CONCLUSION ON PESTICIDES PEER REVIEW

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

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Abstract

The conclusions of EFSA following the peer review of the initial risk assessments carried out by the competent authorities of the rapporteur Member State, Greece, and the co-rapporteur Member State, the United Kingdom, for the pesticide active substance etoxazole 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 etoxazole as an acaricide on pome fruits, plums, peaches, nectarines, apricots, cherries (sweet), citrus, grapes, strawberries, tomatoes/eggplants, cucurbits inedible peel, cotton seeds and ornamental plants. MRLs were assessed in strawberries, cucurbits inedible peel, plums, tomatoes and aubergines/eggplants. 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 identified.

Keywords: etoxazole, peer review, risk assessment, pesticide, acaricide

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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. Etoxazole 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), Greece, and the co-rapporteur Member State (co-RMS), the United Kingdom, received an application from Sumitomo Chemical Agro Europe S.A.S for the renewal of approval of the active substance etoxazole. In addition, Sumitomo Chemical Agro Europe S.A.S 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 (the United Kingdom), the European Commission and the European Food Safety Authority (EFSA) about the admissibility.

The RMS provided its initial evaluation of the dossier on etoxazole in the renewal assessment report (RAR), which was received by EFSA on 20 September 2016. 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, Sumitomo Chemical Agro Europe S.A.S, for comments on 4 November 2016. EFSA also provided comments. In addition, EFSA conducted a public consultation on the RAR. EFSA collated and forwarded all comments received to the European Commission on 6 January 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 and ecotoxicology.

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

The conclusions laid down in this report were reached on the basis of the evaluation of the representative uses of etoxazole as an acaricide on pome fruits, plums, peaches, nectarines, apricots, cherries, citrus, grapes, strawberries, tomatoes/eggplants, cucurbits inedible peel, cotton and ornamental plants, as proposed by the applicant. MRLs were assessed in strawberry, cucurbits inedible peel, plums, tomatoes and aubergines/eggplants. 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 uses of etoxazole according to the representative uses proposed at the European Union (EU) level result in a sufficient acaricidal efficacy against the target organisms.

In the area of identity, physical/chemical properties and analytical methods, data gaps were identified for a monitoring method for the determination of etoxazole residues in commodities with high oil content and for a method for monitoring of the etoxazole residues in body fluids.

In the area of mammalian toxicology and non-dietary exposure, further data are needed to address the phototoxic potential of etoxazole at ultraviolet B (UVB) ranges and the toxicological profile of dietary metabolites R-4 and R-7.

In the residue section, the consumer dietary risk assessment cannot be finalised considering the outstanding data to conclude on the residue definition for risk assessment for processed commodities and the fate of high persistent soil metabolites in rotational crops. Further data are requested on the magnitude of R-4 and R-7 residues in relevant processed commodities and on the fate of R-3, R-7 and R-8 in rotational crops. Information on etoxazole and metabolites residues in pollen and bee products is also requested. Information on the relative toxicity of each enantiomer of etoxazole and their potential degradation in plant and animal matrices was not given, and provide therefore an additional uncertainty with regard to the consumer exposure assessment (data gap). A chronic intake concern was not identified using the MRL proposals for the representative uses on plums, strawberries, tomatoes, aubergines/eggplants and cucurbits with inedible peel submitted in the framework of a MRL application (theoretical maximum daily intake (TMDI): 3.8% of acceptable daily intake (ADI), German child). The data gaps identified following the review of MRLs according to Article 12 of Regulation (EC) No 396/2005 have been addressed in the framework of the renewal.

A data gap was identified for a search of the scientific peer-reviewed open literature on the active substance and its relevant metabolites dealing with environmental fate and behaviour/environmental exposure.

The data available on environmental fate and behaviour are sufficient to carry out the required environmental exposure assessments at EU level for the representative uses, with the notable exception that information is missing regarding effect of water the treatment processes on the nature of the residues that might be present in surface water, when surface water is abstracted for drinking water. Consequently, the consumer risk assessment from the consumption of drinking water could not be finalised. The potential for groundwater exposure above the parametric drinking water limit of 0.1 μg/L consequent to the uses assessed, was assessed as low for etoxazole and all its soil metabolites identified as triggering a groundwater exposure assessment, in geoclimatic situations represented by all nine FOCUS groundwater scenarios.

In the area of ecotoxicology, some data gaps were identified for the risk assessment for bees. A high risk to aquatic invertebrates and to non-target arthropods was concluded for all representative uses of etoxazole. A high risk to soil mites was concluded for etoxazole for uses in tomato, cucurbit, ornamentals, pome/stone fruits, grapes, strawberry and cotton. For metabolite 2,6-difluorobenzamide, long-term risk cannot be concluded for small herbivorous mammals such as 'vole' for uses in pome and stone fruits, citrus, tomato, cucurbits and cotton. A low risk cannot be concluded for both birds and wild mammals from secondary poisoning for metabolite R-13.

A critical area of concern was identified in relation to the fact that etoxazole might be considered to exhibit persistent, bioaccumulative and toxic (PBT) properties. Decision makers will have to come to a view on this, in particular whether the weight of evidence indicates that etoxazole should be considered persistent (P) in this context.

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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 Greece and the co-RMS, the United Kingdom, received an application from Sumitomo Chemical Agro Europe S.A.S for the renewal of approval of the active substance etoxazole. In addition, Sumitomo Chemical Agro Europe S.A.S 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 (the United Kingdom), the European Commission and EFSA about the admissibility.

The RMS provided its initial evaluation of the dossier on etoxazole in the RAR, which was received by EFSA on 20 September 2016 (Greece, 2016). 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, Sumitomo Chemical Agro Europe S.A.S, for consultation and comments on 4 November 2016. EFSA also provided comments. In addition, EFSA conducted a public consultation on the RAR. EFSA collated and forwarded all comments received to the European Commission on 6 January 2017. At the same time, the collated comments were forwarded to the RMS for compilation and evaluation in the format of a reporting table. The applicant was invited to respond to the comments in column 3 of the reporting table. The comments and the applicant's response were evaluated by the RMS in column 3.

The need for expert consultation and the necessity for additional information to be submitted by the applicant in accordance with Article 13(3) of the Regulation were considered in a telephone conference between EFSA, the RMS and the co-RMS on 2 March 2017. On the basis of the comments received, the applicant's response to the comments and the RMS's evaluation thereof, it was concluded that additional information should be requested from the applicant, and that EFSA should conduct an expert consultation in the areas of mammalian toxicology, residues 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.

[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.

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 August 2017.

