Approved: 12 December 2024

DOI: 10.2903/j.efsa.2025.9193

CONCLUSION ON PESTICIDES PEER REVIEW

efsa JOURNAL

Updated peer review of the pesticide risk assessment of the active substance spinosad

European Food Safety Authority (EFSA) | Fernando Álvarez | Maria Arena | Domenica Auteri | Sofia Batista Leite | Marco Binaglia | Anna Federica Castoldi | Arianna Chiusolo | Angelo Colagiorgi | Mathilde Colas | Federica Crivellente | Chloe De Lentdecker | Isabella De Magistris | Mark Egsmose | Gabriella Fait | Franco Ferilli | Monica Fittipaldi Broussarad | German Giner Santonja | Varvara Gouliarmou | Katrin Halling | Alessio Ippolito | Frederique Istace | Samira Jarrah | Dimitra Kardassi | Aude Kienzler | Anna Lanzoni | Roberto Lava | Renata Leuschner | Alberto Linguadoca | Jochem Louisse | Christopher Lythgo | Oriol Magrans | Iris Mangas | Andrea Mioč | Ileana Miron | Tunde Molnar | Laura Padovani | Vincenzo Padricello | Martina Panzarea | Juan Manuel Parra Morte | Alexandra Piti | Simone Rizzuto | Agnès Rortais | Miguel Santos | Rositsa Serafimova | Rachel Sharp | Csaba Szentes | Andrea Terron | Anne Theobald | Manuela Tiramani | Giorgia Vianello | Laura Villamar-Bouza

Correspondence:
pesticides.peerrevieew@efsa.europa.eu

The declarations of interest of all scientific experts active in EFSA's work are available at https://open.efsa.europa.eu/experts

Abstract

The conclusions of the European Food Safety Authority (EFSA) following the peer review of the initial risk assessments carried out by the competent authorities of the rapporteur Member State, the Netherlands, and co-rapporteur Member State, France, for the pesticide active substance spinosad and the assessment of applications for maximum residue levels (MRLs) 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 spinosad as insecticide on bulb/dry onions, maize (fodder and grain), sweet corn, grapes (table and wine), lettuce, potato, aubergine, pepper and tomato. MRLs were assessed in field leek and field and greenhouse strawberries, cane fruits, lettuce & plants salad (others), spinach and similar leaves (others), herbs and edible flowers (others), cardoons, rhubarb and animal commodities. The conclusions from 2018 were updated in 2024 following the request from the European Commission with regard to the endocrine-disrupting properties. The reliable end points, appropriate for use in regulatory risk assessment and the proposed MRLs, are presented. Missing information identified as being required by the regulatory framework is listed. Concerns are reported where identified.

KEYWORDS

insecticide, peer review, pesticide, risk assessment, Spinosad

CONTENTS

SUMMARY

Commission Implementing Regulation (EU) No 844/2012 (hereinafter referred to as 'the Regulation') lays down the procedure for the renewal of the approval of active substances submitted under Article 14 of Regulation (EC) No 1107/2009. The list of those substances is established in Commission Implementing Regulation (EU) No 686/2012. Spinosad 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), the Netherlands, and co-rapporteur Member State (co-RMS), France, received an application from Dow AgroSciences Ltd. for the renewal of approval of the active substance spinosad. In addition, Dow AgroSciences Ltd. submitted applications for maximum residue levels (MRLs), as referred to in Article 7 of Regulation (EC) No 396/2005. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicant, the co-RMS (France), the European Commission and the European Food Safety Authority (EFSA) about the admissibility.

The RMS provided its initial evaluation of the dossier on spinosad in the renewal assessment report (RAR), which was received by EFSA on 30 March 2017. The RAR included a proposal to set MRLs, submitted under Article 7 of Regulation (EC) No 396/2005. In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicant, Dow AgroSciences Ltd., for comments on 26 April 2017. EFSA also provided comments. In addition, EFSA conducted a public consultation on the RAR. EFSA collated and forwarded all comments received to the European Commission on 7 July 2017.

Following consideration of the comments received on the RAR, it was concluded that additional information should be requested from the applicant, and that EFSA should conduct an expert consultation in the areas of mammalian toxicology, residues, environmental fate and behaviour and ecotoxicology.

In accordance with Article 13(1) of the Regulation, EFSA should adopt a conclusion on whether spinosad 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 and give a reasoned opinion concerning MRL applications as referred to in Article 10(1) of Regulation (EC) No 396/2005.

EFSA published its conclusion on the peer review of the pesticide risk assessment of spinosad on 3 May 2018 (EFSA, 2018a). On 14 January 2019, the European Commission sent a mandate to EFSA with a request to review the endocrine-disrupting properties of spinosad. The conclusions laid down in this report were reached on the basis of the evaluation of the representative uses of spinosad as insecticide on bulb/dry onions, maize (fodder and grain), sweet corn, grapes (table and wine), lettuce, potato, aubergine, pepper and tomato. MRLs were assessed in field leek and field and greenhouse strawberries, cane fruits, lettuce & plants salad (others), spinach and similar leaves (others), herbs and edible flowers (others), cardoons, rhubarb and animal commodities. Full details of the representative uses and the proposed MRLs can be found in Appendix A of this report.

Data were submitted to conclude that the representative uses of spinosad proposed at EU level result in a sufficient insecticidal efficacy against the target organisms.

A data gap was identified for a search of the scientific peer-reviewed open literature on the active substance and its relevant metabolites.

In the area of identity, physical and chemical properties, data gaps were identified for additional data to identify the impurities expected to exceed 1 g/kg in the technical material and for determination of the octanol/water partition coefficient of all components of the residue definition for risk assessment.

Data gaps were identified in the mammalian toxicology area for the identification and validation of analytical methods for the dietary material used in key toxicological studies, for an in vitro interspecies comparative metabolism study and for a developmental neurotoxicity study. These issues could not be finalised (analytical methods for the dietary material used in key toxicological studies, in vitro interspecies comparative metabolism study and a developmental neurotoxicity study). Data gaps were also identified to address the genotoxicity and general toxicity of metabolites potentially relevant to consumer exposure.

Several data gaps were identified in the residue section related to the representative uses including the magnitude of residues in pollen and bee products, analysed according to the proposed risk assessment residue definition. An indicative consumer risk assessment was conducted based on available residue data and an acute intake concern was identified for the lettuce indoor use. This consumer risk assessment should be regarded as provisional pending upon the final decision on the risk assessment residue definition for plants and the comprehensive livestock assessment.

As regards the MRL application, MRLs were proposed only in cases where the data were considered sufficient to support the intended GAP and no indicative consumer intake concern was identified. For the authorised uses assessed under the Article 12 MRL review and considering only the exposure to spinosyn A and D, an acute intake concern for several crops is flagged.

The data available on environmental fate and behaviour are sufficient to carry out the required environmental exposure assessments at EU level, with the exception that a data gap was identified for information on the effect of water treatment processes on the nature of residues of both the active substance and its identified metabolites potentially present in surface water, when surface water is abstracted for drinking water. This gap leads to the consumer risk assessment from the consumption of drinking water being not finalised for all the representative uses.

In the area of ecotoxicology, data gaps were identified for further information to address the risk to birds and mammals, aquatic organisms, honeybees (issues that could not be finalised) and non-target arthropods.

According to the available evidence and assessment both for humans and non-target organisms, spinosad does not meet the criteria for **endocrine disruption** according to point 3.6.5 and 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605, for oestrogen, androgen, thyroid and steroidogenesis (EATS)-modalities.

BACKGROUND

Commission Implementing Regulation (EU) No 844/2012[1] (hereinafter referred to as 'the Regulation') lays down the provisions for the procedure of the renewal of the approval of active substances, submitted under Article 14 of Regulation (EC) No 1107/2009.[2] This regulates for the European Food Safety Authority (EFSA) the procedure for organising the consultation of Member States, the applicant(s) and the public on the initial evaluation provided by the rapporteur Member State (RMS) and/or co-rapporteur Member State (co-RMS) in the renewal assessment report (RAR), and the organisation of an expert consultation where appropriate.

In accordance with Article 13 of the Regulation, unless formally informed by the European Commission that a conclusion is not necessary, EFSA is required to adopt a conclusion on whether the active substance can be expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009 within 5 months from the end of the period provided for the submission of written comments, subject to an extension of an additional 3 months where additional information is required to be submitted by the applicant(s) in accordance with Article 13(3).

In accordance with Article 1 of the Regulation, the RMS, the Netherlands, and co-RMS, France, received an application from Dow AgroSciences Ltd. for the renewal of approval of the active substance spinosad. In addition, Dow AgroSciences Ltd. submitted applications for maximum residue levels (MRLs) as referred to in Article 7 of Regulation (EC) No 396/2005.[3] Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicant, the co-RMS (France), the European Commission and EFSA about the admissibility.

The RMS provided its initial evaluation of the dossier on spinosad in the RAR, which was received by EFSA on 30 March 2017 (Netherland, 2017). The RAR included a proposal to set MRLs, submitted under Article 7 of Regulation (EC) No 396/2005.

In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicant, Dow AgroSciences Ltd., for consultation and comments on 26 April 2017. EFSA also provided comments. In addition, EFSA conducted a public consultation on the RAR. EFSA collated and forwarded all comments received to the European Commission on 7 July 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 were considered in a telephone conference between EFSA, the RMS on 24 August 2017. On the basis of the comments received, the applicant's response to the comments and the RMS's evaluation thereof, it was concluded that additional information should be requested from the applicant, and that EFSA should conduct an expert consultation in the areas of mammalian toxicology, residues, 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 written consultation on the assessment of additional information, where these took place, were reported in the final column of the evaluation table.

A final consultation on the conclusions arising from the peer review of the risk assessment and on the proposed MRLs took place with Member States via a written procedure in February–March 2018, leading to the finalisation of the EFSA Conclusion (EFSA, 2018a).

Commission Regulation (EU) 2018/605[4] introduced new scientific criteria for the determination of endocrine-disrupting (ED) properties, applicable as of 10 November 2018 to all applications for the approval/renewal of active substances, including pending applications. The peer review on the active substance spinosad was already completed at the time of entry into force of the new criteria, and an assessment of the ED potential in line with the EFSA/ECHA (2018) guidance document[5] for this substance was not available.

Since on the basis of the EFSA Conclusion published on 3 May 2018, it was not possible for risk managers to conclude whether or not the active spinosad is an endocrine disruptor, on 14 January 2019, the European Commission requested EFSA to re-assess the information and update its Conclusion on the ED potential of the substance in accordance with the

[1]Commission Implementing Regulation (EU) No 844/2012 of 18 September 2012 setting out the provisions necessary for the implementation of the renewal procedure for active substances, as provided for in Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market. OJ L 252, 19.9.2012, p. 26–32.

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

[3]Regulation (EC) No 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC. OJ L 70, 16.3.2005, p. 1–16.

[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.

[5]ECHA and EFSA (European Chemicals Agency and European Food Safety Authority) with the technical support of the Joint Research Centre (JRC), Andersson, N., Arena, M., Auteri, D., Barmaz, S., Grignard, E., Kienzler, A., Lepper, P., Lostia, A. M., Munn, S., Parra Morte, J. M., Pellizzato, F., Tarazona, J., Terron, A., & Van der Linden, S. (2018). Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009. EFSA Journal, 16(6), 5311. https://doi.org/10.2903/j.efsa.2018.5311. ECHA-18-G-01-EN.

new criteria. For this purpose, EFSA has performed an assessment of the ED properties of the active substance spinosad in line with the EFSA/ECHA (2018) guidance for further consideration in the peer review.

In the context of this process, following a consultation with Member States in the Pesticide Peer Review Meeting PREV 10 Mammalian toxicology – Ecotoxicology joint session (July 2019), spinosad was not considered to meet the criteria for endocrine disruption for humans for the thyroid (T) modality according to point 3.6.5 of Annex II of Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) No 2018/605. However, additional testing was required to complete the current data package about the EAS-mediated adverse effects in relation to human health and to further investigate the ED properties of the substance for non-target organisms. Therefore, as permitted in the mandate, the applicant was given the opportunity on 9 August 2019, to submit, within a period of 30 months, additional information to address the approval criteria set out in point 3.6.5 and point 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) No 2018/605, and/or documentary evidence demonstrating that spinosad may be used such that exposure is negligible, and/or the conditions for application of the derogation under Art.4(7) of Regulation (EC) No 1107/2009 are met.

The additional information submitted by the applicant on 9 February 2022 was subsequently evaluated by the RMS, the Netherlands. EFSA received the revised RAR from the RMS with the RMS evaluation of the endocrine properties assessment, on 27 June 2023 (The Netherlands, 2023). Subsequently, a public consultation on the revised RAR was conducted in August–October 2023. All comments received, including those from the applicant, EFSA and Member States, were collated in the format of a reporting table and were considered during the finalisation of the peer review. As a result of the consultation, in light of the comments received, a consultation with Member States in the Pesticide Peer Review teleconference (TC) 136 Mammalian toxicity and Ecotoxicology joint session was conducted in May 2024.

As a consequence, the RMS, the Netherlands, provided an updated RAR, in line with the outcome of the experts' discussion (The Netherlands, 2024).

A final consultation on the updated conclusions arising from the peer review following the mandate from the European Commission took place with Member States via a written procedure in October–November 2024.

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 spinosad as insecticide on bulb/dry onions, maize (fodder and grain), sweet corn, grapes (table and wine), lettuce, potato, aubergine, pepper and tomato. MRLs were assessed in field leek and field and greenhouse strawberries, cane fruits, lettuce & plants salad (others), spinach and similar leaves (others), herbs and edible flowers (others), cardoons, rhubarb and animal commodities. In addition, the conclusions were updated with regard to the endocrine-disrupting properties following the mandate received from the European Commission on 14 January 2019. A list of the relevant end points for the active substance and the formulation and the proposed MRLs is provided in Appendix A.

