2015). The toxicological relevance of an impurity, considered as relevant previously (EFSA, 2015), was not concluded in the current assessment (see Section 2); however, an updated specified level of < 10 g/kg was proposed for this impurity based on the current toxicological assessment (see Section 2). As a consequence, it is recommended to update the reference specification of the renewal of approval. The batches used in the toxicological and ecotoxicological assessments support the proposed updated specification.

The data submitted for amendment of approval conditions do not change the previous conclusions (EFSA, 2015) relevant to the physical and chemical properties; the analytical methods used for the generation of renewal pre-approval data; and the methods for post-approval control and monitoring purposes. Adequate methods were available for the generation of pre-approval data required for the amendment of approval conditions.

2. Mammalian toxicity

The following guidance documents were followed in the production of this conclusion: European Commission (2012).

In the occasion of the amendment to the conditions of approval, an updated search of the scientific peer-reviewed open literature was conducted and included in the RAR (Belgium, 2021, 2023); however, the results did not indicate new information that could have an impact on the toxicological assessment previously conducted (EFSA, 2015).

During the renewal assessment, three impurities (including CGA72649 and CGA363736) were considered toxicologically relevant. As previously agreed, the maximum acceptable levels in the reference specification for CGA72649 and CGA363736 are 0.5 and 1 g/kg respectively. Based on the new data provided, the third impurity can finally be concluded as unlikely to be genotoxic; however, the limited assessment provided for the other toxicological endpoints (e.g. developmental toxicity and neurotoxicity) does not allow a full conclusion on its toxicological relevance. On this basis, a maximum level below 10 g/kg in the reference specification can be considered of no toxicological concern.

The groundwater metabolite NOA409045 is also concluded as unlikely to be genotoxic based on the available data including a new *in vivo* micronucleus assay. Since NOA409045 (formed from metalaxyl-M) is the R-isomer of CGA62826 (racemate), it is assumed that, as the parent molecules (metalaxyl and metalaxyl-M), the metabolites are toxicologically equivalent. Based on the 28-day rat study with CGA62826, the derived ADI also applicable to NOA409045 is 0.5 mg/kg body weight (bw) per day, applying to the no observed adverse effect level (NOAEL) of 1,000 mg/kg bw per day an increased uncertainty factor (UF) of 2,000 (using a standard UF of 100, an additional UF of 10 due to the limited data package and an additional UF of 2 to cover the possibility that the R-isomer would be of higher toxicity than the racemate).

For the representative uses of the product APRON XL EC (A9642C) supported with the application for amendment to the conditions of approval, the decreased application rates on spinach seed (i.e. 50 and 100 mL product/100 kg seed) are covered by the one supported for the renewal (200 mL product/100 kg spinach seed). Consequently, the conclusions of the peer review for the renewal process can be retained (EFSA, 2015).

3. Residues

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

In the occasion of the amendment of approval conditions only an update from the open literature was conducted and included in the RAR (Belgium, 2021, 2023); however, the new information has no impact on the consumer risk assessment via dietary intake conducted previously.

Since no new studies were submitted for metalaxyl-M under current procedure in the residue section, the assessment of representative uses in sunflower and spinach conducted under the peer review process for which no data gaps were identified and the consumer dietary risk assessment was finalised, is still valid (see EFSA, 2015).

Following the submission of new data in environmental fate (see Section 4), an update of the consumer risk assessment via consuming drinking water was conducted for the groundwater metabolite NOA409045 (see Table 2, Section 7) resulting in an exposure below 0.1% of the ADI. However, the consumer risk assessment from the consumption of drinking water is not finalised considering the lack of appropriate information to address the effect of water treatment processes on the nature of residues, potentially present in surface water and groundwater, when surface water or groundwater is abstracted for drinking water (see Sections 4 and 9.1).