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 etoxazole as an acaricide on pome fruits, plums, peaches, nectarines, apricots, cherries, citrus, grapes, strawberries, tomatoes/eggplants, cucurbits inedible peel, cotton and ornamental plants, as proposed by the applicant. MRLs were assessed in strawberries, cucurbits, inedible peel, plums, tomatoes and aubergines/eggplants. 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 conclusion is the peer review report (EFSA, 2017), which is a compilation of the documentation developed to evaluate and address all issues raised in the peer review, from the initial commenting phase to the conclusion. The peer review report comprises the following documents, in which all views expressed during the course of the peer review, including minority views, where applicable, can be found:

- the comments received on the RAR;
- the reporting table (2 March 2017);
- the evaluation table (5 September 2017);
- the reports of the scientific consultation with Member State experts (where relevant);
- the comments received on the assessment of the additional information (where relevant);
- the comments received on the draft EFSA conclusion.

Given the importance of the RAR, including its revisions (Greece, 2017), and the peer review report, both documents are considered as background documents to this conclusion and thus are made publicly available.

It is recommended that this conclusion 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

Etoxazole is the ISO common name for (*RS*)-5-*tert*-butyl-2-[2-(2,6-difluorophenyl)-4,5-dihydro-1,3-oxazol-4-yl]phenetole (IUPAC).

The representative formulated product for the evaluation was 'ETOXAZOLE 11 SC', a suspension concentrate (SC) containing 110 g/L etoxazole.

The representative uses evaluated were foliar applications in pome and stone fruits, citrus, grapevine, cotton, strawberry (field and protected) tomato/eggplants (field and protected), cucurbits inedible peel and ornamentals against mites of the families Tetranychidae and Eriophyidae. Full details of the good agricultural practices (GAPs) can be found in the list of end points in Appendix A.

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

Conclusions of the evaluation

1. Identity, physical/chemical/technical properties and methods of analysis

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

The proposed specification for etoxazole is based on batch data from industrial scale production. The proposed minimum purity of the technical material is 948 g/kg. The batches used in the (eco)toxicological assessment support the original reference specification (see Sections 2 and 5). However, it should be noted that based on the data of the renewal procedure a higher minimum purity for the active substance and lower levels for some of the impurities could be set. There is no FAO specification available for etoxazole.

The assessment of the data package revealed no issues that need to be included as critical areas of concern with respect to the identity, physical, chemical and technical properties of etoxazole or the

representative formulation. The main data regarding the identity of etoxazole and its physical and chemical properties are given in Appendix A.

Adequate methods are available for the generation of pre-approval data required for the risk assessment. Although some of them did not meet the requirements of the relevant guidance document, they were still considered fit for purpose. Methods of analysis are available for the determination of the active substance in the technical material and in the representative formulation.

Etoxazole residues can be monitored in the commodities with high water and high acid content by the Quick, Easy, Cheap, Effective, Rugged, and Safe (QuEChERS) method using gas chromatography with mass spectrometry (GC–MS) with a limit of quantification (LOQ) of 0.01 mg/kg in both commodity groups. Etoxazole residues in dry commodities can be determined by liquid chromatography with tandem mass spectrometry (LC–MS/MS) with a LOQ of 0.01 mg/kg. A data gap for a method for monitoring of etoxazole residues in commodities with high oil content was identified. Etoxazole residues in food of animal origin can be determined by LC–MS/MS with a LOQ of 0.01 mg/kg in all animal matrices.

Etoxazole residues in soil and water can be monitored by LC–MS/MS with LOQs of 0.004 mg/kg and 0.10 μg/L, respectively. Appropriate gas chromatography with nitrogen–phosphorus detector (GC-NPD) method exists for monitoring etoxazole residues in air with a LOQ of 0.4 $\mu g/m^3$.

The method for monitoring of etoxazole in food of animal origin can be used for determination of etoxazole in body tissues. A data gap for a method for monitoring of the etoxazole residues in body fluids was identified.

2. Mammalian toxicity

The toxicological profile of the active substance etoxazole and its metabolites was discussed at the Pesticides Peer Review Teleconference 142 and assessed based on the following guidance documents: SANCO/221/2000-rev. 10-final (European Commission, 2003), SANCO/10597/2003-rev. 10.1 (European Commission, 2012a), Guidance on Dermal Absorption (EFSA PPR Panel, 2012) and Guidance on the Application of the CLP Criteria (ECHA, 2015).

To assess the toxicological profile of **active substance**, the applicant submitted a set of valid toxicity studies. The toxicity studies were considered to support both, the old and new technical specification for the active substance and associated impurities (see Section 1). Impurities are considered not relevant from the toxicological point of view. The toxicity studies were performed with the racemic mixture (i.e. two enantiomers).

In the toxicokinetics studies, etoxazole was rapidly absorbed. Oral absorption was estimated to be 52%. There was low evidence for accumulation. Excretion of etoxazole was predominantly through the faecal route. Etoxazole was extensively metabolised. Results from *in vitro* metabolism studies showed that qualitatively no unique human metabolite is expected. Quantitatively the results showed that there is some difference in the metabolic rate between human and rat and some preferential degradation of etoxazole enantiomers could be detected.

In the acute toxicity studies, the substance has low acute toxicity when administered orally, dermally or by inhalation to rats. It is not a skin or eye irritant or a skin sensitiser. Etoxazole is not phototoxic in the OECD 3T3 Neutral Red Uptake Phototoxicity Test (NRU-PT) test (OECD, 2004). The 3T3 NRU-PT test might not be the appropriate test for ultraviolet B (UVB) absorbers like etoxazole. This leads to a data gap.

In short-term oral toxicity studies with rats, mice and dogs, the target organs of toxicity included the liver in all species and also the prostate at higher dose levels in dogs. The dog was the most sensitive species. The relevant short-term oral no observed adverse effect level (NOAEL) is 5 mg/kg body weight (bw) per day (90-day and 1-year dog study).

Based on available genotoxicity studies, the substance is unlikely to be genotoxic *in vivo*.

In long-term oral toxicity and carcinogenicity studies with rats and mice, the target organ of toxicity is the liver. Etoxazole showed abnormal amelogenesis (incisors) and hyperplasia of bone tissue in rats at higher doses attributed to fluorosis. The rat was the most sensitive species. The relevant long-term NOAEL is 4 mg/kg bw per day (2-year rat). The carcinogenic potential of etoxazole was discussed during the experts' meeting: The majority of experts agreed that substance is not carcinogenic and considered testicular findings in rats not treatment related. No carcinogenic potential was observed in mice.

In the reproductive toxicity studies, an increased incidence of pup mortality was observed in the absence of substantial maternal toxicity. The effects might be initiated during the *in utero* development

of embryos as the effects were not observed after post-natal day 4. The severity of the effect, and whether classification for reproductive toxicity might be needed, was discussed by experts. The RMS and the majority of the experts did not support a classification for reproductive toxicity effects. NOAELs for parental and offspring are 24.5 mg/kg bw per day, whereas the reproductive NOAEL is 140 mg/kg bw per day.

In the developmental toxicity studies, there was no evidence of teratogenicity, and the relevant maternal NOAELs are 200 mg/kg bw per day for the rat and rabbit. The developmental NOAELs are 1,000 and 200 mg/kg bw per day, respectively, for the rat and the rabbit.