In addition, a key supporting document to this updated conclusion is the peer review report (EFSA, 2018b, updated 2024), 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 tables (24 August 2017 and 8 January 2024[6]);
- the evaluation tables (20 March 2018, updated October 2024);
- 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 EFSA ED assessment[7];
- the comments received on the draft EFSA conclusion and the updated conclusion.

Given the importance of the RAR, including its revisions (Netherlands, 2018, 2023, 2024), and the Peer Review Report (EFSA, 2018b, updated 2024) and the EFSA ED assessment (EFSA, 2019), 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 EU for which the applicant has not demonstrated that it has regulatory access to the information on which this conclusion report is based.

THE ACTIVE SUBSTANCE AND THE FORMULATED PRODUCT

Spinosad is the ISO common name for a mixture of 50%–95% (2*R*,3a*S*,5a*R*,5b*S*,9*S*,13*S*,14*R*,16a*S*,16b*R*)-2-(6-deoxy-2,3,4-tri-*O*-methyl-α-L-mannopyranosyloxy)-13-(4-dimethylamino-2,3,4,6-tetradeoxy-β-D-erythropyranosyloxy)-9-ethyl-2,3,3a,5

[6]Reporting table following consultation on the revised RAR on the assessment of the endocrine-disrupting properties made available after the 30-month clock stop.

[7]ED assessment performed by EFSA before the timepoint of the ED additional information request (stop of the clock). The ED assessment including evaluation of the newly provided additional information on the endocrine disruption properties following the ED clock stop is available in the revised RAR (The Netherlands, 2024) with the final outcome presented in the current EFSA Conclusion (see Section 6).

a,5b,6,7,9,10,11,12,13,14,15,16a,16b-hexadecahydro-14-methyl-1*H*-as-indaceno[3,2-*d*]oxacyclododecine-7,15-dione (spinosyn A) and 50%–5% (2*S*,3a*R*,5a*S*,5b*S*,9*S*,13*S*,14*R*,16a*S*,16b*S*)-2-(6-deoxy-2,3,4-tri-*O*-methyl-α-L-mannopyranosyloxy)-13-(4-dimethylamino-2,3,4,6-tetradeoxy-β-D-erythropyranosyloxy)-9-ethyl-2,3,3a,5a,5b,6,7,9,10,11,12,13,14,15,16a,16b-hexadecahydro-4,14-dimethyl-1*H*-as-indaceno[3,2-*d*]oxacyclododecine-7,15-dione (spinosyn D) (IUPAC).

The representative formulated product for the evaluation was 'GF-976', a suspension concentrate (SC) containing 480 g/L of spinosad. A Food and Agriculture Organization (FAO) specification exists for the SC formulations based on the technical material from Dow AgroSciences Ltd. (636/SC, January 2006).

The representative uses evaluated comprise field applications by spraying to control a variety of pests in bulb onions, maize (fodder and grain) and sweet corn, grapes (table and wine), lettuce, potato, aubergine, pepper and tomato, and spray applications in greenhouse on lettuce, aubergine and tomato, in the EU. Full details of the GAPs can be found in the list of end points in Appendix A.

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

A complete overview of the relevant studies identified in the search for peer review open literature on the active substance and its relevant metabolites, dealing with side effects on health and non-target species and published within the 10 years before the date of submission of the dossier, should be conducted and reported in accordance with EFSA guidance on the submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (EFSA, 2011).

CONCLUSIONS OF THE EVALUATION

1 | IDENTITY, PHYSICAL/CHEMICAL/TECHNICAL PROPERTIES AND METHODS OF ANALYSIS

The following guidance documents were followed in the production of this conclusion: SANCO/3029/99-rev. 4 (European Commission, 2000a), SANCO/3030/99-rev. 4 (European Commission, 2000b), SANCO/10597/2003-rev. 10.1 (European Commission, 2012) and SANCO/825/00-rev. 8.1 (European Commission, 2010).

Spinosad is produced by a fermentation process using a strain of *Saccharopolyspora spinosa*. After the fermentation process is completed, spinosad is recovered from the fermentation broth by solvent extraction.

The proposed specification for spinosad is based on batch data from industrial scale production. The minimum purity of the active substance as manufactured is 850 g/kg, with 50%–95% of spinosyn A and 5%–50% of spinosyn D. Based on the manufacturing data, a higher minimum purity could have been proposed. It is proposed to update the reference specification because of the identification of new compounds due to the use of more modern analytical techniques. A data gap was identified for additional data to identify the impurities expected to exceed 1 g/kg in the technical material. An FAO specification exists for the TC based on the technical material from Dow AgroSciences with a minimum purity of 850 g/kg spinosad (636/TC, January 2006).

The assessment of the data package revealed no issues that need to be included as critical areas of concern with respect to the identity, physical and chemical properties of the active substance or technical properties of the respective formulation. A data gap was identified for the determination of the octanol/water partition coefficient of all components of the residue definition for risk assessment. The main data regarding the identity of spinosad and its physical and chemical properties are given in Appendix A.

Analytical methods are available for the determination of spinosyn A and spinosyn D in the technical material and in the representative formulation. It should be noted that CIPAC methods also exist for the determination of spinosyn A and spinosyn D in the TC and SC formulations. Data gaps were identified for validation data of the analytical methods used in certain key toxicological studies (see Section 2).

The residue definition for monitoring in all matrices was defined as spinosad, sum of spinosyn A and spinosyn D.

Spinosad residues can be monitored in food and feed of plant origin by the QuEChERS (quick, easy, cheap, effective and safe method) multi-residue method using LC–MS/MS with a limit of quantification (LOQ) of 0.005 mg/kg for both spinosyn A and D in all plant commodity groups. Determination of the compounds of the residue definition for monitoring in animal matrices can be done by the QuEChERS multi-residue method using LC–MS/MS with an LOQ of 0.005 mg/kg for both spinosyn A and D in milk, egg, meat, fat and liver. Appropriate LC–MS/MS methods exist for monitoring spinosyn A and spinosyn D in the environmental matrices with LOQs for each individual compound of 0.005 mg/kg in soil, 0.01 µg/L in water and 0.36 µg/m^3 in the air, respectively. It should be noted that an LC–MS/MS method exists also for the determination of spinosyn B and *N*-demethyl spinosyn D in soil with a LOQ of 0.005 mg/kg for each compound.

An appropriate LC–MS/MS method exists for monitoring spinosyn A and spinosyn D in blood and urine with a LOQ of 0.025 mg/L for each compound.

2 | MAMMALIAN TOXICITY

The following guidance documents were followed in the production of this conclusion: SANCO/221/2000-rev. 10-final (European Commission, 2003), SANCO/10597/2003-rev. 10.1 (European Commission, 2012), Guidance on dermal absorption (EFSA PPR Panel, 2012) and Guidance on the application of the CLP Criteria (ECHA, 2017).

Spinosad was discussed during the Pesticides Peer Review Experts' Meetings 170 in December 2017, 10 in July 2019 and TC 136 in May 2024.

The newly proposed technical specification that include additional impurities with regard to the current specification is supported by the batches used in toxicity studies according to a Tier II assessment (toxicological assessment), including QSAR analysis for several components. No relevant impurities have been identified. Validated analytical methods have been provided for the analysis of dietary preparations used in short-term dog studies, key studies to derive the acceptable operator exposure level (AOEL). However, analytical methods for the dietary material used in long-term toxicity and carcinogenicity studies, reproductive and developmental toxicity studies (key studies for setting the acceptable daily intake (ADI), acute reference dose (ARfD) and acute acceptable operator exposure level (AAOEL)) have not been identified; it is therefore unknown whether they were appropriate or validated (data gap and issue that could not be finalised).

Spinosad absorption is limited; 40% oral absorption was determined based on bile analysis and this value was used for the setting of non-dietary reference values. The substance is widely distributed and metabolised and rapidly excreted, mostly via faeces. A number of metabolites may be recovered in blood and urine as N- and O-demethylated spinosyns and/or glutathion conjugates; the residue definition is, therefore, established as sum of spinosyn A and spinosyn D. An in vitro interspecies comparative metabolism study was not originally provided, and a data gap was identified leading to an issue not finalised. Data on in vitro comparative metabolism were subsequently submitted and evaluated as part of the evidence for the mode of action analysis for the ED assessment.[8] It has to be noted that since the submitted studies were not conducted according to the EFSA opinion on testing and interpretation of comparative in vitro metabolism studies (EFSA PPR Panel, 2021) and were not intended to fill the previously identified data gap on comparative in vitro metabolism, the data gap and issue not finalised are maintained.

Low acute toxicity was observed when spinosad was administered by the oral, dermal or inhalation routes, no skin or eye irritation, skin sensitisation or phototoxic potential were attributed to the active substance. Comparative short-term toxicity between spinosad, spinosyn A and spinosyn D resulted in similar toxicity overall, but somehow with fewer and less severe effects for spinosyn D. Spinosad induce cytoplasmic vacuolation of epithelial cells or macrophages in various organs and tissues in the majority of animal studies (in rats, mice and dogs). Many cationic amphiphilic substances are reported to cause this condition in animals and humans that may be attributed to a lysosomal storage disorder characterised by an excessive accumulation of phospholipids in tissue (phospholipidosis). Aggregates of reticuloendothelial (RE) cells were seen in several tissues, and haematological alterations and signs of regenerative and non-regenerative anaemia were also observed, particularly in dogs. The relevant short-term no-observed adverse effect level (NOAEL) is 4.89 mg/kg body weight (bw) per day overall from the 90-day and 1-year toxicity studies in dogs and the relevant long term NOAEL is 2.4 mg/kg bw per day from the 2-year study in rats. The active substance is unlikely to be genotoxic. Increased incidences of ovarian adenomas in mice were considered unrelated to spinosad exposure by the majority of the experts, while a minority, including the RMS and co-RMS expressed the opinion that classification regarding carcinogenicity may be required based on these findings. The majority of experts in the peer review meeting agreed that no classification is required regarding carcinogenicity and the NOAEL for carcinogenicity was set at the highest dose level of 41.5 mg/kg bw per day tested in mice. Reduced male and female fertility index and dystocia were observed in a two-generation reproductive toxicity study in rats and there was a consensus in the peer review experts' meeting that Spinosad may be proposed for classification as Repr. 2, H361f 'suspected of damaging fertility'. It is unknown to EFSA whether the studies considered by the peer review were available to the experts assessing spinosad classification with regard to the human health entry in Annex VI of Reg. 1272/2008.[9] With regard to developmental toxicity, delayed ossification was observed at maternal toxic doses in rats and no classification was proposed by consensus, additionally in rabbits, no developmental toxic effects were observed. In a repeated dose (1-year) neurotoxicity study in rats, degeneration of trigeminal ganglion was observed at the low-observed adverse effect level (LOAEL) of 46 mg/kg bw per day. Considering this effect in conjugation with vacuolation observed in multiple organs and haematological changes at doses relevant for classification lead to the proposal by the peer review for classification of spinosad as STOT-RE 2, H373 'may cause damage to organs through prolonged or repeated exposure'. In addition, considering the neurotoxic pesticidal mode of action of the chemical and the reported signs of neurotoxicity in rats, the experts agreed that a developmental neurotoxicity (DNT) study is needed and a data gap and issue not finalised was set for the submission a DNT study. Potential immunotoxic effects (decrease in the IgM response) were observed at doses exhibiting general toxicity (haematological changes and increased liver weights).

QSAR analysis was conducted on a number of spinosad metabolites (spinosyn K, J, H, J of D, O, N-formyl spinosyn B, N-demethyl spinosyn L and N-demethyl spinosyn D and O) showing that they are unlikely to be genotoxic or clastogenic. Pending on the magnitude of residue levels from field trials and animal commodities (see Section 3), additional toxicological data relevant to consumer exposure (repeated-dose toxicity studies) may be needed on metabolites spinosyn B and K

[8]Refer to experts' consultation 2.7 in the Report of the Pesticides Peer Review TC 136 (EFSA, 2018b, updated 2024).

[9]Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. OJ L 353, 31.12.2008, p. 1–1355.

(data gap). Genotoxicity data are required for the metabolite MET A-Li-4(5b) pending on the identification of its chemical structure; and pending on the outcome of its assessment in the residue section, further toxicological data may be needed (data gap). In addition, toxicological data (repeated-dose toxicological studies) are needed on the metabolite pseudoaglycone of spinosyn A, including clarification of its genotoxicity potential (see Section 3 – data gap). The **ADI** of spinosad is 0.024 mg/kg bw per day based on the 2-year rat NOAEL of 2.4 mg/kg bw per day for haematological and clinico-chemical changes, thyroid and kidney vacuolation, accumulation of RE cells and degeneration of the heart and muscle fibres, applying an uncertainty factor (UF) of 100. It is noted that the margin of safety to the reproductive toxicity NOAEL is around 400 and to the neurotoxicity LOAEL is around 2000. The **AOEL** is 0.02 mg/kg bw per day, based on the overall 90-day and 1-year dog studies NOAEL of 4.89 mg/kg bw per day for reduced body weight, anaemia, clinico-chemical changes and vacuolation of several organs, corrected for limited oral absorption of 40% and UF of 100. The **ARfD** is 0.1 mg/kg bw based on the maternal NOAEL of 10 mg/kg bw per day for early maternal body weight changes in the developmental toxicity study in rabbits, UF of 100. The reference values (except ADI) have been changed compared to the first inclusion peer review (European Commission, 2006). The details are in the List of Endpoints (Appendix A). The **AAOEL** is 0.04 mg/kg bw, on the same basis as the ARfD corrected for limited oral absorption of 40% and UF of 100.

