CONCLUSION ON PESTICIDES PEER REVIEW

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Peer review of the pesticide risk assessment for the active substance spiroxamine in light of confirmatory data submitted

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Abstract

The conclusions of the EFSA following the peer review of the initial risk assessment carried out by the competent authority of the rapporteur Member State, Germany, for the pesticide active substance spiroxamine are reported. The context of the peer review was that requested by the European Commission following the submission and evaluation of confirmatory ecotoxicology data. The conclusions were reached on the basis of the evaluation of the representative uses of spiroxamine as a fungicide on grapes, wheat, triticale, rye, barley and oats. The reliable end points concluded as being appropriate for use in regulatory risk assessment, derived from the available studies and literature in the dossier peer reviewed, are presented.

Keywords: spiroxamine, peer review, confirmatory data, risk assessment, pesticide, fungicide

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Summary

Spiroxamine has been approved under Regulation (EC) No 1107/2009 by Commission Implementing Regulation (EU) No 797/2011. It was a specific provision of the approval that the applicant was required to submit to the European Commission further studies on:

a) the possible impact on the worker, the consumer and the environmental risk assessment of the potential stereo-selective degradation of each isomer in plant, animals and the environment;
b) the toxicity of the plant metabolites formed in fruit crops and the potential hydrolysis of fruit crop residues in processed commodities;
c) the groundwater exposure assessment for metabolite M03;
d) the risk to aquatic organisms.

The applicant was required to submit the information set out in point (a) by 2 years after the adoption of specific guidance and the information set out in points (b), (c) and (d) by 31 December 2013.

In accordance with the specific provision, the applicant, Bayer CropScience, submitted an updated dossier in December 2013, which was evaluated by the designated rapporteur Member State (RMS), Germany, in the form of a revised assessment report. In compliance with guidance document SANCO 5634/2009-rev. 6.1, the RMS distributed the revised assessment report to Member States, the applicant and EFSA for comments on 10 April 2017. The RMS collated all comments in the format of a reporting table, which was submitted to the European Commission on 22 November 2017.

Following consideration of the comments received, the European Commission requested EFSA to organise a peer review of the evaluation by RMS of the confirmatory data submitted and to deliver its conclusions on the consumer risk assessment taking into account the change of the toxicological reference value for metabolites M13 and M28, and the risk assessment for fish taking into account general risk mitigation measures.

Regarding the mammalian toxicology section, the use of additional uncertainty factors was discussed for the derivation of the acceptable daily intake (ADI) and acute reference dose (ARfD) for both metabolites M13 and M28. The reference values of metabolites M13 and M28 were confirmed. No data gaps or critical areas of concern were identified regarding the confirmatory data procedure.

In the area of residue, no critical areas of concern were identified. The risk assessment residue definition for the fruit category was amended. A novel, non-standard risk assessment approach was applied, using assumptions to refine the conservative risk assessment that indicated an exceedance of the ARfD for table grapes. It can be assumed that with the new residue definition and respective ARfDs, the acute intake assessment for table grapes is unlikely to result in an exceedance; however, confirmation of this assumption by residue data is missing. The additional uncertainty introduced by using a non-standard assessment approach is highlighted and should be taken into account by risk managers.

In the area of ecotoxicology, no critical areas of concern were identified. High risk to fish was identified for the uses in grapes and for the majority of the relevant FOCUS scenarios for winter cereals. Low risk was concluded for spring cereals.

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Background

Spiroxamine has been approved under Regulation (EC) No 1107/2009[1] by Commission Implementing Regulation (EU) No 797/2011[2]. EFSA previously finalised a Conclusion on this active substance on 1 September 2010 (EFSA, 2010).

It was a specific provision of the approval that the applicant was required to submit to the European Commission further studies on:

a) the possible impact on the worker, the consumer and the environmental risk assessment of the potential stereo-selective degradation of each isomer in plant, animals and the environment;
b) the toxicity of the plant metabolites formed in fruit crops and the potential hydrolysis of fruit crop residues in processed commodities;
c) the groundwater exposure assessment for metabolite M03;
d) the risk to aquatic organisms.