The substance did not show a neurotoxic potential in acute and short-term neurotoxicity studies in rats. The substance did not show an immunotoxic potential in the 4-week oral immunotoxicity study in rats.

Etoxazole is not classified or proposed to be classified as toxic for reproduction category 2 or carcinogenic category 2, in accordance with the provisions of Regulation (EC) No 1272/2008, and therefore, the conditions of the interim provisions of Annex II, Point 3.6.5 of Regulation (EC) No 1107/2009 concerning human health for the consideration of endocrine disrupting properties are not met. With regard to the scientific risk assessment, the majority of the experts agreed that the only evidence of potential endocrine disrupting properties was coming from studies in dogs where the effects on prostate were observed at the highest dose level tested; however, no further evidence from other species were observed. Results from ToxCast showed no exhibit androgenic, oestrogenic and thyroid activities. Overall, the experts agreed with the RMS not to consider etoxazole as an endocrine disruptor.

The existing reference values (European Commission, 2004) were maintained. The acceptable daily intake (ADI) is 0.04 mg/kg bw per day, on the basis of the relevant long-term NOAEL of 4 mg/kg bw in the 2-year study in rats based on liver toxicity at 64 mg/kg bw per day. An uncertainty factor (UF) of 100 was applied. An acute reference dose (ARfD) was not allocated and not needed. The systemic acceptable operator exposure level (AOEL) is 0.03 mg/kg bw per day on the basis of the relevant short-term NOAEL of 5 mg/kg bw per day in the 90-day study and the 1-year study in dogs based on liver toxicity at 23.5 mg/kg bw per day. An UF of 100 was applied. Correction factor of 52% for oral absorption is needed to derive the AOEL. The experts agreed that no acute acceptable operator exposure level (AAOEL) was needed for etoxazole.

The RMS estimated the **non-dietary exposure** considering dermal absorption values of etoxazole in 'ETOXAZOLE 11 SC' of 0.04 % for the concentrate and of 5 % for the dilution as input values. Non-dietary exposure scenarios for all representative uses were below the AOEL for all exposure groups (operators, workers, bystander and residents). For some scenarios, operators should use personal protective equipment (PPE) as described in Section 8.

The dietary **metabolite** R-7 showed low acute oral toxicity study in rats and it was negative in the Ames test. No toxicity studies are available on the dietary metabolites R-4, 1, R-16 and R-20. The experts discussed whether the toxicological profile of these metabolites can be considered covered by the parent (as proposed by the RMS). The assumption was based on the results of quantitative structure–activity relationship (QSAR) analysis and the metabolic pathway in rats. The majority of experts considered that the information available is not sufficient and further data on all these metabolites would be needed if required in the section on residues. Considering the representative uses and final assessment by the section on residues (i.e. livestock metabolism studies not triggered) data gaps are only identified for metabolites R-4 and R-7 (both metabolites are relevant for processing, see Section 3).

The dietary metabolite 2,6-difluorobenzamide is a common metabolite of some active substances including diflubenzuron. During the peer review of diflubenzuron (EFSA, 2015), the toxicological profile of this metabolite was considered covered by parent diflubenzuron and therefore is considered unlikely to be genotoxic.

Etoxazole and the metabolites R-7 and R-4 are racemic mixtures. No information is available on the toxicity of each isomer; should isomerisation occur in residues, further assessment on potential changes in isomerisation ratio for dietary risk assessment should be done (see Section 3).

3. Residues

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

Etoxazole was discussed at the Pesticides Peer Review experts' TC 143 (June 2017).

From the residue data package, information is available regarding the rate of degradation of the two enantiomers of etoxazole in leaves of fruits and in cotton only where the *R* to *S* isomer ratio of etoxazole remained 1:1.

Metabolism of etoxazole was investigated after foliar application in the fruits (apples, oranges, aubergines) and pulses and oilseeds (cotton) crop groups using etoxazole ^{14}C-labelled on the *tert*-butylphenyl ring and the oxazole ring (fruit crops) and on the difluorophenyl ring and *tert*-butylphenyl ring (cotton). Etoxazole metabolism was also described in the leafy parts of citrus fruits, cotton and aubergines using etoxazole ^{14}C-labelled on the *tert*-butylphenyl ring only. In all fruit crops, etoxazole was the predominant compound of the total radioactive residues (TRR) at all sampling intervals and accounting for 41–95% TRR in apples, 36–94% TRR in oranges and 68.5–88.6% TRR in aubergines. In the leafy parts of the plants, most of the radioactivity remains in the surface rinse extract with etoxazole being the major compound of the residues (47–95% TRR). In cotton seed labelled with ^{14}C-difluorophenyl moiety, etoxazole was extensively degraded (5% TRR) while 2,6-difluorobenzamide compound was recovered at a significant proportion (20% TRR) although its actual concentration was very low (0.006 mg eq/kg) in the study conducted at *ca*. 2.7 N rate. Since this compound was found to be the precursor of metabolite R-11 (2,6-difluorobenzoic acid), a common terminal residue of the degradation pathway of etoxazole in all plant parts and also in the rat and in view of the label position on the oxazole ring (N-O bond), the experts' meeting agreed that 2,6-difluorobenzamide is not expected to be present in fruit crops and no additional data on the fate of the difluorophenyl ring moiety in fruit crops is needed. Etoxazole was therefore considered as a valid marker of the total residues in plants, and the residue definition for monitoring was limited to the parent compound only (sum of isomers). For risk assessment, the inclusion of the metabolite 2,6-difluorobenzamide compound in the residue definition for pulses and oilseeds was discussed during the peer review. Since this metabolite was considered as not genotoxic (see Section 2) and in view of its extremely low concentration (< 0.01 mg eq/kg), EFSA proposes not to include this metabolite in the residue definition for risk assessment. The proposed residue definitions for monitoring and risk assessment as etoxazole (sum of isomers) only are limited to fruits and pulses and oilseeds crops group following foliar treatment. Although a comparable metabolic pattern of etoxazole was observed in the leafy parts of citrus, aubergines and cotton, EFSA highlights that additional metabolism data on representative leafy crops should be requested in case additional uses on this crop category are applied for.

In a confined rotational crop metabolism study, the soil was treated once at a dose rate of 112 g a.s./ha (2 N) with ^{14}C-etoxazole labelled either on difluorophenyl ring or on the *tert*-butylphenyl ring. Radish, lettuce and wheat were planted at 30 and 120 days plant back intervals (PBIs). In the different crops investigated and at 30 days PBI, the TRR were < 0.01 mg/kg and no further analysis were conducted at longer PBIs. However and having regard to the moderate to high persistence of the soil metabolites R-3, R-7 and R-8, confined rotational crops metabolism data addressing the fate of these compounds in leafy, small grains and root crops and at the different plant back intervals should be provided (data gap).