Non-dietary exposure risk assessment was performed for the representative formulation GF-976 SC, a suspension concentrate formulation containing 480 g spinosad/L. According to the German model, estimated operator exposure does not exceed the AOEL even when no personal protective equipment (PPE) is worn for vehicle-mounted applications in low and high crops and for hand-held applications in high crops. For hand-held applications in low crops, gloves and coverall have to be worn by operators to ensure that the AOEL is not exceeded (according to the UK POEM). Operator exposure in greenhouses does not exceed the AOEL even when no PPE is worn according to the southern greenhouse model (Southern European Greenhouse model, 2010). Worker, bystander and resident's exposure are estimated to remain below the AOEL, also when no PPE is considered for workers.

3 | RESIDUES

The assessment in the residue section is based on the OECD guidance document on overview of the residue chemistry studies (OECD, 2009), the OECD publication on the MRL calculations (OECD, 2011), the European Commission guideline document on the MRL setting (European Commission, 2017) and the Joint Meeting on Pesticide Residues (JMPR) recommendations on livestock burden calculations (JMPR, 2004, 2007).

Spinosad was discussed at the Pesticides Peer Review Experts' Meeting 171 in December 2017.

Several primary crops' metabolism studies were conducted separately with ^{14}C-spinosyn A and ^{14}C-spinosyn D upon foliar spray application in fruits (apple, tomatoes and grapes), pulses/oilseeds (cotton), leafy (cabbage) and root crops (turnip). For the present renewal process, new metabolism studies in tomato following foliar application and cabbage following soil drench application were submitted.

From the studies conducted with spinosyn A, spinosyn A was the main compound of the total residues in almost all crops (12%–87% TRR) except in tomato and cabbage (new studies) where it was recovered at a level < 10% TRR. Metabolites spinosyn B/K (not separated) were recovered in grape bunches and apple peel up to 11% TRR, and separately spinosyn B (10%–20% TRR) and spinosyn K (10% TRR) in cabbage. Moreover, pseudoaglycone of spinosyn A (PsA) metabolite was formed in cabbage leaves (16%–64% TRR) and in turnip root/leaves (up to 31% TRR).

In the studies conducted with spinosyn D, the spinosyn D was also the main compound in all investigated crops, from 48% TRR in cabbage up to 85% TRR in apples. Metabolite *N*-demethyl spinosyn D occurred at significant levels in cabbage leaves (up to 19% of TRR) and in turnip leaves and roots up to 16% TRR, while in grape bunches, it was recovered together with *O*-demethyl spinosyn D metabolite up to 24% TRR.

It is noted that a different metabolic pattern was observed between the old and new metabolism studies, and throughout all studies, a low rate of characterisation of radioactivity was noted. Therefore, additional data on the analytical attempts to further characterise/identify the unknown radioactive residues from the metabolism studies on plants are required (data gap). In addition, further toxicological data (see Section 2) are necessary for PsA metabolite.

The photolysis degradation of the residues was investigated in apples and grape spiked with spinosyn A and D and a faster degradation of apples and grapes TRRs under sunlight conditions was observed compared to the dark conditions. Thus, the unprotected uses exposed to the sunlight may be considered less critical in view of magnitude of residues.

Considering the overall information, the risk assessment residue definition in plants is provisionally proposed as: sum of spinosyn A, D, B, K, pending the outcome of residue levels for each representative crop from field trials analysed for the relevant compounds included in the risk assessment residue definition and their toxicological relevance (see Section 2). For monitoring, the residue definition in plants is proposed as sum of spinosyn A and D.

A confined rotational study was conducted only with spinosyn A in leafy (lettuce), root (radish) and cereals (wheat) covering three PBIs. Although from the spinosyn A study on wheat a significant decrease of residue levels from the second PBI (0.302 mg/kg) to the third PBI (0.009 mg/kg) is noted, the investigation of spinosyn D is still required (data gap).

As regards the stability of residues during sample storage, it was demonstrated that spinosyn A, D, B and K are stable for 23 months in apples, 18 months in peppers, grapes and strawberries and for 12 months in tomatoes and cotton. For potatoes, the available study is not sufficient since only spinosyn A and D were analysed and reported together while, for cereal grains, no data were provided (data gap). Although no storage stability data on bulb onions and leafy vegetable are

available (data gap), based on the available data in other high water content commodities by weight of evidence a degradation of residues is not expected in these commodities. Yet, a broader extrapolation of the storage stability to all crops from group was not possible.

The nature of residues under processing was investigated with spynosin A and D, and the residues are stable under pasteurisation/boiling and baking while under sterilisation, pseudoaglycone of spinosyn A and D (PsA/PsD) is formed up 14% of AR.

Livestock metabolism studies were provided in poultry and goats with ^{14}C spinosyn A and spinosyn D at a dosing level of 10 mg/kg DM. Although some deficiencies were noted (only 3 days of study duration; no plateau level was reached for eggs and milk), the studies were considered valid.

For poultry, spinosyn A and D were the predominant compounds in fat (81% TRR), muscle (55% TRR) and eggs (34% TRR). In addition, spinosyn B was recovered up to 12% TRR in liver, muscle and eggs while N-demethyl spinosyn D accounted in muscle for up to 15% TRR, in liver up to 21% and eggs 25% TRR.

In ruminants, spinosyn A and spinosyn D were the major compounds in all matrices (up to 86% TRR and 85% TRR, respectively). Other metabolites such as spinosyn B, MET A-Li-4(5b) for the spinosyn A labelling and N-demethyl spinosyn D and MET D-Li-3b for spinosyn D labelling were also recovered at or above 10% TRRs level. Since (MET A-Li-4(5b)) was found in relevant amount (16%TRRs in liver), further elucidation of the structures of open macrolides is required (data gap). Its toxicological relevance should be considered pending upon the finalisation of the livestock dietary burden estimates.

The animal RA-RD was provisionally proposed as: (1) poultries: sum of spinosyn A, D, B and N-demethyl spinosyn D and (2) ruminants: sum of spinosyn A, D, B, N-demethyl spinosyn D and MET A-Li-4(5b). For monitoring, the residue definition in animals is proposed as sum of spinosyn A and D.

Storage stability studies were provided for poultry matrices with spinosyn A and D. Although deficiencies were noted (decline of residues in muscle beyond 30% after 568 days), the studies were considered acceptable to prove the stability of residues for 18 months in poultry matrices except for spinosyn D residues in eggs which was considered stable only for 9 months. It should be noted, however, that the proposed risk assessment residue definition includes additional compounds; therefore, additional storage stability studies covering all the compounds have to be provided (data gap). For ruminants, storage stability data were not provided and the RMS used data from the metabolism studies following extraction efficiency tests to demonstrate the stability of residues. Based on those studies, spinosyn A and D were demonstrated to have acceptable stability for up to 18 months in all matrices while for spinosyn B and N-demethyl spinosyn D, the data were not considered acceptable. Therefore, clarification on the sample preparation (including extraction and analysis) is needed (data gap) to decide on the validity of the stability tests with spinosyn B and N-demethyl spinosyn D. Pending this clarification, additional storage stability in ruminant commodities might be required.

Fish bioconcentration studies with spinosyn A and D (see Section 5 of Appendix A) with identification of several metabolites were provided. The acceptability of a flow-through study to address dietary exposure scenarios for fish and the dietary burden assessment approach are pending further agreement. For the time being, a data gap for fish metabolism studies is identified (data gap).

With regard to the determination of the residues in pollen and bee products for human consumption resulting from residues taken up by honeybees from crops at blossom, the provided study (see Section 5) does not address the data requirement appropriately and did not analyse according to the risk assessment residue definition (data gap).

3.1 | Representative use residues

As it regards the representative uses on bulb onions, sweet corn, grapes, lettuce, tomatoes, aubergines and peppers, sufficient residue trials were submitted. Additional data to demonstrate the stability of the residues in high water content commodities still have to be submitted. In maize (including maize fodder), the number of residue trials was not considered sufficient for maize in SEU; therefore, additional residue trials are required (data gap). For potatoes, the provided trials from outside Europe to complement the number of residue trials are acceptable if it can be demonstrated that the climatic zone and agricultural conditions are comparable with NEU (including sunlight exposure and agronomic practice); otherwise, a sufficient number of trials on potatoes from NEU should be provided (data gap). Although some trials were partially or completely analysed according to the risk assessment residue definition (see Appendix A), additional field trials covering all the representative uses and analysed for all relevant compounds are still needed (data gap).

Sufficient processing trials to derive valid processing factors for tomatoes (canned, paste) and pomace (dry/wet) are required (data gap).

Triggered by dietary intakes, feeding studies in poultries and ruminants conducted with four feeding levels of spinosyn A and D were submitted. However, additional data on the residue level in animal commodities analysed for all relevant compounds for risk assessment are required (data gap). A consumer risk assessment and MRL proposals for animal commodities could not be completed since the assessment in livestock can currently not be finalised but should be revisited pending the outcome on final risk assessment residue definition for plant and animals.

An indicative consumer risk assessment was conducted for the representative uses on onions, grapes, lettuce, aubergines, peppers and tomatoes considering the residue levels from field trials analysed according to the risk assessment residue definition (see Appendix A) by using EFSA PRIMo rev.2. The chronic intake was below the ADI, max TMDI 15.1% (WHO Cluster diet B) while the acute intake (IESTI) exceeds the ARfD for lettuce (219%, indoor use) while lettuce (outdoor)

accounted for 58% ARfD. For the remaining crops, the max IESTI accounted for 24% ARfD and 22% of ARfD for table grapes and peppers, respectively. An updated consumer risk assessment was conducted also by using EFSA PRIMo 3.1. The chronic intake, max TMDI was 11% of the ADI (ES adult), while for the acute intake, the max IESTI was 309% of ARfD (lettuce, indoor use) and 82% of ARfD (lettuce, outdoor use). It is highlighted that the consumer risk assessment should be regarded as provisional considering all the data gaps identified, and the limited number of the field trials analysed according to the proposed risk assessment residue definition.

3.2 | Maximum residue levels

MRLs were assessed in strawberries, cane fruits, lettuce and plants salad (others), spinach and similar leaves (others), herbs and edible flowers, cardoons, leek, rhubarbs and several animal commodities. An MRL was proposed only for those uses that were fully supported by the residue trials compliant with the GAP, covered by sufficient storage stability data and validated analytical methods, and where an indicative consumer risk was not identified (see Appendix A). An additional dietary burden calculation is not triggered for the crops assessed under the MRL application.

An indicative consumer risk assessment using the same approach as for the representative uses (see Section 3.1) was conducted for all the intended uses supported by sufficient data and the EU representative uses whenever more critical. The chronic (TMDI) and acute dietary intakes (IESTI) were below the ADI and ARfD for all considered European consumer groups (max ADI 15.3% WHO Cluster diet B, and max 58% ARfD lettuce, DE adult). An updated consumer risk assessment was conducted also by using EFSA PRIMo 3.1. The chronic intake, max TMDI was 11% of the ADI (ES adult), while for the acute intake, the max IESTI account for 97% of ARfD for lettuce outdoor use.

It is highlighted that, in the framework of the peer review of spinosad compared with the Article 12 MRL review, the derivation of an ARfD was considered necessary (see Section 2), and that the proposed residue definitions for risk assessment for plant and animal are more complex in view of new residue data. By using PRIMo ver.2, taking into account the derived ARfD (0.1 mg/kg) and the established MRLs under Article 12 of Regulation (EC) No 396/2005, there is a short-term consumer intake concern for scarole, witloof, spinach, lettuce, chards, peppers, while for melons, the IESTI was calculated 97% of ARfD when residues of only spinosyn A and D are considered (EFSA, 2012). Following the peer review process, EFSA performed a focussed review of the existing maximum residue levels for Spinosad under Article 43 of Regulation (EC) No 396/2005, taking into consideration the new toxicological reference value (EFSA, 2021).

Five of the submitted studies for the renewal of spinosad cover data gaps identified during the Art. 12 MRL review (EFSA, 2012): hydrolysis studies in processed commodities, poultry feeding studies, four NEU residue trials on globe artichoke, four indoor residue trials in raspberries and two SEU residue trials in cauliflower.

4 | ENVIRONMENTAL FATE AND BEHAVIOUR

Spinosad was discussed at the Pesticides Peer Review TC 158 in December 2017.

Spinosad is a mixture of two components, spinosyn A and spinosyn D. Exposure assessments were done separately for the two components, using application rates calculated by correcting for the occurrence of each component considering only a ratio of 85:15 in the technical material. Overall, PEC values for spinosad were derived summing PEC values from the individual spinosyn components.