4. Environmental fate and behaviour

Metalaxyl-M was discussed at the Pesticides Peer Review Experts' Meeting Teleconference (TC) 90 in 20 September 2022.[5]

In soil laboratory incubations under aerobic conditions in the dark, metalaxyl-M exhibited low to medium persistence, forming the major (>10% applied radioactivity (AR)) metabolite NOA409045 (max. 72% AR) which exhibited low to high persistence. The metabolites CGA67868 (max. 6% AR) and SYN546520 (max. 4% AR, still increasing at study end) were assessed as needing consideration for groundwater exposure, they exhibited low persistence and moderate to high persistence, respectively. Mineralisation of the phenyl ring ^{14}C radiolabel to carbon dioxide accounted for 2–33% AR after 84–86 days. The formation of unextractable residues (not extracted by acetone/water, methanol/water or acetonitrile/water) for this radiolabel accounted for 14–73% AR after 84–86 days. In anaerobic soil incubations, metalaxyl-M degraded more slowly than under aerobic conditions with the route of degradation being the same as in the aerobic investigations. Data indicated that in soil, epimerisation of metalaxyl-M, NOA409045 or SYN546520 to their racemates was not observed. Metalaxyl-M exhibited very high to low mobility in soil. NOA409045 exhibited very high to high soil mobility with CGA67868 and SYN546520 exhibiting very high soil mobility. It was concluded that the adsorption of these compounds was not pH dependent. In satisfactory European field dissipation studies carried out at 10 sites (spray application to the soil surface on bare soil plots in late spring), metalaxyl-M and NOA409045 both exhibited low to moderate persistence.

Lysimeter studies where racemic metalaxyl was dosed have been evaluated in the DAR and included in the list of reliable endpoints. It should be noted that the experimental designs did not reflect the representative uses being assessed in this conclusion, so the annual average leachate concentrations indicated in the list of endpoints are not directly relevant for the representative uses.

In laboratory incubations in dark aerobic natural sediment water systems, the racemic metalaxyl dosed exhibited moderate persistence, forming the major metabolite CGA62826 (code given to the racemate of NOA409045, max. 69% AR in water at 112 days, exhibiting very high persistence). This metabolite also accounted for up to 23% AR of the extractable residue in sediment. The unextractable sediment fraction (not extracted by acetone/water followed by methanol water) was a limited sink for the phenyl ring ^{14}C radiolabel, accounting for 10–14% AR at study end (240 days). Mineralisation of this radiolabel accounted for 4–8% AR at the end of the study. The peer review accepted the applicant's case that based on the behaviour in soil where metalaxyl-M was dosed and it was confirmed by chiral analyses that epimerisation had not occurred, it would be expected that only NOA409045 would be formed in natural sediment water systems when exposed to metalaxyl-M. The peer review also accepted that, based on the soil evidence, the transformation rate of metalaxyl-M in

[5] Metalaxyl-M was also discussed at the Pesticides Peer Review Meeting in September 2014 (EFSA, 2014) in the course of the peer review for renewal (EFSA, 2014, 2015). For completeness, Section 4 from EFSA (2015) has been updated in the current text in line with the new information provided in the updated RAR (Belgium, 2023) aiming to remove restriction to greenhouses for seed treatment uses.

natural sediment water systems might be expected to be faster than that had been estimated in the available experiments in these systems dosed with racemic metalaxyl. The necessary surface water and sediment exposure assessments (predicted environmental concentrations (PEC) calculations) were carried out for metalaxyl-M and the metabolite NOA409045, using the FOCUS (FOCUS, 2001) step 1 and step 2 approach (version 3.2 of the Steps 1–2 in FOCUS calculator).