Under standard hydrolysis conditions, etoxazole was degraded into R-7 metabolite under pasteurisation, baking/brewing and boiling (23.7% of the applied radioactivity (AR) and 28.7% AR, respectively) and into R-4 metabolite under sterilisation (26.4% AR). Currently, insufficient toxicological data are available on these compounds and are requested (see Section 2). Processing trials were submitted on apples, grapes, tomatoes and cotton analysing for etoxazole residues in processed commodities. Processing trials on apples and tomatoes analysed R-4 and R-7 compounds in apples puree/juice and in tomatoes paste/juice showing quantifiable residues of R-7 in apple puree (0.01–0.02 mg/kg), in tomatoes paste (0.03 mg/kg) and residue levels of R-4 in tomatoes paste (0.01 mg/kg). Additional processing residue trials on apples (pomace, wet), tomatoes (canned/cooked), grapes, stone fruits, citrus fruits and strawberries analysing for R-4 and R-7 residues are required (data gap). Meanwhile, the inclusion of R-4 and R-7 besides the parent compound in a separate residue definition for risk assessment for processed commodities is proposed and will be reconsidered pending the toxicity profile of R-4 and R-7 and their respective magnitude in the relevant processed matrices.

Sufficient residue trials were submitted to derive MRL proposals for all the representative uses and for the representative uses on plums, strawberries, tomatoes, aubergines/eggplants and cucurbits with inedible peel submitted in the framework of an MRL application. The submitted residue data are supported by acceptable storage stability studies.

A provisional livestock dietary burden calculation has been performed considering the magnitude of etoxazole residues only in cotton seed/meal, citrus (dried pulp) and apples pomace, wet and should be finalised once the magnitude of R-4 and R-7 residues in processed commodities has been addressed. Meanwhile and having regard to the estimated provisional livestock dietary intake, livestock metabolism data are not triggered. However, ruminant and poultry metabolism studies were conducted with ^{14}C-etoxazole labelled on the *tert*-butylphenyl and difluorophenyl rings, respectively. Etoxazole was found to be the major compound of the total residues in poultry fat (92% TRR), muscle (50–85.5% TRR) and in eggs yolk (62% TRR) while it was extensively degraded in liver (3% TRR) and in eggs white (22.5% TRR). The predominant compound of the total residues in liver was R-16 metabolite (58–66% TRR) and occurred also at a significant proportion in muscle (19% TRR). R-7 metabolite was predominant in eggs white only (24% TRR). The total residues were shown to be below 0.01 mg eq/kg in all ruminant matrices except in liver and kidney (0.230 and 0.938 mg eq/kg, respectively). The parent compound was extensively degraded in liver and accounted for only 3.8% TRR and was not detected in kidney. The major identified components in liver were R-20 (11.5% TRR), metabolite 1 (11.7% TRR) and two unidentified compounds (tBLi17, dFPLi3) detected at 14.5% and 33% TRR, respectively, while significant levels of metabolite 1 were recovered in kidney (81% TRR). In case of future uses with feed items leading to an increase of the dietary burden the validity of the studies should be reconsidered concerning the dosing period mainly for poultry, the deficiencies identified in terms of metabolites' identification in ruminant liver and the need for further toxicity data on the predominant metabolites recovered in all matrices. Meanwhile, residue definitions for monitoring and risk assessment for livestock matrices are not proposed and MRLs for animal matrices are not required according to the representative uses.

A fish metabolism study was not provided and is not requested as etoxazole residues in cotton seed are below the LOQ of the method (0.01 mg/kg) and the other representative uses are not feed items for fish.

Since grapes show attractiveness to bees for pollen and nectar collection (EFSA, 2013) and treatment can take place at flowering, residues of etoxazole and metabolites in pollen and bee products cannot be excluded and further information is requested (data gap). These data are not requested for the other representative uses where the treatment takes place after flowering.

For the time being, a provisional consumer dietary risk assessment can only be conducted considering the outstanding data to finalise the residue definition for risk assessment for processed commodities and the requested additional rotational crops metabolism data. A chronic intake concern was not identified using the MRL proposals for the representative uses (theoretical maximum daily intake (TMDI): 3.8% of ADI, German child). An acute dietary intake calculation was not carried out as the setting of an ARfD was not considered necessary (see Section 2). Information on the relative toxicity of each enantiomer of etoxazole and their potential degradation in plant and animal matrices was not given and provide therefore an additional uncertainty with regard to the consumer exposure assessment (data gap).

The toxicological reference values and the residue definition for both enforcement and risk assessment in primary crops have not been changed compared to those used in the review of the existing MRLs for etoxazole (EFSA, 2012). It is however not excluded that the established MRLs under Article 12 of Regulation (EC) No 396/2005 and the overall consumer dietary risk assessment may need to be revised pending upon the finalisation of the residue definition for risk assessment in processed commodities. The data gaps identified following the review of MRLs according to Article 12 of Regulation (EC) No 396/2005 have been addressed in the framework of the renewal.

4. Environmental fate and behaviour

A data gap was identified for a transparent evaluation of the applicant's literature search on the active substance and its metabolites reaching levels triggering an assessment, dealing with environmental fate and behaviour/environmental exposure and published within the last 10 years before the date of submission of dossier in accordance with the Guidance of EFSA on the submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009.

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, etoxazole exhibited moderate to medium persistence, forming the major (> 10% AR) metabolites R-3 (max. 10.4% AR, exhibiting low to medium persistence), R-4 (sum of isomers, max. 12% AR,

exhibiting low persistence), R-7 (sum of isomers, max. 24% AR, exhibiting very low to low persistence), R-8 (sum of isomers, max. 45% AR, exhibiting low to moderate persistence) and R-13 (sum of isomers, max. 23% AR, exhibiting medium to high persistence). The metabolite R-12 also reached levels that triggered consideration for exposure assessment (max. 8% AR, exhibiting low persistence). Mineralisation of the butylphenyl ring ^{14}C radiolabel to carbon dioxide accounted for 5.7–12.8% AR after 120 days with this value for the difluorophenyl ring ^{14}C radiolabel being 50% AR. The formation of unextractable residues (not extracted by methanol/water followed by acidified methanol and Soxhlet with acetone) for these radiolabels accounted for 10–33% AR after 120 days. The extracts from two of the aerobic soil incubations were analysed for etoxazole residues using chiral chromatography. The results from this analysis indicated that etoxazole residues remained as a racemic mixture, i.e. the R to S isomer ratio remained 1:1 as the incubations progressed. Chiral analysis results were not available for the other transformation products that have chiral centres. In anaerobic soil incubations etoxazole transformed more slowly than under aerobic conditions with the metabolite R-11 (not formed in aerobic investigations) accounting for up to 38% of AR. Under aerobic conditions R-11 exhibited low to moderate persistence. In a laboratory, 40% maximum water-holding capacity (MWHC) soil photolysis study transformation in irradiated soil was faster than in the dark control, but novel photometabolites were not identified accounting for more than 5% AR. The major photometabolites were R-3 and R-11 (max. both ca. 12% AR) with R-12 accounting for max 8% AR.