The rates of dissipation and degradation in the environmental matrices investigated were estimated using FOCUS (2006) kinetics guidance. In soil laboratory incubations under aerobic conditions in the dark, spinosyn A exhibited low to moderate persistence, forming the major (> 10% applied radioactivity (AR)) metabolite spinosyn B (max. 67% AR), which exhibited moderate to high persistence. Spinosyn D exhibited moderate to medium persistence, forming the major (> 10% applied radioactivity (AR)) metabolite N-demethyl spinosyn D (max. 68% AR), which exhibited moderate to high persistence. Mineralisation of ^{14}C radiolabel spinosyn A to carbon dioxide accounted for 19.5% AR after 150 days, and mineralisation of ^{14}C radiolabel spinosyn D to carbon dioxide accounted for 16% AR after 152 days. The formation of unextractable residues (not extracted by acetonitrile/water) for this radiolabel accounted for max. 31% AR after 120 days for spinosyn A and for max. 29% AR after 152 days spinosyn D. In anaerobic soil incubations, spinosyn A and D were essentially stable and no additional major metabolites were formed. In a soil photolysis study, metabolite spinosyn B was formed at 21.6% AR and metabolite N-demethyl spinosyn D was formed at 10.8% AR. Photolytic transformation processes on soil surfaces slightly contribute to the dissipation of spinosad from the soil environment. Spinosyn A and D exhibited low mobility to immobility in soil. Metabolite spinosyn B exhibited low mobility to immobility, and metabolite N-demethyl spinosyn D exhibited medium mobility to immobility in soil. It was concluded that the adsorption of spinosyn A and D and its metabolites was not pH dependent. Experts agreed that there was no clear correlation between K_F and organic carbon. Therefore, it was agreed to use the geometric mean K_{Foc} values in FOCUS modelling as a first tier and K_F geometric mean to refine the exposure as a higher tier modelling approach in future evaluations. Field study $DegT_{50}$ values were derived following normalisation to FOCUS reference conditions (20°C and pF2 soil moisture) following the EFSA (2014) $DegT_{50}$ guidance. The field data endpoints were combined with lab values to derive modelling endpoints. Furthermore, exceptionally field study normalised DT_{50} values were accepted for the calculation of PEC soil. In the field studies, spinosyn A exhibited very low to medium persistence and spinosyn D exhibited low to moderate persistence.

In laboratory incubations in dark aerobic natural sediment water systems, spinosyn A and spinosyn D exhibited medium to high persistence, forming the major metabolites spinosyn B (max. 17.3% in sediment and max 7.4% in water) and N-demethyl spinosyn D (max. 14.5% in sediment and max. 6.1% in water), respectively. The unextractable sediment fraction accounted for 8.7%–68.8% AR at study end (150–120 days). In a laboratory sterile aqueous photolysis study, spinosyn A was fast degraded forming the major (> 10% applied radioactivity (AR)) metabolites spinosyn B (max. 5.7% AR) and 13,14β-dihydro-C17-pseudoaglycone-spinosyn A (max. 14.9% AR), also spinosyn D was fast degraded forming the major (> 10% applied radioactivity (AR)) metabolites N-demethyl spinosyn D (max. 12.6% AR) and 13,14β-dihydro-C17-pseudoaglycone-spinosyn D (max. 15.3% AR).

The necessary surface water and sediment exposure assessments (Predicted environmental concentrations (PEC) calculations) were carried out for spinosad and the metabolites spinosyn B, N-demethyl spinosyn D, 13,14β-dihydro-C17-pseudoaglycone-spinosyn A and 13,14β-dihydro-C17-pseudoaglycone-spinosyn D, using the FOCUS (FOCUS, 2001) step 1 and step 2 approach (version 3.2 of the Steps 1–2 in FOCUS calculator). For the active substance spinosad and metabolites spinosyn B and N-demethyl spinosyn D, step 3 (FOCUS, 2001) and step 4 calculations were available and calculated using geometric mean K_P in order to consider the weak correlation between K_F and organic carbon as explained above. The step 4 calculations appropriately followed the FOCUS (FOCUS, 2007) guidance, with no-spray drift buffer zones of up to 20 m being implemented for the drainage scenarios (representing a 57%–91% spray drift reduction), and combined no-spray buffer zones with vegetative buffer strips of up to 20 m (reducing solute flux in run-off by 80% erosion runoff by 95%) being implemented for the run-off scenarios. The SWAN tool (version 4.0.1) was appropriately used to implement these mitigation measures in the simulations. However, risk managers and others may wish to note that while run-off mitigation is included in the step 4 calculations available, the FOCUS (FOCUS, 2007) report acknowledges that for substances with K_{Foc} < 2000 mL/g, the general applicability and effectiveness of run-off mitigation measures had been less clearly demonstrated in the available scientific literature, than for more strongly adsorbed compounds. For the representative protected uses (lettuce and aubergine, pepper and tomato), the necessary surface water and sediment exposure assessments (predicted environmental concentrations (PEC)) for the active substance and the metabolites as discussed above were appropriately carried out using the FOCUS (2001) step 1 and step 2 approach (version 3.2 of the steps 1–2 in FOCUS calculator), which was then modified by post processing the spray drift input results (option no run-off or drainage was selected) to obtain a 0.1% emission of spinosad from greenhouses being re-deposited on adjacent surface water bodies. This approach has been accepted by Member State experts as an assumption that can be used in EU level surface water exposure assessments for greenhouse uses and is referred to in FOCUS (2008) guidance as being appropriate, except when applications are made with ultra low volume application techniques when 0.2% emission is prescribed.

The necessary groundwater exposure assessments were appropriately carried out using FOCUS (FOCUS, 2009) scenarios and the models PEARL 4.4.4, PELMO 5.5.3 and MACRO 5.5.4 for the active substance spinosad (spinosyn A and spinosyn D were modelled separately and then the results were combined) and metabolites spinosyn B and N-demethyl spinosyn D. The potential for groundwater exposure from the representative uses by spinosad above the parametric drinking water limit of 0.1 µg/L was concluded to be low in geoclimatic situations that are represented by all nine FOCUS groundwater scenarios for spinosad and these metabolites. The results of the groundwater exposure assessment for field crops were assumed to cover the uses of protected crops.

The exposure assessment for lettuce was done using an interval between applications of 7 days instead of 14 days, as proposed in section D1 in the dossier. However, the shorter interval used represents a worst case.

The applicant's dossier did not include enough information to address the effect of water treatments processes on the nature of the residues that might be present in surface water, when surface water is abstracted for drinking water. The applicant made the case that oxidation would produce major groups of degradates (mono, di and tetrahydroxylated derivatives of spinosyn and the degradate formed by mono-N-demethylation of the forosamine sugar of spinosad) but did not satisfactorily support / demonstrate their subsequent statement that further oxidation of these degradates would only result in the formation of carbon dioxide, water and NOx. This has been identified in Section 8 as a data gap and as an assessment not finalised (see Section 10.1.5).

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

5 | ECOTOXICOLOGY

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

Some aspects of the risk assessment of spinosad were discussed at the Pesticide Peer Review teleconference 159 in December 2017.

It is noted that the representative uses included uses in greenhouse on fruiting and leafy vegetables. From the available information, the use in non-permanent structures could not be excluded; therefore, for terrestrial organisms, a risk envelope approach was taken and the risk assessment was performed by considering the greenhouse uses as in non-permanent structures. The exposure assessment for aquatic organisms did take into account emission from non-permanent greenhouses for the uses on leafy and fruity vegetables (see Section 4).

Some ecotoxicological tests were performed with the formulation 'NAF-85', this was deemed acceptable since this formulation is considered comparable in terms of toxicity to the representative one (GF-976).

Spinosad is composed of two components (A and D) and toxicity data are not available for the single components. The ratio of the two components in the active substance and in the formulated product is variable. This adds uncertainties in the provided risk assessment (see also Section 4).

It is noted that, for the representative use on lettuce, the risk assessment was performed considering an interval between applications of 7 days. This represents a worst case with respect to the interval proposed in Section D1 in the dossier (14 days), see also Section 4.

A low acute and long-term risk to **birds** to spinosad was concluded for all the representative uses. It is noted that in the available reproductive toxicity study on mallard duck at the lowest tested dose 16% of reduction in eggs laid with respect to the control was observed. An EC_{10} was, therefore, calculated by the RMS and used in the risk assessment; considering the uncertainties in the derived EC_{10}, in line with EFSA (2015), the lower confidence interval of the derived EC_{10} was used by EFSA in the risk assessment. A low acute and long term risk to **wild mammals** was concluded for all the representative uses with the exception of the uses on grape and fruiting and leafy vegetables (field and greenhouse uses) for which a high long-term risk was concluded (data gap). It is noted that, due to the potential neurotoxicity of spinosad, a data gap was identified in Section 2. Pending on this data gap further consideration on the endpoint to be used in the wild mammals risk assessment might be needed. A low risk to birds and mammals via secondary poisoning and via exposure to contaminated water was concluded for spinosad and its pertinent metabolites. A risk assessment for birds and mammals for metabolites formed in plants was not available; this is needed in particular for metabolite spinosyn K (data gap).

A high acute and chronic risk for spinosad to **aquatic organisms** (i.e. aquatic invertebrates including sediment dwellers) was concluded for all the representative field uses at FOCUS Step 3 level with the exception of the use on potatoes where, for aquatic invertebrates, a high chronic risk only was identified. Based on PEC calculated with FOCUS Step 4 level, when mitigation measures are considered, a high chronic risk was still concluded for some scenarios for all the representative field uses (data gap). A low risk to the fish and algae was concluded for all the representative uses.

A low risk to aquatic organism was concluded for metabolites β-13,14-dihydropseudoaglycone metabolite of spinosyn A and β-13,14-dihydropseudoaglycone metabolite of spinosyn D.

For metabolite spinosyn B, a high acute and chronic risk to aquatic invertebrates was identified while a high risk to sediment dwellers could not be excluded based on a screening risk assessment assuming this metabolite as 10 times more toxic than the parent. At Step 4 level a high risk to aquatic organisms was identified for some scenarios only for the uses on grapes (acute risk to aquatic invertebrates), leafy vegetables -field use (acute and chronic risk to aquatic invertebrates) and bulb vegetables (acute and chronic risk to aquatic invertebrates). A low risk was concluded for the remaining scenarios and uses provided that mitigation measures are considered. A high risk to sediment dwellers could not be excluded for part of the scenarios for all uses except grape, bulb vegetables and maize (data gap). A low risk to fish and algae was concluded for all the representative uses.

For metabolite N-demethylated spinosyn D, a high risk to sediment dwellers could not be excluded at FOCUS Step 3 level while a low risk was concluded for all uses and remaining aquatic organisms. At Step 4 level, when mitigation measures are considered, a low risk to sediment dwellers was concluded for all uses except potatoes for which a high risk could not be excluded for part of the FOCUS scenarios (data gap). A low risk to the fish and algae was concluded for all the representative uses.

A low risk for aquatic organisms for spinosad and its pertinent metabolites was concluded for all the representative uses in greenhouse.

In the case of honey**bees**, only acute toxicity data were available. A chronic toxicity study and a study assessing the effects to bee larvae under laboratory conditions were not available. In addition, a study addressing the sub-lethal effects was not available (data gap). An acute risk assessment based on European Commission guidance (2002a) was provided by the RMS which indicated a high risk for all the uses assessed. The available higher tier studies were discussed the Pesticide Peer Review teleconference 159. Shortcomings were identified in the study design of some of them; in addition, the available higher tier studies did not cover the representative uses in terms of number of applications and/or maximum application rate; therefore, the level of exposure in the studies may not cover the exposure expected from the representative uses and residues analysis was available to confirm adequate exposure. It is noted that the experts at the meeting considered as appropriate to identify measures to mitigate the risk to bees for some representative uses; however, on the basis of the available data, risk reductions could not be quantified. The experts considered this could be considered further at Member State level. It is noted that, for the uses on bulb/dried onions and on lettuce, if the uses are not intended for seed production, exposure to bees in the treated crop is considered unlikely, however, exposure in the landscape via different routes could not be excluded. In consideration of the above, data gaps to further address the risk to bees by using EFSA (2013) were identified. The available information was not sufficient to address the risk to bees for metabolites formed in pollen and nectar (data gap). A suitable assessment for accumulative effects was not available.

Considering the available acute toxicity data and higher tier studies on bumblebees further consideration of the risk to bumblebees is considered necessary (data gap).

Data were not available for solitary bees.

At tier 1 level, a high risk to **non-target arthropods** was concluded for all the representative uses. The available extended laboratory studies were not suitable for addressing the risk identified at Tier 1 level. The available semi-field and field studies on non-target arthropods were discussed at the Pesticide Peer Review teleconference 159. The experts agreed

to use in the higher tier risk assessment the available study investigating the effects 'GF-976' on non-target arthropod populations under field conditions after one spray application to maximum 96 g a.s./ha. It was, however, noted that this study did not fully cover the representative uses in terms of number of applications; a low off-field risk was concluded exclusively for the use on maize with single application. Considering all the available information and the potential for recolonisation, a low in-field risk was also concluded for that representative use. A data gap was identified for further information to address the risk to non-target arthropods for all the remaining uses.

A low risk to soil **macroorganisms** (including earthworms) and **microorganisms** for spinosad and its pertinent metabolites and for **non-target terrestrial plants** and to organism involved in the **biological methods of sewage treatment** for spinosad was concluded.

6 | ENDOCRINE DISRUPTION PROPERTIES

Spinosad was discussed at the Pesticides Peer Review Experts' Meeting 10 (Mammalian Toxicology and Ecotoxicology in July 2019) and at the Pesticides Peer Review Experts' TC 136 (Mammalian Toxicology and Ecotoxicology in May 2024).

With regard to the assessment of the endocrine disruption (ED) potential of spinosad for **humans** according to the ECHA/EFSA guidance (ECHA/EFSA, 2018), in determining whether spinosad interacts with the oestrogen, androgen and steroidogenesis (EAS) and thyroid (T)-mediated pathways, the number and type of effects induced, and the magnitude and pattern of responses observed across studies were considered. Additionally, the conditions under which effects occur were considered, in particular, whether or not endocrine-related responses occurred at dose(s) that also resulted in overt toxicity. The assessment is therefore providing a weight-of-evidence analysis of the potential interaction of spinosad with the EAS and T signalling pathways using the available evidence in the data set.