The necessary groundwater exposure assessments were appropriately carried out using FOCUS (European Commission, 2014) scenarios and the models PEARL 5.5.5, PELMO 6.6.4 (and MACRO 5.5.4 for spinach uses)[6] for the active substance metalaxyl-M and its metabolites NOA409045, CGA67868 and SYN546520. The FOCUS crop cabbage was used for the simulations for the spinach uses. Which of the available kinetic formation fractions for SYN546520 from NOA409045 to use in the groundwater modelling were discussed in the teleconference 90. The value the experts agreed for use with the data that were available to them was 0.013, being the arithmetic mean kinetic formation fraction from reliable incubations in three different soils. The potential for groundwater exposure from the representative uses by metalaxyl-M above the parametric drinking water limit of 0.1 μg/L was concluded to be low in geoclimatic situations that are represented by all eight pertinent FOCUS groundwater scenarios. This was also the case for both pertinent FOCUS groundwater scenarios (Piacenza and Sevilla) for the representative use on sunflower for the three metabolites NOA409045, CGA67868 and SYN546520. For the uses on spinach NOA409045, SYN546520 and CGA67868, 80th percentile annual average concentrations moving below 1 m depth were predicted to be above the parametric drinking water limit of 0.1 μg/L in all 7, 6/7 and 1/7 of the pertinent FOCUS groundwater scenarios, respectively, for the seed loading rate of 200 mL/100 kg seed. This was reduced to 6/7, 2/7 and none of the pertinent FOCUS groundwater scenarios, respectively, for the seed loading rate of 100 mL/100 kg seed and 6/7, none and none, respectively, for the loading rate of 50 mL/100 kg seed. These three metabolites were assessed as being non relevant (see Sections 2 and 7).

The applicant did not provide appropriate information to address the effect of water treatments processes on the nature of the residues that might be present in surface water and groundwater, when surface water or groundwater is abstracted for drinking water. This has led to the identification of a data gap and results in the consumer risk assessment not being finalised (see Section 9.1).

The PEC in soil, surface water, sediment and groundwater covering the representative uses assessed can be found in Appendix B of this conclusion. A key to the wording used to describe the persistence and mobility of the compounds assessed can be found in Appendix C of this conclusion.

5. Ecotoxicology

In the remit of the amendment of approval conditions, an update of the risk assessment for birds and mammals was submitted following EFSA (2009). Metalaxyl-M was discussed at the Pesticides Peer Review Experts' Meeting TC 91 in September 2022.

Sufficient data were available to perform a risk assessment for birds and wild mammals.

The risk assessment for **birds** was conducted using the reproductive endpoint agreed at the meeting.[7]

For the representative seed treatment use in sunflower and for the use in spinach at 81.4 g a.s./ha (67.8 g a.s./100 kg seeds; hereafter 'high rate'), a high acute and reproductive risk to small granivorous birds consuming seeds and a high reproductive, but not acute, risk to small omnivorous birds consuming seedlings were identified at Tier I.

For the representative seed treatment use in spinach at 40.7 g a.s./ha (33.92 g a.s./100 kg seeds; hereafter 'medium rate'), a low acute risk to birds consuming seeds and seedlings and a high reproductive risk to small granivorous and omnivorous birds consuming seeds and seedlings were identified at Tier I.

For the representative seed treatment use in spinach at 20.4 g a.s./ha (16.96 g a.s./100 kg seeds; hereafter 'low rate'), a low acute risk to birds consuming seeds and seedlings and a high reproductive risk to small birds consuming seeds (but not seedlings) were identified at Tier I.

At the meeting,[8] the (i) higher tier acute and reproductive risk assessment for birds consuming sunflower seeds and seedlings; (ii) the higher tier acute (high rate) and reproductive risk assessment for birds consuming spinach seeds (low, medium and high rate) and (iii) the reproductive risk

[6] Simulations complied with EFSA, 2004 and correctly utilised the agreed Q10 of 2.58 (following EFSA, 2008) and Walker equation coefficient of 0.7.
[7] Refer to experts' consultation 5.1 in the Report of Pesticides Peer Review Experts' Meeting TC 91 (EFSA, 2023).
[8] Refer to experts' consultation 5.2 in the Report of Pesticides Peer Review Experts' Meeting TC 91 (EFSA, 2023).

assessment for birds consuming seedlings (medium and high rate) were discussed in relation to the acceptability of the following refinements in risk assessment:

- Ecological data, such as specific focal species studies, studies quantifying the proportion of food items in their diet (PD) or the refined proportion of food obtained in the treated area (i.e. PT).[9]
- The energy and moisture content of crop seeds.
- Residue and metabolism data in seeds and seed shoots.
- The weight of evidence (WoE), including (i) the number of treated seeds required to reach toxicity; (ii) the foraging area required to reach toxicity; (iii) the de-husking and avoidance of seeds/

Overall, the higher tier risk assessment was deemed insufficient to address (i) the acute and long-term risk for birds consuming sunflower seeds and (ii) the long-term risk assessment for birds consuming sunflower seedlings (data gap, see Section 9).[10] Additionally, the higher tier risk assessment was deemed insufficient to address the acute (high rate) and long-term (all rates) risk identified at Tier I for birds consuming spinach seeds[11] and the long-term risk assessment for birds consuming spinach seedlings (medium and high rate).[10]

The risk assessment for wild **mammals** is summarised hereafter:

For the representative seed treatment use in sunflower, a high acute and long-term risk was identified for small mammals consuming seeds and seedlings at Tier I. Additionally, for the representative seed treatment uses in spinach (all rates), a high acute and long-term risk was identified for small mammals consuming seeds, but not seedlings at Tier I.

At the meeting,[12] the higher tier acute and reproductive risk assessment for mammals consuming sunflower seeds and seedlings and the higher tier acute and reproductive risk assessment for mammals consuming spinach seeds were discussed in relation to the acceptability of the following refinements in risk assessment:

- Ecological data, such as specific focal species studies, PD and PT studies.
- The energy and moisture content of crop seeds.
- Residue and metabolism data in seeds and seed shoots.
- The weight of evidence (WoE), including (i) the number of treated seeds required to reach toxicity; (ii) the foraging area required to reach toxicity; (iii) the de-husking and avoidance of seeds.

Overall, the higher tier risk assessment was deemed insufficient to address the acute and long-term risk for mammals consuming sunflower seeds and seedlings and the acute[13] and long-term risk for mammals consuming spinach seeds for sowing techniques other than precision drilling.[14]

The risk for birds and mammals from exposure to plant metabolites was not quantified, under the assumption that it would be covered by the risk assessment conducted for the parent compound.

An updated literature search was submitted, including relevant ecotoxicity studies in fish, which were discussed at the meeting.[15] However, such information was not considered to impact the hazard assessment previously conducted by EFSA (2015).

6. Endocrine disruption properties

Endocrine-disrupting (ED) properties according to the ECHA/EFSA Guidance (2018) were not assessed in this application to amend the approval conditions. It was agreed by risk managers that this was out of the scope of the evaluation since according to Commission Regulation (EU) 2020/617 the ED assessment should be dealt as part of the confirmatory information process.

[9] A formal data gap for the submission of a final report of the PT study used for the refined reproductive risk assessment for greenfinch, linnet and crested lark consuming spinach seeds in SEU was identified (see Section 10).
[10] The refined risk assessment did not cover for the small(er) granivorous species in CEU.
[11] The RMS concluded that a subset of the scenarios would indicate low acute and long-term risk when precision drilling techniques are used. However, such assessment would still not cover for smaller granivorous species in CEU.
[12] Refer to experts' consultation 5.3 in the Report of Pesticides Peer Review Meeting TC 91 (EFSA, 2023).
[13] However, the RMS noted that based on the weight of evidence and the qualitative consideration of the PD value for the Algerian mouse in SEU, the acute risk from consumption of spinach seeds in this zone might be lower than quantified in situations where the formulation for representative uses is applied at the low rate and when sowing is carried out using precision drilling. Additionally, the RMS noted that high acute risk for mammals consuming spinach seeds (medium and high rate) was still identified when precision drilling techniques are used.
[14] The Northern Zone (NEU) of the EU was not covered by the higher tier risk assessment for birds and mammals.
[15] Refer to experts' consultation 5.4 in the Report of Pesticides Peer Review Experts'Meeting TC 91 (EFSA, 2023).