Etoxazole and R-3 exhibited slight mobility to being immobile in soil. R-13 was immobile, with R-7 exhibiting low mobility to being immobile. R-4 exhibited medium mobility, R-8 exhibited high to medium mobility, R-12 exhibited very high to high mobility and R-11 exhibited very high mobility. It was concluded that the soil adsorption of all these compounds was not pH dependent. In satisfactory field dissipation studies carried out at 4 sites in France and 1 each in the UK, Belgium, Spain and Italy and 3 sites in the USA (California, Mississippi and Idaho) (all spray application to the soil surface on bare soil plots in late spring) etoxazole exhibited low to moderate persistence. Sample analyses were carried out for the etoxazole and R-8 (sum of isomers) at the French sites. Samples were analysed for etoxazole, R-3, R-4 (sum of isomers), R-7 (sum of isomers), R-8 (sum of isomers), R-11, R-12 and R-13 (sum of isomers) at the other sites. Residues of R-4 and R-12 were never found above the limit of determination (USA sites)/quantification (European sites where analysed) [0.01/0.004 mg/kg]. Consequently following European Commission (2002) guidance, R-4 and R-12 have been excluded from the residue definitions triggering assessment of effects data on soil dwelling organisms. It was only possible to estimate dissipation kinetics for R-7 and R-13 (as sum of isomers) which exhibited moderate persistence and low persistence, respectively, results from just two trial sites for each metabolite. The peer review concluded field study DT_{50} and DT_{90} (period required for 50% or 90% dissipation) values could only be used as persistence endpoints representing transformation. They were not accepted as representing degradation rates for modelling due to it not being possible to evaluate the data in a way that photolysis would be excluded, in addition there was uncertainty regarding the normalisation of trial conditions to FOCUS reference conditions at the sites where sufficient information might have been available.

In laboratory incubations in dark aerobic natural sediment water systems, etoxazole moved to the sediment and exhibited medium persistence, forming the major metabolite R-13 (sum of isomers, max. ca. 13% AR in sediment). Mineralisation of the butylphenyl ring ^{14}C radiolabel to carbon dioxide accounted for 2–7% AR at study end (100 days) with this value for the difluorophenyl ring ^{14}C radiolabel being 14% AR. The unextractable sediment fraction (not extracted by methanol/water) was a sink for these radiolabels, accounting for 7–12% AR at study end. The extracts from a suspended sediment aerobic mineralisation study were analysed for etoxazole residues using chiral chromatography. The results from this analysis indicated that etoxazole residues remained as a racemic mixture, i.e. the R to S isomer ratio remained 1:1 as the incubation progressed. The rate of decline of etoxazole in a laboratory sterile aqueous photolysis experiment was enhanced compared to that which occurred in the dark aerobic sediment water incubations. Metabolite R-11 accounted for up to 64% AR, R-12 and R-15 both max. ca. 30% AR and R-3 12% AR. The necessary surface water and sediment exposure assessments (predicted environmental concentrations (PEC) calculations) were carried out for the metabolites R-3, R-4, R-7, R-8, R-11, R-12 and R-13, using the FOCUS (2001) step 1 and step 2 approaches (version 3.2 of the Steps 1-2 in FOCUS calculator). For the active substance etoxazole, appropriate step 3 (FOCUS, 2001) and step 4 calculations were available.[4] The step 4

[4] Simulations utilised the agreed Q10 of 2.58 (following EFSA, 2008) and Walker equation coefficient of 0.7.

calculations appropriately followed the FOCUS (2007) guidance, with just no-spray drift buffer zones of widths of up to 25 m being implemented (representing a 86.5–93.5% spray drift reduction).

The necessary groundwater exposure assessments were appropriately carried out using FOCUS (2009) scenarios and the models PEARL 4.4.4 and PELMO 5.5.3.[4] The potential for groundwater exposure from the representative uses by etoxazole and its soil metabolites, R-3, R-4, R-7, R-8, R-11, R-12 and R-13 above the parametric drinking water limit of 0.1 μg/L was concluded to be low in geoclimatic situations that are represented by all 9 FOCUS groundwater scenarios.

The applicant did not provide appropriate information to address the effect of water treatment processes on the nature of the residues that might be present in surface water, when surface water is abstracted for drinking water. This has led to the identification of a data gap (see Section 7) and results in the consumer risk assessment not being finalised (see Section 9).

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

With the available information etoxazole may be considered to fulfil the persistence (P) criterion in relation to its persistent, bioaccumulative and toxic (PBT) properties. This regards the soil transformation rate in one of the available investigations. In just one of the six available aerobic laboratory soil incubations, the half-life when normalised to 12°C was 157.4 days (soil trigger = 120 days). In the other five laboratory soil incubations, half-lives were less than 101.3 days (when normalised to 12°C), so below this trigger. In field dissipation studies (11 sites), the longest half-life was 23.2 days, so also below this trigger. Regarding the aquatic environmental compartment, transformation in the available OECD 309 aquatic mineralisation study with suspended sediment from a fresh water system, resulted in a half-life at 12°C of 86.4 days (sediment trigger for this system = 120 days). The relevant environmental condition is indicated as being 12°C when criteria in the relevant ECHA Guidance are followed (ECHA, 2014, 2017). A pertinent working document (European Commission, 2012b) did not provide definitive information on what would be considered relevant environmental conditions, just making reference to the fact that that conditions of the available investigations should be reported (which has been done here), that half-lives should not be aggregated and that a weight of evidence approach considering both laboratory and field studies should be used. (Note, if the ECHA guidance temperature is not adhered to and results for 20°C were considered as a relevant environmental condition, all the soil and sediment half-lives would be below the 120 day trigger.) The RMS disagrees that etoxazole may be considered to fulfil the persistence (P) criterion.

5. Ecotoxicology

The risk assessment was based on the following documents: European Commission (2002), SETAC (2001), EFSA (2009), EFSA PPR Panel (2013) and EFSA (2013). According to Commission Regulation (EU) No 283/2013[5], data should be provided regarding the acute and chronic toxicity to honeybees and data to address the development of honeybee brood and larvae. As the European Commission (2002) does not provide a risk assessment scheme which is able to use the chronic toxicity data for adult honeybees and the honeybee brood, when performing the risk assessment according to European Commission (2002), the risk to adult honeybees from chronic toxicity and the risk to bee brood, could not be finalised due to the lack of a risk assessment scheme. Therefore, the EFSA guidance document (EFSA, 2013) was used for risk assessment in order to reach a conclusion for the representative uses.

Etoxazole was discussed at the Pesticides Peer Review experts' TC 145 (July 2017).