For the **T-modality**, a pattern of T-mediated adversity was not identified in a sufficiently investigated dataset. Therefore, the ED criteria for humans for the T-modality are not met, and **scenario 1a** of the ECHA/EFSA ED Guidance (2018) is applicable.[10]

For the **EAS-modalities**, EAS-mediated parameters were not sufficiently investigated; however, no EAS-mediated adversity was observed in the available data set of studies. The endocrine activity was sufficiently investigated (i.e. the following level 2 and 3 studies OECD TG 455, OECD TG 456, OPPTS 890.1200, OECD TG 458, OECD TG 440 and OECD TG 441 were available) and negative. Therefore, the ED criteria for humans for the EAS-modalities are not met, and **scenario 2a(ii)** of the ECHA/EFSA ED Guidance (2018) is applicable.[10]

For **wild mammals**, the same conclusions reached for humans apply for the EATS-modalities.

For other **non-target organisms**, an amphibian metamorphosis assay (AMA, OECD 231) and a fish short-term reproductive assay (FSTRA, OECD 229) were available to sufficiently investigate the endocrine activity for the T- and EAS-modalities, respectively. Both studies were considered valid.[11]

In the AMA, the pattern of effects observed on growth parameters, developmental stage and thyroid histopathology did not follow any known thyroidal mode of action (MoA) and was likely due to systemic toxicity and/or the intrinsic MoA of the substance (i.e. macrocyclic lactone acting as nicotine acetylcholine receptor agonist).

The FSTRA was considered as sufficiently reliable for use in the ED assessment, although some drawbacks were identified i.e. deviations in the methodology for vitellogenin (VTG) analysis and slight under performance of fecundity in controls. Overall, when considering the available data and the overall weight of evidence, the pattern of effects observed i.e. slight effects on fertility and female gonad histopathology was not considered as indicative of potential endocrine activity through the EAS-modalities.

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) No 2018/605, it can be concluded that spinosad does not meet the ED criteria for humans and non-target organisms (Tables 1–5).

[10]Refer to experts' consultation 2.6 in the Report of the Pesticides Peer Review TC 136 (EFSA, 2018b, updated 2024).

[11]Refer to experts' consultations 5.5 and 5.6 in the Report of the Pesticides Peer Review TC 136 (EFSA, 2018b, updated 2024).

7 | OVERVIEW OF THE RISK ASSESSMENT OF COMPOUNDS LISTED IN RESIDUE DEFINITIONS TRIGGERING ASSESSMENT OF EFFECTS DATA FOR THE ENVIRONMENTAL COMPARTMENTS

TABLE 1 Soil.

Compound (name and/or code)	Persistence	Ecotoxicology
Spinosyn A	Low to moderate persistence single first-order and bi-phasic kinetics DT_{50} 6.5–46.3 days (DT_{90} 22.6–170.9 days; laboratory conditions at 20–25°C, 26%–75% MWHC soil moisture) Very low to medium persistence European field dissipation studies single first-order and bi-phasic kinetics DT_{50} 0.77–100 days	Low risk
Spinosyn D	Moderate to medium persistence single first-order and bi-phasic kinetics DT_{50} 11.3–62.6 days (DT_{90} 40.5–268.1 days; laboratory conditions at 20–25°C, 26%–75% MWHC soil moisture) Low to moderate persistence European field dissipation studies single first-order and bi-phasic kinetics DT_{50} 1.85–23.9 days	Low risk
Spinosyn B	Moderate to high persistence single first-order DT_{50} 58.8–291 days (DT_{90} 201.3–966 days; laboratory conditions at 20–25°C, 26%–75% MWHC soil moisture)	Low risk
N-demethyl spinosyn D	Moderate to high persistence single first-order DT_{50} 36.9–179 days (DT_{90} 122.7–594 days; laboratory conditions at 20–25°C, 26%–75% MWHC soil moisture)	Low risk

TABLE 2 Groundwater.

Compound (name and/or code)	Mobility in soil	>0.1 μg/L at 1 m depth for the representative uses[a]	Pesticidal activity	Toxicological relevance
Spinosyn A	Low mobility to immobile K_{Foc} 647–165,429 mL/g	No	Yes	Yes
Spinosyn D	Low mobility to immobile K_{Foc} 564–123,400 mL/g	No	Yes	Yes
Spinosyn B	Low mobility to immobile K_{Foc} 672–44,655 mL/g	No	Yes	Open (insufficient data available to conclude) Mouse acute oral LD_{50} > 2000 mg/kg bw Negative Ames test
N-demethyl spinosyn D	Medium mobility to immobile K_{Foc} 404–40,759 mL/g	No	Yes	Open No data available

[a]FOCUS scenarios or relevant lysimeter.

TABLE 3 Surface water and sediment.

Compound (name and/or code)	Ecotoxicology
Spinosyn A	High risk
Spinosyn D	High risk
Spinosyn B (soil, aqueous photolysis)	High risk to aquatic organisms, data gap for sediment dwellers
N-demethyl spinosyn D (soil, aqueous photolysis)	Data gap
β isomer of 13,14-dihydro of pseudoaglycone of spinosyn A (Pseudo-A) (aqueous photolysis)	Low risk
β isomer of 13,14-dihydro of pseudoaglycone of spinosyn D (Pseudo-D) (aqueous photolysis)	Low risk

TABLE 4 Air.

Compound (name and/or code)	Toxicology
Spinosyn A **Spinosyn D**	**Spinosad**: Rat LC_{50} inhalation > 5.18 mg/L air /4h (nose only) – no classification required

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).

8.1 | Data gaps identified for the representative uses evaluated

- A complete overview of the relevant studies identified in the search for peer review open literature on the active substance and its relevant metabolites, dealing with side effects on health and non-target species and published within the 10 years before the date of submission of the dossier, to be conducted and reported in accordance with EFSA guidance on the submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (EFSA, 2011; relevant for all representative uses evaluated; submission date proposed by the applicant: unknown).
- Additional data to identify the impurities expected to exceed 1 g/kg in the technical material (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 1).
- Determination of the octanol/water partition coefficient of all components of the residue definition for risk assessment (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 1).
- Identification and validation of the analytical methods for the dietary material used in long-term toxicity and carcinogenicity studies, reproductive and developmental toxicity studies (key studies for setting the ADI, ARfD and AAOEL) (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- In vitro interspecies comparative metabolism study (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- Developmental neurotoxicity study (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- Pending on the magnitude of residue levels from field trials and animal commodities analysed according to the proposed risk assessment residue definition, additional toxicological data (repeated-dose toxicity studies) may be needed on metabolites spinosyn B and K (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Sections 2 and 3).
- Additional data from the analytical attempts to further characterise/identify the unknown radioactive residues from the metabolism studies on plants (MET A-Li-4(5b)) and its genotoxicity potential; pending the outcome, further data may be needed including repeated-dose toxicological data (relevant for leafy crops; submission date proposed by the applicants: unknown; see Sections 2 and 3).
- Additional toxicological data relevant to consumer exposure (repeated-dose toxicological studies) are needed on the metabolite pseudoaglycone of spinosyn A, including clarification of its genotoxicity potential (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Sections 2 and 3).
- Rotational metabolism studies conducted with spinosyn D (relevant for all representative uses; submission date proposed by the applicant: unknown; see Section 3).
- Storage stability studies for residues as proposed in the risk assessment residue definition in high starch commodities (maize grain, potatoes) in high water commodities (leafy or bulb onion), (submission date proposed by the applicants: unknown; see Section 3).
- Clarification on the sample preparation (including extraction and analysis) are needed to decide on the validity on the stability of spinosyn B and N-demethyl spinosyn D (relevant for ruminant matrices; submission date proposed by the applicants: unknown; see Section 3).
- Storage stability studies for spinosyn B and N-demethyl spinosyn D residues for poultries matrices are needed (relevant for poultry matrices; submission date proposed by the applicants: unknown; see Section 3)
- Further elucidation of the structures of open macrolides (MET A-Li-4(5b)) and assessment of its genotoxicity potential, pending on this information, further investigations might be necessary (relevant for animal commodities; submission date proposed by the applicant: unknown; see Sections 2 and 3).
- Fish metabolism studies (relevant for maize; submission date proposed by the applicant: unknown; see Section 3).
- Sufficient residue trials analysed for the magnitude of residues for all compounds included in RA-RD (relevant for maize and maize fodder in SEU). For potatoes, complete information on the climatic condition for the trials submitted, or additional residue trials from NEU (submission date proposed by the applicants: unknown, see Section 3).
- Additional field trials covering all the representative uses and animal commodities analysed for all relevant compounds included in the risk assessment residue definitions for plant and animals are required (relevant for all uses and the animal commodities; submission date proposed by the applicants: unknown; see Section 3)
- Sufficient processing trials to derive valid processing factors for tomatoes (canned, pasta) and pomace (dry/wet) are required (submission date proposed by the applicants: unknown; see Section 3)
- Determination of the residues in pollen and bee products for human consumption resulting from residues taken up by honeybees from crops at blossom and analysed according to the risk assessment residue definition for plant submission

(relevant for representative uses in tomatoes, pepper and aubergines), date proposed by the applicants: unknown; see Section 3).
- The effect of water treatment processes on the nature of residues present in surface, when surface water is abstracted for drinking water (Article 4 (approval criteria for active substances) 3. (b) of Regulation (EC) No 1107/2009) has not been adequately assessed. Demonstration that further oxidation of the major groups of degradates proposed (mono, di, and tetrahydroxylated derivatives of spinosyn and the degradate formed by mono-N-demethylation of the forosamine sugar of spinosad) to carbon dioxide, water and NOx were not available (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 4).
- Further information to address the long-term risk to wild mammals (relevant for uses on grapes and fruiting and leafy vegetables; submission date proposed by the applicant: unknown; see Section 5).
- A risk assessment for birds and mammals for metabolites formed in plants, in particular metabolite spinosyn K (relevant all the representative uses; submission date proposed by the applicant: unknown; see Section 5).
- Further information to address the chronic risk to aquatic organisms including sediment dwellers (i.e. *Chironumus riparius* exposure via water) for spinosad for scenarios R1, R2, R3 and D6 (use on grapes); R2, R3 and R4 (field uses on leafy vegetables); D6, R1 and R2 (use on onion); R1 and R4 (field use on fruiting vegetables); R1 and R2 (uses on potatoes) and R1, R2 and R4 (use on maize), (submission date proposed by the applicant: unknown; see Section 5).
- Further information to address the acute and chronic risk to aquatic invertebrates for spinosyn B for scenario D6 (relevant for the uses on grapes, field uses on leafy vegetables and bulb vegetables; submission date proposed by the applicant: unknown; see Section 5).
- Further information to address the risk to sediment dwellers for spinosyn B for scenarios R1, R3 and R4 (field use on leafy vegetables); R2, R3 and R4 (field use on fruiting vegetables); R1, R2 and R3 (use on potatoes) (submission date proposed by the applicant: unknown; see Section 5).
- Further information to address the risk to sediment dwellers for N-demethylated spinosyn D for scenarios R1, R2 and R3 (reuse on potatoes) (submission date proposed by the applicant: unknown; see Section 5).
- A risk assessment for honeybees for spinosad and its pertinent metabolites formed in pollen and nectar in line with EFSA (2013) (relevant for all the representative uses; submission date proposed by the applicant: unknown; see Section 5).
- Further information to address the chronic risk to honeybees (larvae and adult) and the potential sublethal effects (e.g. effects on the hypopharyngeal gland) (relevant for all the representative uses; submission date proposed by the applicant: unknown; see Section 5).
- Further information to address the risk to bumblebees (relevant for all the representative uses; submission date proposed by the applicant: unknown; see Section 5).
- Further information to address the risk to non-target arthropods (relevant for the uses on grape, leafy and fruiting vegetables, bulb vegetables and potatoes; submission date proposed by the applicant: unknown; see Section 5).

8.2 | Data gaps identified for the maximum residue level applications

- Sufficient GAP compliant residue trials conducted according to the intended use in leek analysed according to proposed RD-RA covered by the storage stability studies and validated analytical method have to be provided (relevant for use in leek; submission date proposed by the applicant: see Section 3.2).
- To support the intended use on cardoon and rhubarb, sufficient GAP compliant residue trials have to be provided analysed according to proposed RD-RA covered by the storage stability studies and validated analytical method have (relevant for use in cardoon and rhubarb; submission date proposed by the applicant; see Section 3.2).
- Additional field trials on strawberries and raspberries analysed according to the RD-RA, covered by the storage stability and validated analytical method to support the indoor use are required (relevant for use in strawberries and raspberries; submission date proposed by the applicant; see Section 3.2).