The applicant was required to submit the information set out in point (a) by 2 years after the adoption of specific guidance and the information set out in points (b), (c) and (d) by 31 December 2013.

In accordance with the specific provision, the applicant, Bayer CropScience, submitted an updated dossier in December 2013 which was completed in April 2014, and evaluated by the designated rapporteur Member State (RMS), Germany, in the form of updates of the assessment report (Germany, 2017). In compliance with guidance document SANCO 5634/2009-rev.6.1 (European Commission, 2013), the RMS distributed the revised assessment report to Member States, the applicant and EFSA for comments on 10 April 2017. The RMS collated all comments in the format of a reporting table, which was submitted to EFSA on 22 November 2017. EFSA added its scientific views on the specific points raised during the commenting phase in column 4 of the reporting table.

Following consideration of the comments received, the European Commission requested EFSA to organise a further peer review of the RMS's evaluation on the confirmatory data, including expert discussion where appropriate and to deliver its conclusions on the update of the consumer risk assessment taking into account the change of the toxicological reference values for metabolites M13 and M28 and the risk assessment for fish, taking into account general risk mitigation measures.

The revised assessment and the reporting table were discussed at the Pesticides Peer Review Meetings on mammalian toxicology and ecotoxicology in June 2020. Details of the issues discussed together with the outcome of these discussions were recorded in the meeting reports.

A final consultation on the conclusions arising from the peer review took place with Member States via a written procedure in November 2020.

The conclusions laid down in this report were reached on the basis of the peer review of the RMS's evaluation of the confirmatory data submitted in relation to the consumer risk assessment taking into account the change of the toxicological reference values for metabolites M13 and M28 and the risk assessment for fish, taking into account general risk mitigation measures. A key supporting document to this conclusion is the peer review report, which is a compilation of the documentation developed to evaluate and address all issues raised in the peer review, from the compilation of comments in the reporting table to the conclusion. The peer review report (EFSA, 2020) comprises the following documents, in which all views expressed during the course of the peer review, including minority views, can be found:

- the reporting table (22 November 2017)[3];
- the report of the scientific consultation with Member State experts;
- the comments received on the draft EFSA conclusion.

[1] Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. OJ L 309, 24.11.2009, p. 1–50.
[2] Commission Implementing Regulation (EU) No 797/2011 of 9 August 2011 approving the active substance spiroxamine, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market, and amending the Annex to Commission Implementing Regulation (EU) No 540/2011. OJ L 205, 10.8.2011, p. 3–8.
[3] published in the EFSA Technical Report (EFSA, 2018).

Given the importance of the assessment report including its final updates of the assessment report (Germany, 2020) and the peer review report, these documents are considered as background documents to this conclusion.

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 to have regulatory access to the information on which this conclusion report is based.

The active substance and the formulated product

Spiroxamine is the ISO common name for 8-*tert*-butyl-1,4-dioxaspiro[4.5]decan-2-ylmethyl(ethyl)(propyl)amine (IUPAC).

The representative formulated products for the evaluation were 'Hoggar, Prosper, Prosper 500 EC' which is a 500 g/L emulsifiable concentrate (EC) and 'Input' and 'Helix' an EC formulation containing 160 g/L prothioconazole and 300 g/L spiroxamine.

The representative uses evaluated comprise outdoor foliar spraying against fungal diseases in grapes with the 'Hoggar' formulation and in wheat, triticale, rye, barley and oats with the 'Input' formulation. Full details of the good agricultural practice (GAP) can be found in the list of end points in Appendix A.

Conclusions of the evaluation

The applicant has submitted to the Commission by the deadline of 31 December 2013 studies to provide further information to assess the possible impact on the worker, the consumer and the environmental risk assessment of the potential stereo-selective degradation of each isomer in plant, animals and the environment, the toxicity of the plant metabolites formed in fruit crops and the potential hydrolysis of fruit crop residues in processed commodities, the groundwater exposure assessment for metabolite M03 and the risk to aquatic organisms. The assessment of the information was presented in a revised assessment report (Germany, 2017).