Acute and chronic toxicity exposure ratios were calculated for the active substance etoxazole and its major plant metabolite 2,6-difluorobenzamide, which was identified in cotton seed. Based on the available data and the risk assessment, a low acute and long-term risk via dietary exposure to **birds** was concluded for all representative uses of etoxazole and its pertinent metabolite 2,6-difluorobenzamide. A low acute and long-term risk via dietary exposure to **wild mammals** was concluded for all representative uses of etoxazole. For metabolite 2,6-difluorobenzamide a low long-term risk cannot be concluded for vole for uses in pome/stone fruits, citrus, tomato, cucurbits and cotton (data gap). A low risk for both birds and wild mammals was also concluded from secondary poisoning and from exposure via contaminated water with residues of etoxazole and its metabolites R-3, R-4 and R-7 following application of 'ETOXAZOLE 11 SC' according to the proposed uses. For metabolite R-13 a low risk cannot

[5] Commission Regulation (EU) No 283/2013 of 1 March 2013 setting out the data requirements for active substances, 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. OJ L 93, 3.4.2013, p. 1–84.

be concluded for both birds and wild mammals from secondary poisoning for all representative uses (data gap).

Etoxazole is a racemic mixture of two stereoisomers. Fate and behaviour data indicated that parent etoxazole residues in both soil and natural water systems would be expected to remain as the racemic mixture (see Section 4) so standard approaches to risk characterisation were used for the parent risk assessments. For metabolites that have a chiral centre (R-7, R-8, R-13 and (R-4 water only)), an additional factor of 2 was considered in risk characterisations to account for the uncertainty that the isomer composition of these transformation products in soil and natural water systems was unknown.

For **aquatic organisms**, a low acute and chronic risk to fish, algae and sediment dwelling species was concluded for all representative uses of etoxazole using PEC_{sw} calculated with FOCUS Steps 1-2 and 3. A high risk to **aquatic invertebrates** was concluded for all representative uses of 'ETOXAZOLE 11 SC' (data gap).

The available microcosm study was discussed at the Pesticides Peer Review experts' TC 145. It was agreed that the study cannot be used for refining the risk assessment due to some identified shortcomings, e.g. high temperatures. Its representativeness for Southern EU could, therefore, be considered further at Member States level.

The risk to aquatic organisms from etoxazole metabolites (R-3, R-4, R-7, R-8, R-11, R-12, R-13 and R-15) was considered low using FOCUS Step 1 exposure estimates for all the proposed uses.

The RMS has assessed the risk to **honeybees** in accordance with the bee guidance document (EFSA, 2013). A low risk to adult (acute oral, acute contact, and chronic) honey bees was concluded at the screening step for all representative uses of etoxazole.

The chronic risk assessment for larvae was not performed (data gap). The risk assessment for consumption of contaminated water was not performed (data gap). No assessment was available for sublethal effects on hypopharyngeal glands (HPG) (data gap). No assessment for accumulative effects was available. No information was available regarding metabolites occurring in pollen and nectar (data gap). No data were available for **bumblebees** and **solitary bees**.

Toxicity data are available for five species of non-target arthropods (*Typhlodromus pyri*, *Aphidius rhopalosiphi*, *Coccinella septempunctata*, *Orius laevigatus* and *Chrysoperla carnea*). High risk was identified at Tier I for **non-target arthropods**.

Further refinements were proposed by the applicant, however the experts at the Pesticides Peer Review experts' TC 145, did not consider them as valid and therefore a high risk was still concluded for all the representative uses (data gap).

Experimental data for etoxazole and all the pertinent soil metabolites (R-3, R-7, R-8, R-11 and R-13) were available for **earthworms** and other **soil macroorganisms**. On the basis of these data, the acute and long-term risk of etoxazole and its metabolites is low for earthworms and collembolan following the representative uses of 'ETOXAZOLE 11 SC'.

For predatory mite (*Hypoaspsis aquleifer*), the long-term risk of etoxazole is low only for the representative uses in citrus, high risk was concluded for the representative uses in tomato, cucurbit, ornamentals, pome/stone fruits, grapes, strawberry and cotton (data gap). The long-term risk of etoxazole metabolites to soil mites is low for all representative uses.

Experimental data for etoxazole were available for **soil microorganisms** and a low risk was concluded for all the representative uses of 'ETOXAZOLE 11 SC'. For metabolites (R-3, R-7, R-8, and R-13), it was concluded that exposure of soil micro-organisms was covered by the parent as they are formed relatively rapidly and their toxicity may be exerted in the tests on the parent compound. For metabolite R-11, the risk assessment was conducted assuming ten times higher toxicity than the parent compound and a low risk was concluded for all the representative uses of 'ETOXAZOLE 11 SC'.

The risk assessment for **non-target terrestrial plants** was based on the endpoints derived from studies with etoxazole for one seedling emergence and one for vegetative vigour. On the basis of these data, a low risk was concluded for 'ETOXAZOLE 11 SC' in grapes, fruiting vegetables (tomato, cucurbit), ornamentals, strawberry and cotton, provided that a 3 m unsprayed zone is maintained, and in pome/stone fruits and citrus, provided that a 5 m unsprayed buffer zone is maintained or 50% drift reducing nozzles are used.

Experimental data for etoxazole were available for **biological methods of sewage treatment** and on the basis of these data a low risk was concluded for all representative uses.

With regard to the endocrine disruption potential, as discussed in Section 2, it is unlikely that etoxazole is an **endocrine disruptor** in mammals; however, no firm conclusion can be drawn regarding fish, birds and amphibians.

With the available information, etoxazole is considered to fulfil the bioaccumulation (B) and toxic (T) criteria in relation to its PBT properties. The agreed experimental endpoints for bioaccumulation of etoxazole in fish are bioconcentration factors (BCF) of 2,500 and 3,300, which are higher than the criterion value of a BCF of 2,000. The long-term no-observed effect concentrations for aquatic invertebrates (0.00013 mg/L *Daphnia magna* and 0.00032 mg/L *Americamysis bahia*) are less than 0.01 mg/L. These facts along with etoxazole possibly also being persistent (P) (see Section 4) means EFSA has identified a critical area of concern, to ensure that decision makers are aware they need to come to a view on the weight of evidence and the relevant environmental conditions when deciding whether etoxazole is P.