9 | PARTICULAR CONDITIONS PROPOSED TO BE TAKEN INTO ACCOUNT TO MANAGE THE RISK(S) IDENTIFIED

- Gloves and coverall have to be worn by operators for hand-held applications in low crops to ensure that the AOEL is not exceeded according to the UK POEM (see Section 2).
- To mitigate the risk to aquatic organisms for spinosad and its pertinent metabolites mitigation measures such as vegetated buffers (up to 20 m) and no-spray buffer (up to 10 m) combined with drift reduction nozzles (90% reduction) are needed. These measures are not sufficient to mitigate the risk to aquatic organisms for scenarios R1, R2, R3 and D6 (use on grapes); R2, R3 and R4, D6 (field uses on leafy vegetables); D6, R1 and R2 (use on onion); R1 and R2 (uses on potatoes); R1 and R4 (field use on fruiting vegetables); and R1, R2 and R4 (use on maize) (see Section 5)

10 | CONCERNS

10.1 | Concerns for the representative uses evaluated

10.1.1 | 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[12] 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. The analytical methods for the dietary material used in long-term toxicity and carcinogenicity studies, reproductive and developmental toxicity studies (key studies for setting the ADI, ARfD and AAOEL) have not been identified to check whether they were validated, which questions the validity of the studies themselves (see Section 2).
2. The need for further tests and risk assessment to unique human metabolites could not be finalised while an in vitro comparative metabolism study is not submitted (see Section 2).
3. The developmental neurotoxicity potential of spinosad could not be finalised based on the neurotoxic pesticidal mode of action of the chemical and reported signs of neurotoxicity in the 1-year neurotoxicity rat study (degeneration of trigeminal ganglion) and the lack of a DNT study.
4. The consumer risk assessment could not be finalised considering the outstanding data to finalise the residue definitions for risk assessment in plant and animal commodities. In addition, no data were available to derive robust conversion factors from monitoring to risk assessment (see Section 3).
5. The consumer risk assessment from the consumption of drinking water could not be finalised, while satisfactory information was not available to address the effect of water treatment processes on the nature of the residues that might be present in surface water, when surface water is abstracted for drinking water (see Section 4).
6. The risk assessment for honeybees could not be finalised; further information is needed to address the chronic effects to adult and larvae. In addition, the risk assessment did not cover exposure in the landscape via different routes than the treated crop (Section 5).

10.1.2 | 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.

No critical areas of concern were identified.

10.1.3 | Overview of the concerns identified for each representative use considered

(If a particular condition proposed to be taken into account to manage an identified risk, as listed in Section 9, has been evaluated as being effective, then 'risk identified' is not indicated in Table 5.)

[12]Commission Regulation (EU) No 546/2011 of 10 June 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards uniform principles for evaluation and authorisation of plant protection products. OJ L 155, 11.6.2011, p. 127–175.

TABLE 5 Overview of concerns.

Representative use		Onion	Sweet corn, fodder maize, grain maize	Table grapes, wine grapes	Leafy vegetable: Lettuce (field)	Leafy vegetable: Lettuce (greenhouse)	Potato	Aubergine, pepper, tomato (field)	Aubergine, pepper, tomato (greenhouse)
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[4,5]	X[4,5]	X[4,5]	X[4,5]	X[4,5]	X[4,5]	X[4,5]	X[4,5]
Risk to wild non-target terrestrial vertebrates	Risk identified			X	X	X		X	X
	Assessment not finalised								
Risk to wild non-target terrestrial organisms other than vertebrates	Risk identified	X	X	X	X	X	X	X	X
	Assessment not finalised	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]
Risk to aquatic organisms	Risk identified	3/7 FOCUS scenarios	3/8 FOCUS scenarios	4/5 FOCUS scenarios	3/7 FOCUS scenarios		2/6 FOCUS scenarios	2/4 FOCUS scenarios	
	Assessment not finalised								
Groundwater exposure to active substance	Legal parametric value breached								
	Assessment not finalised								
Groundwater exposure to metabolites	Legal parametric value breached[a]								
	Parametric value of 10 µg/L[b] breached								
	Assessment not finalised								

Note: Columns are grey if no safe use can be identified. The superscript numbers relate to the numbered points indicated in Sections 10.1 and 10.2. Where there is no superscript number, see Sections 2–6 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).

10.2 | Issues related to the maximum residue level applications

None.

ABBREVIATIONS

AAOEL acute acceptable operator exposure level
ADE actual dermal exposure
ADI acceptable daily intake

ADME	absorption, distribution, metabolism and excretion
AF	assessment factor
AMA	amphibian metamorphosis assay
AOEL	acceptable operator exposure level
AP	alkaline phosphatase
AR	applied radioactivity
ARfD	acute reference dose
AST	aspartate aminotransferase (SGOT)
AUC	area under the blood concentration/time curve
AV	avoidance factor
BCF	bioconcentration factor
bw	body weight
CAS	Chemical Abstracts Service
CFU	colony forming units
CI	confidence interval
CIPAC	Collaborative International Pesticides Analytical Council Limited
CL	confidence limits
CLP	classification, labelling and packaging
CRD	(UK) Chemicals Regulation Directorate
DAA	days after application
DAR	draft assessment report
DAT	days after treatment
DDD	daily dietary dose
DM	dry matter
DNA	deoxyribonucleic acid
DNT	developmental neurotoxicity study
DT_{50}	period required for 50% dissipation (define method of estimation)
DT_{90}	period required for 90% dissipation (define method of estimation)
EAS	oestrogen, androgen and steroidogenesis
EbC_{50}	effective concentration (biomass)
EC_{50}	effective concentration
ECHA	European Chemicals Agency
ED	endocrine disruptor
EEC	European Economic Community
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EMDI	estimated maximum daily intake
ER_{50}	emergence rate/effective rate, median
ErC_{50}	effective concentration (growth rate)
ETR	exposure toxicity ratio
ETR_{HPG}	exposure toxicity ratio for effects on honeybee hypopharygeal glands
EUROPOEM	European Predictive Operator Exposure Model
FAO	Food and Agriculture Organization of the United Nations
FOB	functional observation battery
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
FSTRA	fish short term reproductive assay
GABA	gamma-aminobutyric acid
GAP	Good Agricultural Practice
GC	gas chromatography
GCPF	Global Crop Protection Federation (formerly known as International Group of National Associations of Manufacturers of Agrochemical Products; GIFAP)
GGT	gamma glutamyl transferase
GM	geometric mean
GS	growth stage
GSH	glutathione
HPLC	or high-performance liquid chromatography
HPLC–MS	high-pressure liquid chromatography–mass spectrometry
HPG	hypopharygeal glands
HQ	hazard quotient
HR	hazard rate
IEDI	international estimated daily intake
IESTI	international estimated short-term intake

IgM	Immunoglobulin M
ILV	independent laboratory validation
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)
K_{Foc}	Freundlich organic carbon adsorption coefficient
LC	liquid chromatography
LC_{50}	lethal concentration, median
LC–MS	liquid chromatography–mass spectrometry
LC–MS/MS	liquid chromatography with tandem mass spectrometry
LD_{50}	lethal dose, median; dosis letalis media
LDD_{50}	lethal dietary dose; median
LDH	lactate dehydrogenase
LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOQ	limit of quantification
M/L	mixing and loading
MAF	multiple application factor
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
mm	millimetre (also used for mean measured concentrations)
MRL	maximum residue level
MS	mass spectrometry
MSDS	material safety data sheet
MTD	maximum tolerated dose
MWHC	maximum water-holding capacity
NESTI	national estimated short-term intake
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NPD	nitrogen–phosphorus detector
OECD	Organisation for Economic Co-operation and Development
OM	organic matter content
Pa	Pascal
PD	proportion of different food types
PEC	predicted environmental concentration
PHED	pesticide handler's exposure data
PHI	pre-harvest interval
PIE	potential inhalation exposure
POEM	(UK) Predictive Operator Exposure Model
PPE	personal protective equipment
PT	proportion of diet obtained in the treated area
PTT	partial thromboplastin time
QSAR	quantitative structure–activity relationship
QuEChERS	quick, easy, cheap, effective and safe method
RAR	Renewal Assessment Report
RE	reticuloendothelial cells
REACH	Registration, Evaluation, Authorisation of Chemicals Regulation
RMS	rapporteur Member State
RPE	respiratory protective equipment
RUD	residue per unit dose
SANCO	Directorate-General for Health and Consumers
SC	suspension concentrate
SD	standard deviation
SFO	single first-order
SMILES	simplified molecular-input line-entry system
SPG	specific protection goal
SRBC	sheep red blood cells

SSD	species sensitivity distribution
STMR	supervised trials median residue
STOT-SE	specific target organ toxicity – single exposure
TC	technical material
TER	toxicity exposure ratio
TER_A	toxicity exposure ratio for acute exposure
TER_{LT}	toxicity exposure ratio following chronic exposure
TER_{ST}	toxicity exposure ratio following repeated exposure
TG	test guideline
TLV	threshold limit value
TMDI	theoretical maximum daily intake
TRR	total radioactive residue
TSH	thyroid-stimulating hormone (thyrotropin)
TWA	time-weighted average
UDS	unscheduled DNA synthesis
UF	uncertainty factor
UV	ultraviolet
VTG	vitellogenin
W/S	water/sediment
WBC	white blood cell
WHO	World Health Organization
1/*n*	slope of Freundlich isotherm

ACKNOWLEDGEMENTS

EFSA wishes to thank the rapporteur Member State, the Netherlands, for the preparatory work on this scientific output.

REQUESTOR

European Commission

QUESTION NUMBER

EFSA-Q-2019-00026

REFERENCES

ECHA (European Chemicals Agency). (2017). *Guidance on the Application of the CLP Criteria; Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures*. Version 5.0, July 2017. Reference: ECHA-17-G-21-EN; ISBN: 978–92–9020-050-5. https://echa.europa.eu/guidance-documents/guidance-on-clp

ECHA and EFSA (European Chemicals Agency and European Food Safety Authority) with the technical support of the Joint Research Centre (JRC), Andersson, N., Arena, M., Auteri, D., Barmaz, S., Grignard, E., Kienzler, A., Lepper, P., Lostia, A. M., Munn, S., Parra Morte, J. M., Pellizzato, F., Tarazona, J., Terron, A., & Van der Linden, S. (2018). Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009. *EFSA Journal*, *16*(6), 5311. https://doi.org/10.2903/j.efsa.2018.5311

EFSA (European Food Safety Authority). (2009). Guidance on risk assessment for birds and mammals on request from EFSA. *EFSA Journal*, *7*(12), 1438. https://doi.org/10.2903/j.efsa.2009.1438

EFSA (European Food Safety Authority). (2011). Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009. *EFSA Journal*, *9*(2), 2092. https://doi.org/10.2903/j.efsa.2011.2092

EFSA (European Food Safety Authority). (2012). Reasoned opinion on the review of the existing maximum residue levels (MRLs) for spinosad according to Article 12 of Regulation (EC) No 396/2005. *EFSA Journal*, *10*(3), 2630. https://doi.org/10.2903/j.efsa.2012.2630

EFSA (European Food Safety Authority). (2013). EFSA guidance document on the risk assessment of plant protection products on bees (*Apis mellifera, Bombus* spp. and solitary bees). *EFSA Journal*, *11*(7), 3295. https://doi.org/10.2903/j.efsa.2013.3295

EFSA (European Food Safety Authority). (2014). EFSA guidance document for evaluating laboratory and field dissipation studies to obtain DegT50 values of active substances of plant protection products and transformation products of these active substances in soil. *EFSA Journal*, *12*(5), 3662. https://doi.org/10.2903/j.efsa.2014.3662

EFSA (European Food Safety Authority). (2015). Technical report on the outcome of the pesticides peer review meeting on general recurring issues in ecotoxicology. EFSA supporting publication 2015:EN-924. 62 pp.

EFSA (European Food Safety Authority). (2018a). Conclusion on the peer review of the pesticide risk assessment of the active substance spinosad. *EFSA Journal*, *16*(5), 5252. https://doi.org/10.2903/j.efsa.2018.5252

EFSA (European Food Safety Authority). (2018b, updated in 2024). Updated Peer review report to the conclusion regarding the peer review of the pesticide risk assessment of the active substance spinosad. www.efsa.europa.eu

EFSA (European Food Safety Authority). (2019). *EFSA addendum: Updated assessment on the endocrine disrupting properties of the active substance spinosad in accordance with commission regulation (EU) 2018/605*. .

EFSA (European Food Safety Authority). (2021). Focussed assessment of certain existing MRLs of concern for Spinosad. *EFSA Journal*, *19*(2), 6404. www.efsa.europa.eu

EFSA PPR Panel (EFSA Panel on Plant Protection Products and their Residues). (2012). Guidance on dermal absorption. *EFSA Journal*, *10*(4), 2665. https://doi.org/10.2903/j.efsa.2012.2665

EFSA PPR Panel (EFSA Panel on Plant Protection Products and their Residues). (2013). Guidance on tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters. *EFSA Journal*, *11*(7), 3290. https://doi.org/10.2903/j.efsa.2013.3290

EFSA PPR Panel (EFSA Panel on Plant Protection Products and their Residues). (2021). Scientific opinion of the scientific panel on plant protection products and their residues (PPR panel) on testing and interpretation of comparative *in vitro* metabolism studies. *EFSA Journal*, *19*(12), 6970. https://doi.org/10.2903/j.efsa.2021.6970

European Commission. (2000a). *Residues: guidance for generating and reporting methods of analysis in support of pre-registration data requirements for Annex II (Part A, Section 4) and Annex III (Part A, Section 5) of Directive 91/414*. SANCO/3029/99-rev. 4, 11 July 2000.

European Commission. (2000b). *Technical material and preparations: guidance for generating and reporting methods of analysis in support of pre- and post-registration data requirements for Annex II (Part A, Section 4) and Annex III (Part A, Section 5) of Directive 91/414*. SANCO/3030/99-rev. 4, 11 July 2000.

European Commission. (2002a). *Guidance Document on Terrestrial Ecotoxicology Under Council Directive 91/414/EEC*. SANCO/10329/2002-rev. 2 final, 17 October 2002.

European Commission. (2002b). *Guidance Document on Aquatic Ecotoxicology Under Council Directive 91/414/EEC*. SANCO/3268/2001-rev. 4 final, 17 October 2002.

European Commission. (2003). *Guidance Document on Assessment of the Relevance of Metabolites in Groundwater of Substances Regulated under Council Directive 91/414/EEC. SANCO/221/2000-rev.* 10 final, 25 February 2003.