The report highlighted the need to update the consumer risk assessment based on the comments received and listed several issues for which further peer review is proposed. Therefore, EFSA was asked to arrange a further peer review, including expert discussion where appropriate, to consider the following points:

- An update of the consumer risk assessment taking into account the change of the toxicological reference values for the metabolites M13 and M28;
- The risk assessment for fish, taking into account general risk mitigation measures.

The assessment of the above points was presented in a revised assessment report (Germany, 2020).

1. Mammalian toxicology

Spiroxamine confirmatory data on metabolites M13 and M28 were discussed at the Pesticides Peer Review Experts' Meeting TC 16 in June 2020. During the experts' meeting, the discussion was focused on the confirmation of the updated references values and the RMS's proposal of applying an uncertainty factor (UF) of 3,000 for the acceptable daily intake (ADI) of both metabolites M13 and M28. Based on available data, there are qualitative differences between the toxicological profiles of the metabolites M13, M28 and the parent, and between the two metabolites M13 and M28. Therefore, specific reference values were set for these two metabolites.

Based on an acute oral study in rats and an acute dermal study in rabbits, M13 was concluded of low acute toxicity. M13 was negative in a bacterial reverse mutation assay and in an *in vitro* chromosomal aberration assay. A quantitative structure–activity relationship (QSAR) analysis was performed and no alerts were reported for genotoxicity. It was concluded that M13 is unlikely to be genotoxic *in vitro*. In a 28-day oral toxicity study in rats performed with M13, a no observed adverse effect level (NOAEL) of 50 mg/kg body weight (bw) per day was set based on clinical signs and transient signs of neurotoxicity. An oral developmental toxicity study in rat conducted with M13 acetate was also submitted to assess the general toxicity of M13. In this study, a maternal toxicity NOAEL of 40 mg/kg bw per day was identified based on clinical signs, corresponding to 31.5 mg/kg bw per day for M13 after correction of the difference in molecular weight between M13 and M13 acetate. For metabolite M13, the agreed ADI is 0.03 mg/kg bw per day, based on the maternal toxicity NOAEL of

31.5 mg/kg bw per day for clinical signs from the developmental toxicity study in rats performed with M13 acetate, applying an UF of 1000 (100 standard UF and an additional factor of 10 due to incomplete data set). The acute reference dose (ARfD) is 0.1 mg/kg bw, based on the same maternal toxicity NOAEL of 31.5 mg/kg bw per day from the developmental toxicity study in rat performed with M13 acetate and supported by the NOAEL of 50 mg/kg bw per day for transient signs of neurotoxicity observed in the 28-day rat study performed with M13. It was agreed by all experts including the RMS to apply an UF of 300, including an additional factor of 3 due to the lack of a complete data package.

Metabolite M28 is of moderate acute toxicity on the basis of an acute oral toxicity study in rat. A bacterial reverse mutation assay, a hypoxanthine-guanine phosphoribosyltransferase (HGPRT) gene mutation assay and an *in vitro* micronucleus test in human lymphocytes were negative. Therefore, it was concluded that M28 is unlikely to be genotoxic *in vitro*. In a 28-day study in rats, no adverse effects were observed up to the highest dose tested. The top dose of 28.4/31.4 mg/kg bw per day was considered to be the NOAEL. In a developmental toxicity study in rats, the developmental toxicity NOAEL of 30 mg/kg bw per day was based on changes in ossification at 150 mg/kg bw per day and the maternal toxicity NOAEL was 150 mg/kg bw per day based on mortality, clinical observations (gasping and rales), gaseous contents and gas filled parts of the gastrointestinal tract, and individual body weight decreases at 500 mg/kg bw per day. For the metabolite M28, the ADI is 0.03 mg/kg bw per day, based on the developmental toxicity NOAEL of 30 mg/kg bw per day for changes in ossification in the developmental toxicity study in rats, supported by the NOAEL of 30 mg/kg bw per day (top dose) in the 28-day study in rats and applying an UF of 1,000 (including an additional factor of 10 due to incomplete data set). The ARfD is 0.5 mg/kg bw, based on the maternal toxicity NOAEL of 150 mg/kg bw per day for mortality and clinical signs observed in the developmental toxicity study in rats, applying an UF of 300 (including an additional factor of 3 due to the lack of a complete data package). All experts, including the RMS agreed with this conclusion, confirming the outcome indicated in the technical report on the same confirmatory data (EFSA, 2018).