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)	Ecotoxicology
metalaxyl-M	Low risk to soil-dwelling organisms (EFSA, 2015)
NOA409045	Low risk to soil-dwelling organisms (EFSA, 2015)

Table 2: Groundwater[(a)]

Compound (name and/or code)	> 0.1 μg/L at 1 m depth for the representative uses[(b)] Step 2	Biological (pesticidal) activity/ relevance Step 3a.	Hazard identified Steps 3b. and 3c.	Consumer RA triggered Steps 4 and 5	Human health relevance
metalaxyl-M	No	Yes	–	–	Yes
NOA409045	No for sunflower Yes for spinach all 7 scenarios for loading rate of 200 mL/100 kg seed at up to 3.28 μg/L Yes 6/7 scenarios for loading rate of 100 mL and 50 mL/ 100 kg seed at up to 1.55 and 0.732 μg/L respectively.	No	No Rat oral LD50 > 2000 mg/kg bw 28-day rat oral NOAEL 1000 mg/kg bw per day Negative Ames test, gene mutation *in vitro* and micronucleus *in vivo*; positive clastogenicity *in vitro*; unlikely to be genotoxic ADI 0.5 mg/kg bw per day	Yes Consumer intake < 0.1% of the ADI	No for the representative use(s) assessed
CGA67868	No for sunflower Yes for spinach at 1/7 scenarios for loading rate of 200 mL/100 kg seed at 0.119 μg/L No for loading rate of 100 mL and 50 mL/100 kg seed.	No	No (up to stage 3 of step 3) Negative Ames test, gene mutation and chromosome aberration *in vitro* assays	No	No for the representative uses assessed
SYN546520	No for sunflower Yes for spinach at 6/7 scenarios for loading rate of 200 mL/100 kg seed at up to 0.304 μg/L Yes for 2/7 scenarios for loading rate of 100 mL/100 kg seed at up to 0.155 μg/L No for loading rate of 50 mL/ 100 kg seed	No	No Rat oral and dermal LD50 > 2000 mg/kg bw 28-day oral rat NOAEL 200 mg/kg bw per day Negative Ames test, gene mutation and chromosome aberration in vitro assays Reference values of the parent may apply to this metabolite	No	No for the representative uses assessed

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

Table 3: Surface water and sediment

Compound (name and/or code)	Ecotoxicology
metalaxyl-M	Low risk to aquatic organisms (EFSA, 2015)
NOA409045	Low risk to aquatic organisms (EFSA, 2015)

Table 4: Air

Compound (name and/or code)	Toxicology
metalaxyl-M	Rat LC50 by inhalation > 2.29 mg/L air/4 h (nose-only), no classification required

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

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

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

Particular conditions are not proposed considering the scope of this evaluation. However, the RMM already identified in the approval conclusion (EFSA, 2015) are still applicable (Table 5).

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

Representative use	Spinach (100 mL/ha)	Spinach (50 mL/ha)	Sunflower
	Seed treatment + sowing	Seed treatment + sowing	Seed treatment + sowing
Operator risk	Use of PPE is required[(a)]	Use of PPE is required[(a)]	

(a): Based on surrogate exposure study: gloves and respiratory protective equipment for operators during mixing/loading, treatment and cleaning.

9. Concerns and related data gaps

9.1. Issues that could not be finalised

An issue is listed as 'could not be finalised' if there is not enough information available to perform an assessment, even at the lowest tier level, for one or more of the representative uses in line with the uniform principles in accordance with Article 29(6) of Regulation (EC) No 1107/2009 and as set out in Commission Regulation (EU) No 546/2011[16] 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.

[16] 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, pp. 127–175.