6. Overview of the risk assessment of compounds listed in residue definitions triggering assessment of effects data for the environmental compartments (Tables 1–4)

Table 1: Soil

Compound (name and/or code)	Persistence[(a)]	Ecotoxicology
Etoxazole (racemate)	Very low to medium persistence Single first-order DT_{50} 10.4–74.1 days (20°C pF 2 or 40% MWHC soil moisture) When normalised to 12°C the single first-order DT_{50} from a single laboratory incubation exceeds 120 days (DT_{50} 157 days) Field dissipation studies single first-order and biphasic kinetics DT_{50} 0.48–23.2 days (DT_{90} 8.4–77.2 days)	High risk to soil organisms (mites)
R-3	Low to medium persistence Single first-order and biphasic kinetics DT_{50} 9.2–89 days (DT_{90} 92–296 days, 20°C 30–68% MWHC)	Low risk to soil organisms
R-7 (sum of isomers)	Very low to moderate persistence Single first-order and biphasic kinetics DT_{50} 0.21–0.49 days (DT_{90} 2.4–11 days, 20°C 20–45% MWHC) Field dissipation studies single first-order DT_{50} 20–32 days	Low risk to soil organisms
R-8 (sum of isomers)	Low to moderate persistence Biphasic kinetics DT_{50} 2.2–6.5 days (DT_{90} 7.2–167 days, 20°C 20–45% MWHC)	Low risk to soil organisms
R-11	Low to moderate persistence Single first-order DT_{50} 7.9–14.5 days (24°C soil moisture not reported)	Low risk to soil organisms
R-13 (sum of isomers)	Low to high persistence Single first-order and biphasic kinetics DT_{50} 42–206 days (DT_{90} 318–812 days, 20°C 30–68% MWHC) Field dissipation studies biphasic kinetics DT_{50} 2–3 days (DT_{90} 10–18 days)	Low risk to soil organisms

DT_{50}: period required for 50% dissipation; DT_{90}: period required for 90% dissipation; MWHC: maximum water-holding capacity.
(a): The descriptors (in words) used here are unrelated to the 'P' assessment comparison to 'P' triggers in PBT, vPvB and POP hazard cut offs.

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
Etoxazole (racemate)	Slight mobility to immobile K_{Foc} 4,910–11,000 mL/g	No	Yes	Yes
R-3	Slight mobility to immobile K_{Foc} 3,359–6,295 mL/g	No	No	Assessment not triggered

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
R-4 (sum of isomers)	Medium mobility K_{Foc} 216–360 mL/g	No	No	Assessment not triggered
R-7 (sum of isomers)	Low mobility to immobile K_{Foc} 1,125–7,540 mL/g	No	No	Assessment not triggered
R-8 (sum of isomers)	High to medium mobility K_{Foc} 103–351 mL/g	No	No	Assessment not triggered
R-11	Very high mobility K_{Foc} 23–46 mL/g	No	No	Assessment not triggered
R-12	Very high to high mobility K_{Foc} 6–95 mL/g	No	No	Assessment not triggered
R-13 (sum of isomers)	Immobile K_{Foc} 13,670–83,230 mL/g	No	No	Assessment not triggered

K_{Foc}: Freundlich organic carbon adsorption coefficient.
(a): FOCUS scenarios or a relevant lysimeter.

Table 3: Surface water and sediment

Compound (name and/or code)	Ecotoxicology
Etoxazole (racemate)	High risk to aquatic invertebrates
R-3	Low risk to aquatic organisms
R-4 (sum of isomers)	Low risk to aquatic organisms
R-7 (sum of isomers)	Low risk to aquatic organisms
R-8 (sum of isomers)	Low risk to aquatic organisms
R-11	Low risk to aquatic organisms
R-12	Low risk to aquatic organisms
R-13 (sum of isomers)	Low risk to aquatic organisms
R-15	Low risk to aquatic organisms

Table 4: Air

Compound (name and/or code)	Toxicology
Etoxazole	Low acute toxicity by inhalation to rats (LC_{50} > 1.09 mg/L (whole body, max. attainable concentration))

LC_{50}: lethal concentration, median.

7. 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).

- A method for monitoring of etoxazole residues in commodities with high oil content (relevant for a specific representative use evaluated (cotton); submission date proposed by the applicant: unknown; see Section 1).
- A method for monitoring of the etoxazole residues in body fluids (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 1).
- Further phototoxicity assessment on etoxazole at UVB ranges since current OECD Test Guidelines might not be appropriate to UVB absorbers as etoxazole (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- Further data to address the toxicological profile of dietary metabolites R-4 and R-7 (relevant for processing uses; submission date proposed by the applicant: unknown; see Sections 2 and 3).
- The potential changes in isomerisation for dietary risk assessment (relevant for all representative uses; submission date proposed by the applicant: unknown; see Sections 2 and 3).
- Processing residue trials on apples (pomace, wet), tomatoes (canned/cooked), grapes, stone fruits, citrus fruits and strawberries analysing for R-4 and R-7 residues (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).
- Confined rotational crops metabolism studies addressing the fate of R-3, R-7 and R-8 in leafy crops, small grains crops and root crops (relevant for the representative uses on cotton, tomatoes, aubergines/eggplants, cucurbits inedible peel evaluated; submission date proposed by the applicant: 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 with regard to etoxazole and metabolites residues (relevant for the representative use on grapes evaluated; submission date proposed by the applicant: unknown; see Section 3).
- A transparent evaluation of the applicants literature search on the active substance and its metabolites reaching levels triggering an assessment, dealing with environmental fate and behaviour/environmental exposure and published within the last 10 years before the date of submission of dossier in accordance with the Guidance of EFSA on the submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (EFSA, 2011) was not available (relevant for all representative uses evaluated; information is already contained within the applicant's dossier; see Section 4).
- Information to address the effect of water treatment processes on the nature of the residues present in surface water, when surface water is abstracted for drinking water was not available. In the first instances, a consideration of the processes of ozonation and chlorination would appear appropriate. If an argument is made that concentrations at the point of abstraction for drinking water purposes will be low, this argumentation should cover metabolites, as well as the active substance. Should this consideration indicate novel compounds might be expected to be formed from water treatment, the risk to human or animal health through the consumption of drinking water containing them should be addressed (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 4).
- Information to assess the chronic risk to honeybees larvae should be provided (relevant for all representative uses evaluated; submission date proposed by the applicants: unknown; see Section 5).
- Based on EFSA (2013), a suitable risk assessment for bees exposed to etoxazole via consumption of contaminated water (relevant for all representative uses evaluated; submission date proposed by the applicants: unknown; see Section 5).
- Based on EFSA (2013), suitable data to address the risk of sublethal effects (i.e. HPG development effects) to honeybees due to exposure to etoxazole should be provided (relevant

for all representative uses evaluated; submission date proposed by the applicants: unknown; see Section 5).

- Information to assess the risk to honeybees due to plant metabolites occurring in pollen and nectar should be provided (relevant for all representative uses evaluated; submission date proposed by the applicants: unknown; see Section 5).
- Further information to refine the risk assessment for small herbivorous mammal 'vole' are needed for metabolite 2,6-difluorobenzamide (relevant representative uses tomato, cucurbit, ornamentals, pome/stone fruits and cotton; submission date proposed by the applicants: unknown; see Section 5).
- Further information to refine the risk assessment birds and wild mammals from secondary poisoning are needed for metabolite R-13 (relevant for all representative uses evaluated; submission date proposed by the applicants: unknown; see Section 5).
- Further information to refine the aquatic risk assessment for aquatic invertebrates are needed (relevant for all representative uses evaluated; submission date proposed by the applicants: unknown; see Section 5).
- Further information to refine the risk assessment for non-target arthropods are needed (relevant for all representative uses evaluated; submission date proposed by the applicants: unknown; see Section 5).
- Further information to refine the risk assessment for soil mites are needed (relevant representative uses tomato, cucurbit, ornamentals, pome/stone fruits, grapes, strawberry and cotton; submission date proposed by the applicants: unknown; see Section 5).