The grouping concept related for M13 (Group B) and M28 (Group C) has been addressed in the case study included in the EFSA PPR Panel, 2016. In this case study, the metabolite M13 covers the toxicity profile of metabolites M22, M32, M33, M34, tentative for M35 and M36; the metabolite M28 is representative of metabolites M29, M30 and M31. A qualitative comparison of the general toxicity studies confirmed that the metabolite M13 (Group B), the metabolite M28 (Group C) and the parent compound spiroxamine do not share the same toxicological profile.

2. Residues

Confirmatory data were assessed to address a data requirement for 'the toxicity of the plant metabolites formed in fruit crops and the potential hydrolysis of fruit crop residues in processed commodities' laid down in the Commission Implementing Regulation (EU) No 797/2011.

Upon toxicological evaluation of metabolites M13 and M28 (see Section 1) and in view of abundance of these metabolites in fruit crops (M13 conjugates up to 25.3% total radioactive residues (TRR), M28 up to 37.5% TRR), it is proposed to amend the provisional residue definition for risk assessment for the fruit category set as sum of spiroxamine and all metabolites containing the aminodiol (N-ethyl-N-propyl-1,2- dihydroxy-3-amino-propane) moiety,[4] expressed as spiroxamine during the peer review (EFSA, 2010). Metabolites containing the *tert*-butylcyclohexanone moiety[5] (with group representative M13) should also be included in the residue definition for dietary risk assessment for fruit.

A new hydrolysis study simulating industrial and household food processing conditions indicated that spiroxamine may degrade pH dependently, although to a moderate extend. The main hydrolysis products (up to 23% applied radioactivity (AR)) were M28 (spiroxamine aminodiol) and M15 (*tert*-butylcyclohexanone) while significant proportions of unknown metabolites are not formed. M28 is the representative of group C and M15 is covered by group B. Therefore, a different residue definition for processed fruit commodities is not necessary.

The RMS proposed to set the residue definition for dietary risk assessment in fruit as

- Sum of spiroxamine and metabolites containing the aminodiol (N-ethyl-N-propyl-1,2-dihydroxy-3-amino-propane) and the *tert*-butylcyclohexanone moiety, expressed as spiroxamine (Germany, 2017, 2020).

[4] Also called group C metabolites with M28 as the group representative.
[5] Also called group B metabolites with M13 as the group representative.

However, since the toxicological effects of spiroxamine, M13 and M28 have proven to be qualitatively different based on the available studies, separate toxicological reference values were derived for these three compounds (see Section 1). EFSA acknowledges the view of the RMS that co-occurrence of residues with a different toxicological profile requires a type of hazard index (HI) approach to account for potential combination effects for the total residues that consumers will be exposed to. Yet, this is a novel (non-standard) approach introduced to the peer review, while following the conventional approach, the residue definition for risk assessment would consist of three different elements and require three separate risk assessment calculations due to the different toxicological profiles:

- Spiroxamine;
- Sum of 4-tert-butylcyclohexanol and its hydroxy-metabolites, their esters and conjugates, expressed as 4-tert-butylcyclohexanol (M13);
- Sum of metabolites containing the aminodiol (N-ethyl-N-propyl-1,2-dihydroxy-3-amino-propane) moiety, expressed as spiroxamine aminodiol (M28);

In the available residue field trials, a 'total residue' method was employed, in line with the provisional residue definition for risk assessment in fruit of 2010 (EFSA, 2010). This 'total residue' method for fruit determines all residues that are hydrolysable into M28, including spiroxamine and group A metabolites, while the new residue definition for fruit is composed of spiroxamine and two different breakdown structures that are counterparts of each other and are representing group B and group C metabolites, respectively. In the case where residues are analysed by a 'total residue' method, attribution of different residues to the individual toxicological reference values in order to conduct the consumer risk assessment is only possible with assumptions and approximations. Ideally, a sufficient number of residue trials should be available to determine separately the residues corresponding to the different parts of the residue definition for risk assessment in order conduct quantitative assessments against the different toxicity reference values (TRVs) for each of the parts of the residue definition. In the absence of such residue trial data, RMS estimated residue levels of group B metabolites in fruits by application of a conversion factor of 0.5 (grapes) and 0.33 (banana) to the 'total residue' determined in the field trials, and levels of group C metabolites based on the assumption that they were formed in equal amounts as group B metabolites.