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

1) The consumer risk assessment is not finalised with regard to the unknown nature of residues that might be present in drinking water, consequent to water treatment following abstraction of groundwater or surface water when it might contain the active substance (predicted to be for surface water only) and its metabolites (both surface and groundwater) (see Sections 3 and 4).

   a) Satisfactory information regarding the effect of water treatment processes on the nature of residues present in surface water and groundwater, when surface water or groundwater is abstracted for drinking water was not available. Probably in the first instance, a consideration of the processes of ozonation and chlorination would appear appropriate. If an argumentation is made that concentrations at the point of abstraction for drinking water purposes will be low, this argumentation should cover metabolites predicted to be in groundwater and surface water, as well as the active substance. Should this consideration indicate that novel compounds might be expected to be formed from water treatment, the risk to human or animal health through the consumption of drinking water containing them should be addressed (relevant to comply with the conditions of approval, not dependent of any specific use, see Section 4).

9.2. Critical areas of concern

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

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

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

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

2) High acute and long-term risk was identified for birds and mammals for all representative uses (see Section 5).

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

(If a particular condition proposed to be taken into account to manage an identified risk, as listed in Section 8, has been evaluated as being effective, then 'risk identified' is not indicated in Table 6).

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

Representative use		Sunflower field	Spinach field 200 mL/ 100 kg seed	Spinach field 100 mL/ 100 kg seed	Spinach field 50 mL/100 kg seed
		Seed treatment	Seed treatment	Seed treatment	Seed treatment
Operator risk	Risk identified	X(b)			
	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	X1	X1	X1	X1
Risk to wild non-target terrestrial vertebrates	Risk identified	X2	X2	X2	X2
	Assessment not finalised				
Risk to wild non-target terrestrial organisms other than vertebrates	Risk identified				
	Assessment not finalised				
Risk to aquatic organisms	Risk identified				
	Assessment not finalised				
Groundwater exposure to active substance	Legal parametric value breached				
	Assessment not finalised				
Groundwater exposure to metabolites	Legal parametric value breached				
	Parametric value of 10 µg/L(a) breached				
	Assessment not finalised				

The superscript numbers relate to the numbered points indicated in Sections 9.1–9.3. Where there is no superscript number, see Sections 2–7 for further information.
(a): Value for non-relevant metabolites prescribed in SANCO/221/2000-rev. 10 final, European Commission, 2003.
[2]High risk for birds and wild mammals.
(b): based on Seed Tropex model (EFSA, 2015)

10. List of other outstanding issues

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

These data gaps refer only to the representative uses assessed and are listed in the order of the sections. Data gaps from EFSA (2015) that were not addressed in this conclusion have been also listed for completeness:

- Spectra for the relevant impurity CGA363736 (relevant for all representative uses evaluated; see Section 1).

- Methods of analysis for the relevant impurities CGA72649 and CGA363736 in both formulations (relevant for all representative uses evaluated; see Section 1).
- A final study report was not available for the study used to calculate the proportion of food obtained in the treated area (i.e. PT) for greenfinch, linnet and crested lark in SEU in the higher tier long-term risk assessment for birds consuming spinach seeds (relevant for all representative use on spinach; see Section 5).

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Abbreviations

a.s.	active substance
AR	applied radioactivity
bw	body weight
DAR	draft assessment report
DM	dry matter
DT_{50}	period required for 50% dissipation (define method of estimation)
DT_{90}	period required for 90% dissipation (define method of estimation)
dw	dry weight
FAO	Food and Agriculture Organization of the United Nations
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
GAP	Good Agricultural Practice
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
iv	intravenous
JMPR	Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
LC_{50}	lethal concentration, median
MRL	maximum residue level
MS	mass spectrometry
NOAEL	no observed adverse effect level
Pa	pascal
PD	proportion of different food types
PEC	predicted environmental concentration
PEC_{soil}	predicted environmental concentration in soil
pK_a	negative logarithm (to the base 10) of the dissociation constant
P_{ow}	partition coefficient between *n*-octanol and water
PPE	personal protective equipment
PT	proportion of diet obtained in the treated area
RAC	regulatory acceptable concentration
RAR	Renewal Assessment Report
SFO	single first-order
SMILES	simplified molecular-input line-entry system
WG	water-dispersible granule
WHO	World Health Organization