European Commission. (2006). Review report for the active substance spinosad. Finalised in the Standing Committee on the Food Chain and Animal Health at its meeting on 14 July 2006 in view of the inclusion of spinosad in Annex I of Council Directive 91/414/EEC. SANCO/1428/2001 – rev. final, 14 July 2006, 45 pp.

European Commission. (2010). Guidance Document on residue analytical methods. SANCO/825/00-rev. 8.1, 16 November 2010.

European Commission. (2012). *Guidance document on the assessment of the equivalence of technical materials of substances regulated under Regulation (EC) No 1107/2009. SANCO/10597/2003-rev. 10.1, 13 July 2012*.

European Commission. (2014). *Guidance document on the renewal of approval of active substances to be assessed in compliance with Regulation (EU) No 844/2012. SANCO/2012/11251-rev. 4, 12 December 2014*.

European Commission. (2017). *Guidelines on comparability, extrapolation, group tolerances and data requirements for setting MRLs. SANCO 7525/VI/95-rev. 10.3. June 2017. p. 1–58*.

FOCUS (Forum for the Co-ordination of Pesticide Fate Models and their Use). (2001). *FOCUS surface water scenarios in the EU evaluation process under 91/414/EEC. Report of the FOCUS Working Group on Surface Water Scenarios. EC Document Reference SANCO/4802/2001-rev. 2, 245 pp., as updated by Generic guidance for FOCUS surface water scenarios, v. 1.4, May 2015*.

FOCUS (Forum for the Co-ordination of Pesticide Fate Models and their Use). (2006). *Guidance document on estimating persistence and degradation kinetics from environmental fate studies on pesticides in EU Registration Report of the FOCUS Work Group on Degradation Kinetics. EC Document Reference SANCO/10058/2005-v. 2.0, 434 pp*.

FOCUS (Forum for the Co-ordination of Pesticide Fate Models and their Use). (2007). *Landscape and mitigation factors in aquatic risk assessment. Volume 1. Extended summary and recommendations. Report of the FOCUS Working Group on Landscape and Mitigation Factors in Ecological Risk Assessment. EC Document Reference SANCO/10422/2005 v. 2.0, 169 pp*.

FOCUS (Forum for the Co-ordination of Pesticide Fate Models and their Use). (2008). *Pesticides in air: Considerations for exposure assessment. Report of the FOCUS Working Group on Pesticides in Air. EC Document Reference SANCO/10553/2006-Rev. 2, June 2008*.

FOCUS (Forum for the Co-ordination of Pesticide Fate Models and their Use). (2009). *Assessing potential for movement of active substances and their metabolites to ground water in the EU. Report of the FOCUS Workgroup. EC Document Reference SANCO/13144/2010-v. 1, 604 pp., as outlined in Generic guidance for tier 1 FOCUS groundwater assessment, v. 2.0, January 2011*.

JMPR (Joint Meeting on Pesticide Residues). (2004). Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues, Rome, Italy, 20–29 September 2004, 383 pp.

JMPR (Joint Meeting on Pesticide Residues). (2007). *Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues, Geneva, Switzerland, 18–27 September 2007, 164 pp*.

Netherlands. (2017). *Renewal assessment report (RAR) on the active substance spinosad prepared by the rapporteur member state The Netherlands, in the framework of commission implementing regulation (EU) No 844/2012, March 2017*. www.efsa.europa.eu

Netherlands. (2018). *Revised Renewal Assessment Report (RAR) on spinosad prepared by the rapporteur Member State the Netherlands in the framework of Regulation (EC) No 1107/2009*, January 2018: www.efsa.europa.eu

Netherlands. (2023). *Revised Renewal Assessment Report (RAR) with the revised ED assessment on spinosad prepared by the rapporteur Member State the Netherlands, in the framework of EC Mandate (Ares(2018)195786), June 2023*. www.efsa.europa.eu

Netherlands. (2024). Revised Renewal Assessment Report (RAR) with the revised ED assessment on spinosad prepared by the rapporteur Member State the Netherlands, in the framework of EC Mandate (Ares(2018)195786), April 2024, updated July 2024. www.efsa.europa.eu

OECD (Organisation for Economic Co-operation and Development). (2009). *Guidance document on overview of residue chemistry studies. ENV/JM/MONO(2009)31, 28 July 2009*.

OECD (Organisation for Economic Co-operation and Development). (2011). *OECD MRL calculator: spreadsheet for single data set and spreadsheet for multiple data set, 2 March 2011. In: Pesticide Publications/Publications on Pesticide Residues*.

SETAC (Society of Environmental Toxicology and Chemistry). (2001). Guidance document on regulatory testing and risk assessment procedures for plant protection products with non-target arthropods. *Escort*, *2*.

Southern European Greenhouse Model. Version 2.1. The European Crop Protection Association. (2010). *("The greenhouse model"). The model and associated data are freely available from the ECPA on request*.

How to cite this article: EFSA (European Food Safety Authority), Álvarez, F., Arena, M., Auteri, D., Batista Leite, S., Binaglia, M., Castoldi, A. F., Chiusolo, A., Colagiorgi, A., Colas, M., Crivellente, F., De Lentdecker, C., De Magistris, I., Egsmose, M., Fait, G., Ferilli, F., Fittipaldi Broussarad, M., Giner Santonja, G., Gouliarmou, V., … Villamar-Bouza, L. (2025). Updated peer review of the pesticide risk assessment of the active substance spinosad. *EFSA Journal*, *23*(1), e9193. https://doi.org/10.2903/j.efsa.2025.9193

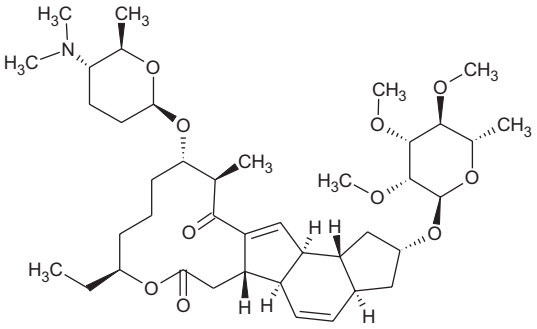
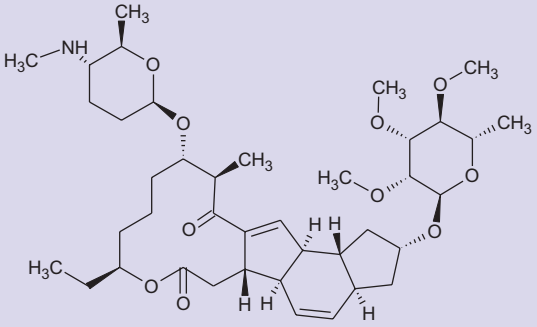
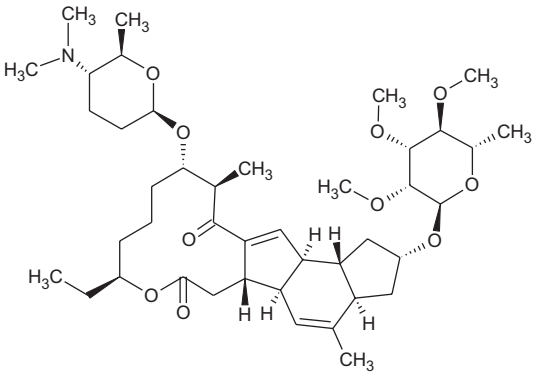
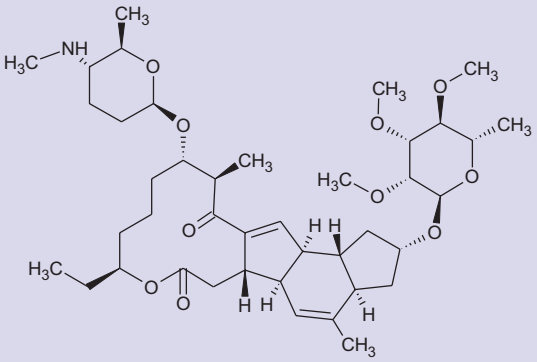
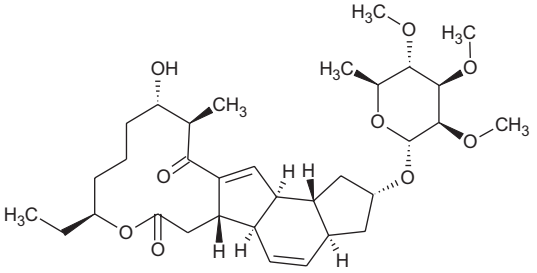
APPENDIX A

List of end points for the active substance and the representative formulation

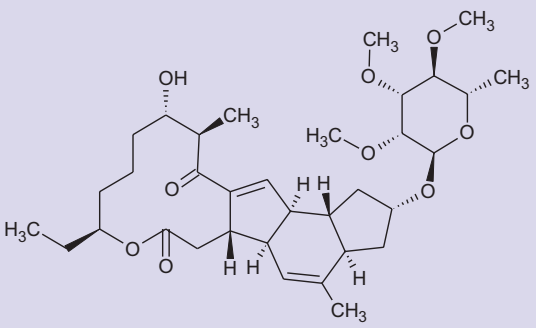
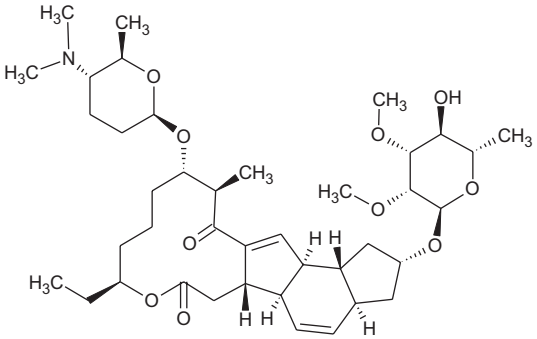
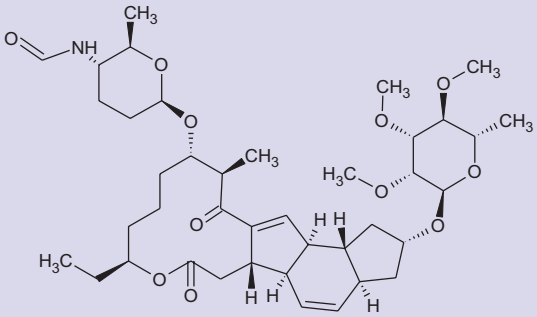
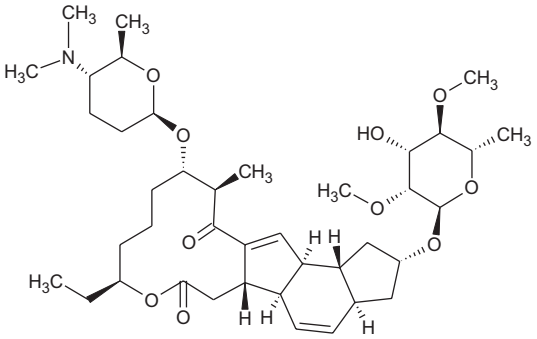
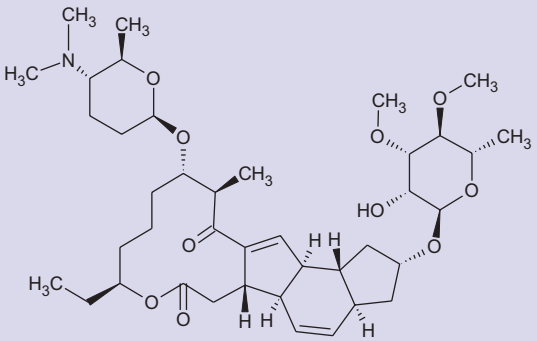
Appendix A can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2025.9193.