In a conservative assessment (Tier 1), consumer exposure to all compounds included in the residue definition for risk assessment was calculated and compared to the ADI and ARfD of parent spiroxamine.

In a novel assessment approach (Tier 2), that was described as similar to the hazard index (HI) approach, RMS derived group specific exposure values, using several assumptions, which were compared with the corresponding TRVs.

The Tier 1 long-term dietary risk assessment conducted with PRIMo rev. 2 and rev. 3 indicated consumer exposure well below the ADI of spiroxamine (less than 20%), and a Tier 2 assessment was therefore not presented.

The Tier 1 acute dietary risk assessment conducted with PRIMo rev. 2 and rev. 3 indicated an acute risk for consumers arising from the representative use of spiroxamine in table grapes (108% and 120% ARfD of spiroxamine, respectively). The ARfD of spiroxamine is not exceeded for uses in wine grapes.

For the representative use in table grapes, an indicative refined acute risk assessment was conducted, considering the specific reference values for spiroxamine, group B and C metabolites in the HI approach (Tier 2). According to the RMS, the risk assessment with PRIMo rev. 2 and rev. 3 indicated acute consumer exposure to residue in table grapes below the individual ARfD and a HI less than 1.

EFSA remarks that the different calculations/estimations and conversion factors derived with regard to the novel assessment approach (Tier 2) are not reproducible down to the last detail, and that the results obtained by this approach are surrounded by several non-standard uncertainties. Based on available information from metabolism studies, it had previously been concluded that in fruit, group B and group C metabolites were observed in similar proportions as spiroxamine (EFSA, 2010). It is therefore reasonable to assume that the acute intake assessment for table grapes, when considering group B, group C and spiroxamine residues separate, is unlikely to result in the exceedance of the respective ARfDs; however, confirmation of this assumption by residue data is missing. Moreover, a general expert discussion on the acceptability of the HI concept applied by the RMS in the new assessment approach in routine assessments, using the example of spiroxamine, is desirable.

3. Ecotoxicology

As part of the confirmatory data, to refine the chronic risk to fish, a fish full life cycle test (FFLCT) with zebrafish under a pulsed exposure regime was submitted. The study was discussed at the Peer Review Experts' meeting TC 20 (June 2020). The experts considered that the study was not suitable for risk assessment as it presented several drawbacks. In particular, it was noted that due to the study design, some sensitive life stages were only exposed to very low concentrations of spiroxamine and delayed effects may not be fully covered. Hatching success, which was one of the most sensitive parameters in the other available fish full life cycle test (Tier 1 FFLCT under constant exposure with the same species), could not be assessed, due to the inclusion of sediment in the aquaria. The exposure in the test system was not compared with the predicted exposure profiles.

By using the available end point from the Tier 1 fish full life cycle test (under constant exposure), high risk was concluded for the representative uses in grapes for all the relevant FOCUS scenarios. For the representative uses on spring cereals, low risk was identified in four out of five relevant FOCUS scenarios and for winter cereals in two out of nine FOCUS scenarios by using step 4 PECsw with the implementation of 20-metre buffer zone.

During the Peer Review Experts' meeting TC 20 (June 2020), by an overall consideration of the available information, it was noted that data indicated a clear shift in sex ratio towards a male-biased sex ratio as well as a decrease in vitellogenin level in females (in the refined exposure study only observed in the group exposed as fertilised eggs).[6] On this basis, strong concerns were raised by the experts that spiroxamine may have an endocrine-disrupting Mode of Action (MoA). However, it is highlighted that the potential of spiroxamine to have endocrine-disrupting properties was not fully assessed i.e. it was not part of the requirements for confirmatory data.

4. Data gaps

No data gaps were identified.