Appendix A – Consideration of cut-off criteria for metalaxyl-M according to Annex II of Regulation (EC) No 1107/2009 of the European Parliament and of the Council

Properties		Conclusion[(a)]
CMR	Carcinogenicity (C)	Metalaxyl-M is not considered to be a carcinogen according to point 3.6.3 of Annex II of Regulation (EC) No 1107/2009.
	Mutagenicity (M)	Metalaxyl-M is not considered to be a mutagen according to point 3.6.2 of Annex II of Regulation (EC) No 1107/2009.
	Toxic for reproduction (R)	Metalaxyl-M is not considered to be a reproductive toxicant according to point 3.6.4 of Annex II of Regulation (EC) No 1107/2009.
Endocrine-disrupting properties		The endocrine disruption properties of metalaxyl-M according to points 3.6.5 and 3.8.2 of Annex II of Regulation No 1107/2009, as amended by Commission Regulation (EU) 2018/605 were not discussed in this conclusion.
POP	**Persistence**	Metalaxyl-M is not considered to be a persistent organic pollutant (POP) according to point 3.7.1 of Annex II of Regulation (EC) 1107/2009.
	Bioaccumulation	
	Long-range transport	
PBT	**Persistence**	Metalaxyl-M not considered to be a persistent, bioaccumulative and toxic (PBT) substance according to point 3.7.2 of Annex II of Regulation (EC) 1107/2009.
	Bioaccumulation	
	Toxicity	
vPvB	**Persistence**	Metalaxyl-M not considered to be a very persistent, very bioaccumulative substance according to point 3.7.3 of Annex II of Regulation (EC) 1107/2009.
	Bioaccumulation	

(a): Origin of data to be included where applicable (e.g. EFSA, ECHA RAC, Regulation).

Appendix B – List of end points for the active substance and the formulation for representative uses relevant for the amendment of approval conditions

Appendix B can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2023.8373.

Appendix C – Wording EFSA used in Section 4 of this conclusion, in relation to DT and Koc 'classes' exhibited by each compound assessed[17]

Wording	DT_{50} normalised to 20°C for laboratory incubations
Very low persistence	< 1 day
Low persistence	1 to < 10 days
Moderate persistence	10 to < 60 days
Medium persistence	60 to < 100 days
High persistence	100 days to < 1 year
Very high persistence	A year or more

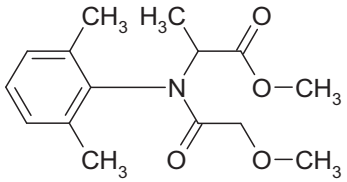
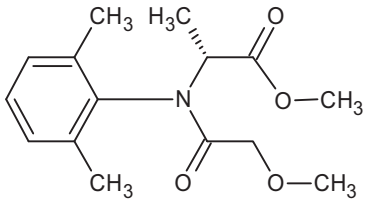
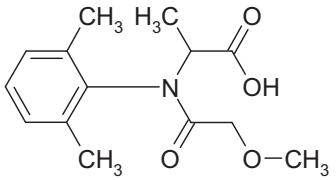
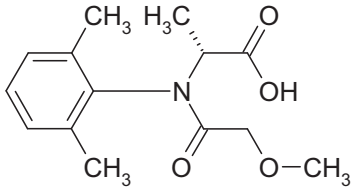
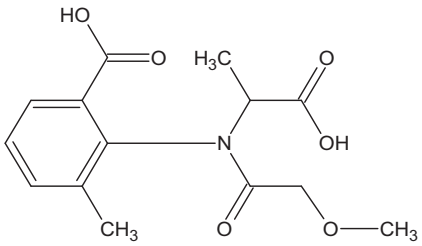
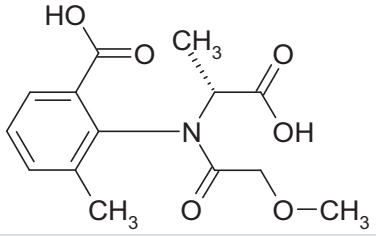
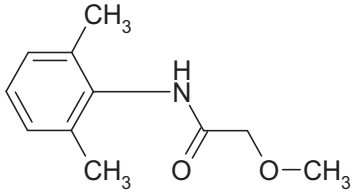
Note these classes and descriptions are unrelated to any persistence class associated with the active substance cut-off criteria in Annex II of Regulation (EC) No 1107/2009. For consideration made in relation to Annex II, see Appendix A.