APPENDIX B

Used compound codes

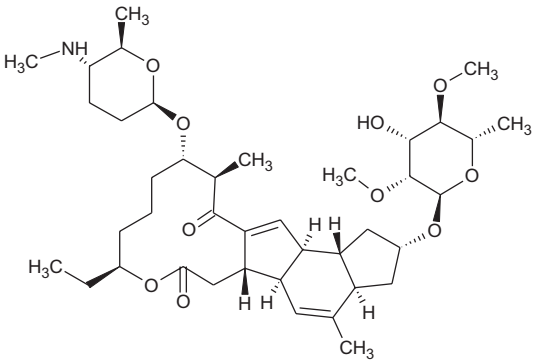
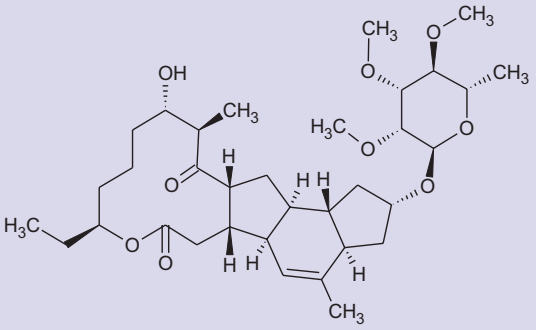
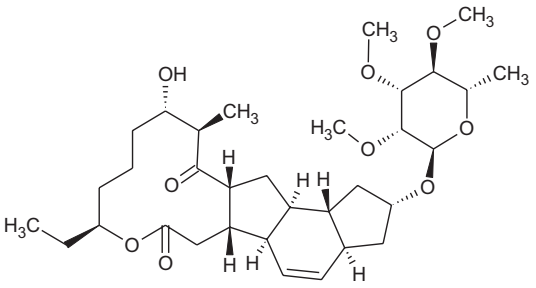
Code/trivial name[a]	Chemical name/SMILES notation/InChiKey[b]	Structural formula[b]
spinosyn A	(2*R*,3a*S*,5a*R*,5b*S*,9*S*,13*S*,14*R*,16a*S*,16b*R*)-2-(6-deoxy-2,3,4-tri-*O*-methyl-α-L-mannopyranosyloxy)-13-(4-dimethylamino-2,3,4,6-tetradeoxy-β-D-erythropyranosyloxy)-9-ethyl-2,3,3a,5a,5b,6,7,9,10,11,12,13,14,15,16a,16b-hexadecahydro-14-methyl-1*H*-as-indaceno[3,2-*d*]oxacyclododecine-7,15-dione CN(C)[C@H]1CC[C@@H](O[C@@H]1C)O[C@H]6CCC[C@H](CC)OC(=O)C[C@@H]5C(=C[C@@H]3[C@H]5C=C[C@@H]2C[C@H](C[C@H]23)O[C@@H]4O[C@@H](C)[C@H](OC)[C@@H](OC)[C@H]4OC)C(=O)[C@@H]6C SRJQTHAZUNRMPR-UYQKXTDMSA-N	
spinosyn B	(2*R*,3a*S*,5a*R*,5b*S*,9*S*,13*S*,14*R*,16a*S*,16b*R*)-2-(6-deoxy-2,3,4-tri-*O*-methyl-α-L-mannopyranosyloxy)-13-(4-methylamino-2,3,4,6-tetradeoxy-β-D-erythropyranosyloxy)-9-ethyl-2,3,3a,5a,5b,6,7,9,10,11,12,13,14,15,16a,16b-hexadecahydro-14-methyl-1*H*-as-indaceno[3,2-*d*]oxacyclododecine-7,15-dione CN[C@H]1CC[C@@H](O[C@@H]1C)O[C@H]6CCC[C@H](CC)OC(=O)C[C@@H]5C(=C[C@@H]3[C@H]5C=C[C@@H]2C[C@H](C[C@H]23)O[C@@H]4O[C@@H](C)[C@H](OC)[C@@H](OC)[C@H]4OC)C(=O)[C@@H]6C VESRDXZDAAOUHS-KXRJSVEISA-N	
spinosyn D	(2*S*,3a*R*,5a*S*,5b*S*,9*S*,13*S*,14*R*,16a*S*,16b*S*)-2-(6-deoxy-2,3,4-tri-*O*-methyl-α-L-mannopyranosyloxy)-13-(4-dimethylamino-2,3,4,6-tetradeoxy-β-D-erythropyranosyloxy)-9-ethyl-2,3,3a,5a,5b,6,7,9,10,11,12,13,14,15,16a,16b-hexadecahydro-4,14-dimethyl-1*H*-as-indaceno[3,2-*d*]oxacyclododecine-7,15-dione CN(C)[C@H]1CC[C@@H](O[C@@H]1C)O[C@H]6CCC[C@H](CC)OC(=O)C[C@@H]5C(=C[C@@H]3[C@H]5C=C(C)[C@@H]2C[C@H](C[C@H]23)O[C@@H]4O[C@@H](C)[C@H](OC)[C@@H](OC)[C@H]4OC)C(=O)[C@@H]6C RDECBWLKMPEKPM-PSCJHHPTSA-N	
***N*-demethyl spinosyn D**	(2*S*,3a*R*,5a*S*,5b*S*,9*S*,13*S*,14*R*,16a*S*,16b*S*)-2-(6-deoxy-2,3,4-tri-*O*-methyl-α-L-mannopyranosyloxy)-13-(4-methylamino-2,3,4,6-tetradeoxy-β-D-erythropyranosyloxy)-9-ethyl-2,3,3a,5a,5b,6,7,9,10,11,12,13,14,15,16a,16b-hexadecahydro-4,14-dimethyl-1*H*-as-indaceno[3,2-*d*]oxacyclododecine-7,15-dione CN[C@H]1CC[C@@H](O[C@@H]1C)O[C@H]6CCC[C@H](CC)OC(=O)C[C@@H]5C(=C[C@@H]3[C@H]5C=C(C)[C@@H]2C[C@H](C[C@H]23)O[C@@H]4O[C@@H](C)[C@H](OC)[C@@H](OC)[C@H]4OC)C(=O)[C@@H]6C XZDDTAKXLUVBPD-VLBVROKKSA-N	
PseudoAglycon A1	(2*R*,3a*S*,5a*R*,5b*S*,9*S*,13*S*,14*R*,16a*S*,16b*R*)-2-(6-deoxy-2,3,4-tri-*O*-methyl-α-L-mannopyranosyloxy)-9-ethyl-13-hydroxy-2,3,3a,5a,5b,6,7,9,10,11,12,13,14,15,16a,16b-hexadecahydro-14-methyl-1*H*-as-indaceno[3,2-*d*]oxacyclododecine-7,15-dione O=C4C5=C[C@@H]2[C@@H](C=C[C@@H]1C[C@H](C[C@H]12)O[C@@H]3O[C@@H](C)[C@H](OC)[C@@H](OC)[C@H]3OC)[C@@H]5CC(=O)O[C@@H](CC)CCC[C@H](O)[C@H]4C KSCLXDPNSMLYPU-WRNUEGBCSA-N	

(Continued)

Code/trivial name[a]	Chemical name/SMILES notation/InChiKey[b]	Structural formula[b]
PseudoAglycon D1	(2*S*,3a*R*,5a*S*,5b*S*,9*S*,13*S*,14*R*,16a*S*,16b*S*)-2-(6-deoxy-2,3,4-tri-*O*-methyl-α-L-mannopyranosyloxy)-9-ethyl-13-hydroxy-2,3,3a,5a,5b,6,7,9,10,11,12,13,14,15,16a,16b-hexadecahydro-4,14-dimethyl-1*H*-as-indaceno[3,2-*d*]oxacyclododecine-7,15-dione CC3=C[C@H]1[C@@H]5CC(=O)O[C@@H](CC)CCC[C@H](O)[C@@H](C)C(=O)C5=C[C@H]1[C@@H]4C[C@H](O[C@@H]2O[C@@H](C)[C@H](OC)[C@@H](OC)[C@H]2OC)C[C@@H]34 PGGPPEHRBUYMQU-DXUWLMMLSA-N	
Spinosin K	(2*R*,3a*S*,5a*R*,5b*S*,9*S*,13*S*,14*R*,16a*S*,16b*R*)-2-(6-deoxy-2,3-di-*O*-methyl-α-L-mannopyranosyloxy)-13-(4-dimethylamino-2,3,4,6-tetradeoxy-β-D-erythropyranosyloxy)-9-ethyl-2,3,3a,5a,5b,6,7,9,10,11,12,13,14,15,16a,16b-hexadecahydro-14-methyl-1*H*-as-indaceno[3,2-*d*]oxacyclododecine-7,15-dione CN(C)[C@H]1CC[C@@H](O[C@@H]1C)O[C@H]6CCC[C@H](CC)OC(=O)C[C@@H]5C(=C[C@@H]3[C@H]5C=C[C@@H]2C[C@H](C[C@H]23)O[C@H]4O[C@@H](C)[C@H](O)[C@@H](OC)[C@H]4OC)C(=O)[C@@H]6C JVXKZYLRDBNKCL-YJJBMAGJSA-N	
***N*-formyl spinosyn B**	(2*R*,3a*S*,5a*R*,5b*S*,9*S*,13*S*,14*R*,16a*S*,16b*R*)-2-(6-deoxy-2,3,4-tri-*O*-methyl-α-L-mannopyranosyloxy)-13-(4-formylamino-2,3,4,6-tetradeoxy-β-D-erythropyranosyloxy)-9-ethyl-2,3,3a,5a,5b,6,7,9,10,11,12,13,14,15,16a,16b-hexadecahydro-14-methyl-1*H*-as-indaceno[3,2-*d*]oxacyclododecine-7,15-dione O=CN[C@H]1CC[C@@H](O[C@@H]1C)O[C@H]6CCC[C@H](CC)OC(=O)C[C@@H]5C(=C[C@@H]3[C@H]5C=C[C@@H]2C[C@H](C[C@H]23)O[C@H]4O[C@@H](C)[C@H](OC)[C@@H](OC)[C@H]4OC)C(=O)[C@@H]6C XXIOPXNOYKNMCC-YJJBMAGJSA-N	
Spinosin J	(2*R*,3a*S*,5a*R*,5b*S*,9*S*,13*S*,14*R*,16a*S*,16b*R*)-2-(6-deoxy-2,4-di-*O*-methyl-α-L-mannopyranosyloxy)-13-(4-dimethylamino-2,3,4,6-tetradeoxy-β-D-erythropyranosyloxy)-9-ethyl-2,3,3a,5a,5b,6,7,9,10,11,12,13,14,15,16a,16b-hexadecahydro-14-methyl-1*H*-as-indaceno[3,2-*d*]oxacyclododecine-7,15-dione CN(C)[C@H]1CC[C@@H](O[C@@H]1C)O[C@H]6CCC[C@H](CC)OC(=O)C[C@@H]5C(=C[C@@H]3[C@H]5C=C[C@@H]2C[C@H](C[C@H]23)O[C@H]4O[C@@H](C)[C@H](OC)[C@@H](O)[C@H]4OC)C(=O)[C@@H]6C IHGXGNJRCONUAC-YJJBMAGJSA-N	
Spinosin H	(2*R*,3a*S*,5a*R*,5b*S*,9*S*,13*S*,14*R*,16a*S*,16b*R*)-2-(6-deoxy-3,4-di-*O*-methyl-α-L-mannopyranosyloxy)-13-(4-dimethylamino-2,3,4,6-tetradeoxy-β-D-erythropyranosyloxy)-9-ethyl-2,3,3a,5a,5b,6,7,9,10,11,12,13,14,15,16a,16b-hexadecahydro-14-methyl-1*H*-as-indaceno[3,2-*d*]oxacyclododecine-7,15-dione CN(C)[C@H]1CC[C@@H](O[C@@H]1C)O[C@H]6CCC[C@H](CC)OC(=O)C[C@@H]5C(=C[C@@H]3[C@H]5C=C[C@@H]2C[C@H](C[C@H]23)O[C@H]4O[C@@H](C)[C@H](OC)[C@@H](OC)[C@H]4O)C(=O)[C@@H]6C IOCQRADVOJDJIS-YJJBMAGJSA-N	

(Continues)

(Continued)

Code/trivial name[a]	Chemical name/SMILES notation/InChiKey[b]	Structural formula[b]
***N*-demethyl spinosyn L**	(2*S*,3a*R*,5a*S*,5b*S*,9*S*,13*S*,14*R*,16a*S*,16b*S*)-2-(6-deoxy-2,4-di-*O*-methyl-α-L-mannopyranosyloxy)-13-(4-methylamino-2,3,4,6-tetradeoxy-β-D-erythropyranosyloxy)-9-ethyl-2,3,3a,5a,5b,6,7,9,10,11,12,13,14,15,16a,16b-hexadecahydro-4,14-dimethyl-1*H*-as-indaceno[3,2-*d*]oxacyclododecine-7,15-dione CN[C@H]1CC[C@@H](O[C@@H]1C)O[C@H]6CCC[C@H](CC)OC(=O)C[C@@H]5C(=C[C@@H]3[C@H]5C=C(C)[C@@H]2C[C@H](C[C@H]23)O[C@H]4O[C@@H](C)[C@H](OC)[C@@H](O)[C@H]4OC)C(=O)[C@@H]6C PGTPZQVUXFPXLO-LHMGCALNSA-N	
13,14β-dihydro-C17-pseudoaglycone-spinosyn D	(2*S*,3a*R*,5a*S*,5b*S*,9*S*,13*S*,14*R*, 15a*R*,16a*S*,16b*S*)-2-(6-deoxy-2,3,4-tri-*O*-methyl-α-L-mannopyranosyloxy)-9-ethyl-13-hydroxy-2,3,3a,5a,5b,6,7,9,10,11,12,13,14,15,15a,16,16a,16b-octadecahydro-4,14-dimethyl-1*H*-as-indaceno[3,2-d]oxacyclododecine-7,15-dione O=C5[C@H](C)[C@@H](O)CCC[C@H](CC)OC(=O)C[C@@H]4[C@H]5C[C@@H]2[C@H]4C=C(C)[C@@H]1C[C@H](C[C@H]12)O[C@H]3O[C@@H](C)[C@H](OC)[C@@H](OC)[C@H]3OC XGERXWGPCWNBGV-JDAWHBOVSA-N	
13,14β-dihydro-C17-pseudoaglycone-spinosyn A	(2*R*,3a*S*,5a*R*,5b*S*,9*S*,13*S*,14*R*, 15a*R*,16a*S*,16b*R*)-2-(6-deoxy-2,3,4-tri-*O*-methyl-α-L-mannopyranosyloxy)-9-ethyl-13-hydroxy-2,3,3a,5a,5b,6,7,9,10,11,12,13,14,15,15a,16,16a,16b-octadecahydro-14-methyl-1*H*-as-indaceno[3,2-*d*]oxacyclododecine-7,15-dione O=C5[C@H](C)[C@@H](O)CCC[C@H](CC)OC(=O)C[C@@H]4[C@H]5C[C@@H]2[C@H]4C=C[C@@H]1C[C@H](C[C@H]12)O[C@H]3O[C@@H](C)[C@H](OC)[C@@H](OC)[C@H]3OC BVUYDKCNUTWSHZ-MLASGGABSA-N	

Note: ACD/Name 2015 ACD/Labs 2015 Release (File version N20E41, Build 75170, 19 Dec 2014).

[a]The compound name in bold is the name used in the conclusion.

[b]ACD/ChemSketch 2015 ACD/Labs 2015 Release (File version C10H41, Build 75059, 17 December 2014).