5. Concerns

5.1. Issues that could not be finalised

An issue is listed as an issue that could not be finalised where 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[7], and where 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).

No issues that could not be finalised were identified.

5.2. Critical areas of concern

An issue is listed as a critical area of concern where 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 where this assessment does not permit to conclude 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 where the assessment at a higher tier level could not be finalised due to lack of information, and where the assessment performed at the lower tier level does not permit to conclude 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

[6] Similar decrease in VTG levels was also observed in the available fish screening assay. However, the validity of that study was questioned considering the poor performance of the control in terms of eggs per female per day.

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

effect on human or animal health or on groundwater or any unacceptable influence on the environment.

No critical areas of concern were identified.

6. Overview of the concerns identified for each representative use considered (Table 1)

Table 1: Overview of concerns

Representative use		Grape (FR, IT)	Wheat & Triticale	Rye	Barley & Oat
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				
	Assessment not finalised				
Risk to aquatic organisms	Risk identified	X (all Focus scenarios)	X (in 7 out of 9 relevant FOCUS scenarios for winter cereals and 1 out 5 for spring cereals)	X (in 7 out of 9 relevant FOCUS scenarios for winter cereals and 1 out 5 for spring cereals)	X (in 7 out of 9 relevant FOCUS scenarios for winter cereals and 1 out 5 for spring cereals)
	Assessment not finalised				

The superscript numbers relate to the numbered points indicated in Sections 5.1 and 5.2. Where there is no superscript number, see Sections 1–3 for further information.

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Abbreviations

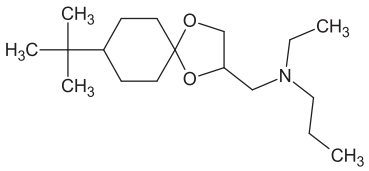
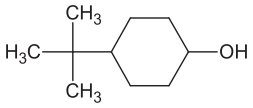
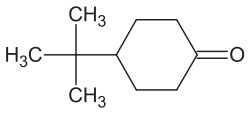
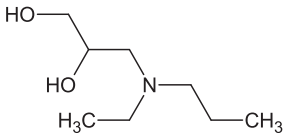
$1/n$	slope of Freundlich isotherm
λ	wavelength
ε	decadic molar extinction coefficient

ADI	acceptable daily intake
AR	applied radioactivity
ARfD	acute reference dose
bw	body weight
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
GAP	Good Agricultural Practice
HGPRT	Hypoxanthine-guanine phosphoribosyltransferase
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
mm	millimetre (also used for mean measured concentrations)
MoA	Mode of Action
NOEL	no observed effect level
OECD	Organisation for Economic Co-operation and Development
Pa	pascal
PD	proportion of different food types
PIE	potential inhalation exposure
PPE	personal protective equipment
QSAR	quantitative structure–activity relationship
SC	suspension concentrate
SMILES	simplified molecular-input line-entry system
TK	technical concentrate
TRR	total radioactive residue

Appendix A – List of end points for the active substance and the representative formulation (relevant for the current assessment)

Appendix A can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2021.6385

Appendix B – Used compound codes

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
spiroxamine	(*RS*)-*N*-[(8-*tert*-butyl-1,4-dioxaspiro[4.5]dec-2-yl) methyl]-*N*-ethylpropylamine CC(C)(C)C1CCC2(CC1)OCC(CN(CC)CCC)O2 PUYXTUJWRLOUCW-UHFFFAOYSA-N	
M13 4-tert-butylcyclohexanol (PTBCOL)	4-*tert*-butylcyclohexanol CC(C)(C)C1CCC(O)CC1 CCOQPGVQAWPUPE-UHFFFAOYSA-N	
Spiroxamine-ketone **M15**	4-*tert*-butylcyclohexanone O=C1CCC(CC1)C(C)(C)C YKFKEYKJGVSEIX-UHFFFAOYSA-N	
Spiroxamine-aminodiol **M28** KWG 4168-aminodiol	(2*RS*)-3-[ethyl(propyl)amino]propane-1,2-diol CCCN(CC(O)CO)CC NLFUPHFCUKBMDH-UHFFFAOYSA-N	

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