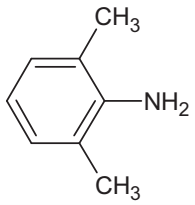
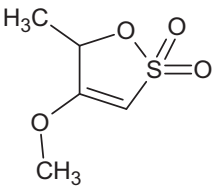
Wording	K_{oc} (either K_{Foc} or K_{doc}) mL/g
Very high mobility	0–50
High mobility	51–150
Medium mobility	151–500
Low mobility	501–2000
Slight mobility	2001–5000
Immobile	>5000

Based on McCall et al. (1980).

[17] For laboratory soil incubations, normalisation was also to field capacity soil moisture (pF2/10 kPa). For laboratory sediment water system incubations, the whole system DT values were used.

Appendix D – Used compound codes

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
Metalaxyl CGA48988	methyl N-(2,6-dimethylphenyl)-N-(methoxyacetyl)-DL-alaninate CC(N(C(=O)COC)c1c(C)cccc1C)C(=O)OC ZQEIXNIJLIKNTD-UHFFFAOYSA-N	
Metalaxyl-M CGA329351	methyl N-(2,6-dimethylphenyl)-N-(methoxyacetyl)-D-alaninate C[C@@H](N(C(=O)COC)c1c(C)cccc1C)C(=O)OC ZQEIXNIJLIKNTD-GFCCVEGCSA-N	
CGA62826	(RS)-2-[(2,6-Dimethyl-phenyl)-(2-methoxy-acetyl)-amino]-propionic acid CC(N(C(=O)COC)c1c(C)cccc1C)C(=O)O ZRIKZVLHMGYCIR-UHFFFAOYSA-N	
NOA409045	(R)-2-[(2,6-Dimethyl-phenyl)-(2-methoxy-acetyl)-amino]-propionic acid C[C@@H](N(C(=O)COC)c1c(C)cccc1C)C(=O)O ZRIKZVLHMGYCIR-LLVKDONJSA-N	
CGA108906	2-[((RS)-1-Carboxy-ethyl)-(2-methoxy-acetyl)-amino]-3-methyl-benzoic acid CC(N(C(=O)COC)c1c(C)cccc1C(=O)O)C(=O)O WFTHOCDLKYPFJX-UHFFFAOYSA-N	
SYN546520	2-[((R)-1-Carboxy-ethyl)-(2-methoxy-acetyl)-amino]-3-methyl-benzoic acid C[C@@H](N(C(=O)COC)c1c(C)cccc1C(=O)O)C(=O)O WFTHOCDLKYPFJX-SECBINFHSA-N	
CGA67868	N-(2,6-Dimethyl-phenyl)-2-methoxy-acetamide O=C(Nc1c(C)cccc1C)COC OXXYGGDIKKXTFB-UHFFFAOYSA-N	

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
CGA72649	2,6-dimethyl-phenylamine Cc1cccc(C)c1N UFFBMTHBGFGIHF-UHFFFAOYSA-N	
CGA363736	4-methoxy-5-methyl-5H-[1,2]oxathiole 2,2-dioxide CC1OS(=O)(=O)C=C1OC IJLLPHSCBOYYAG-UHFFFAOYSA-N	

(a): The metabolite name in bold is the name used in the conclusion.
(b): ACD/Name 2021.1.3 ACD/Labs 2021.1.3 (File Version N15E41, Build 123232, 07 July 2021).
(c): ACD/ChemSketch 2021.1.3 ACD/Labs 2021.1.3 (File Version C25H41, Build 123835, 29 August 2021).