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

- Considering outdoor representative uses on tomato and eggplant and hand-held application, operator exposure is below the AOEL if gloves during mixing/loading and gloves and impermeable coverall are used during application according to the UK POEM. This scenario will also cover outdoor application on strawberry, cucurbit, cotton and low ornamentals (see Section 2).
- Considering indoor representative uses on tomato and eggplant, operator exposure is below the AOEL if gloves and coverall are used according to the NL glasshouse model. This scenario will also cover indoor application on strawberry (see Section 2).
- A low risk was concluded for 'ETOXAZOLE 11 SC' in grapes, fruiting vegetables (tomato, cucurbit), ornamentals, strawberry and cotton, provided that a 3 m unsprayed zone is maintained, and in pome/stone fruits and citrus, provided that a 5 m unsprayed buffer zone is maintained or 50% drift reducing nozzles are used (see Section 5).

9. Concerns

9.1. Issues that could not be finalised

An issue is listed as 'could not be finalised' if there is not enough information available to perform an assessment, even at the lowest tier level, for 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[6] 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) Potential changes in isomerisation for dietary risk assessment cannot be finalised (see Sections 2 and 3).

[6] 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.

2) The consumer dietary risk assessment cannot be finalised considering the outstanding data to conclude on the residue definition for risk assessment for processed commodities and the fate of persistent soil metabolites in rotational crops (see Section 3).
3) 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).

9.2. Critical areas of concern

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

An issue is also listed as a critical area of concern if the assessment at a higher tier level could not be finalised due to lack of information, and if the assessment performed at a 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.

4) The available evidence cannot exclude that etoxazole might be considered a persistent (P), bioaccumulative (B) and toxic (T) or PBT substance. The P criterion may be considered fulfilled for soil, although the evidence for this is from the results of just one of a number of available soil investigations (see Section 4). The B criterion is fulfilled. The T criterion is fulfilled considering the available reliable data regarding the toxicity exerted by etoxazole on aquatic invertebrate species (see Section 5).
5) High risk was concluded for aquatic invertebrates for all representative uses (see Section 5).
6) High risk was concluded for non-target arthropods for all representative uses evaluated (see Section 5).
7) High risk was concluded for soil mites for representative uses in tomato, cucurbit, ornamentals, pome/stone fruits, grapes, strawberry and cotton (see Section 5).

9.3. Overview of the concerns identified for each representative use considered

(If a particular condition proposed to be taken into account to manage an identified risk, as listed in Section 8, has been evaluated as being effective, then 'risk identified' is not indicated in Table 5.)

Table 5: Overview of concerns

Representative use		**Pome and stone fruits**	**Citrus**	**Grapevine**	**Strawberries field**	**Strawberries protected**	**Tomatoes / eggplants field**	**Tomatoes / eggplants protected**	**Cucurbits inedible peel**	**Cotton**	**Ornamentals**
Operator risk	Risk identified										
	Assessment not finalised										

Representative use		Pome and stone fruits	Citrus	Grapevine	Strawberries field	Strawberries protected	Tomatoes / eggplants field	Tomatoes / eggplants protected	Cucurbits inedible peel	Cotton	Ornamentals
Worker risk	Risk identified										
	Assessment not finalised										
Resident/ bystander risk	Risk identified										
	Assessment not finalised										
Consumer risk	Risk identified										
	Assessment not finalised	X[1,2,3]	X[1,2,3]	X[1,2,3]	X[1,2,3]	X[1,2,3]	X[1,2,3]	X[1,2,3]	X[1,2,3]	X[3]	X[3]
Risk to wild non-target terrestrial vertebrates	Risk identified										
	Assessment not finalised										
Risk to wild non-target terrestrial organisms other than vertebrates	Risk identified	X[6,7]	X[6]	X[6,7]	X[6,7]	X[6,7]	X[6,7]	X[6,7]	X[6,7]	X[6,7]	X[6,7]
	Assessment not finalised										
Risk to aquatic organisms	Risk identified	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]
	Assessment not finalised										
Groundwater exposure to active substance	Legal parametric value breached										
	Assessment not finalised										
Groundwater exposure to metabolites	Legal parametric value breached										
	Parametric value of 10 µg/L[(a)] breached										
	Assessment not finalised										

Columns are grey if no safe use can be identified. The superscript numbers relate to the numbered points indicated in Sections 9.1 and 9.2. Where there is no superscript number, see Sections 2–6 for further information.
(a): Value for non-relevant metabolites prescribed in SANCO/221/2000-rev. 10 final, European Commission, 2003.

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Abbreviations

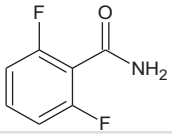
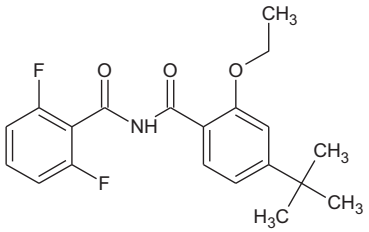
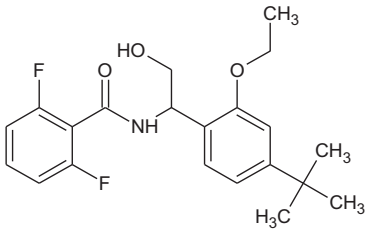
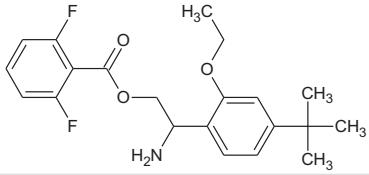
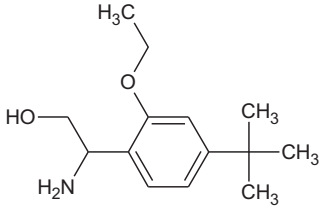
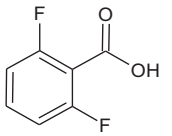
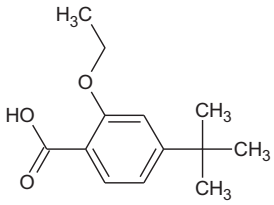
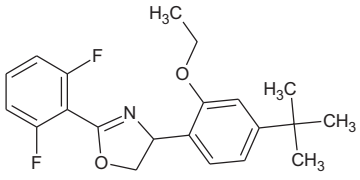
a.s.	active substance
AAOEL	acute acceptable operator exposure level
ADI	acceptable daily intake
AOEL	acceptable operator exposure level
AR	applied radioactivity
ARfD	acute reference dose
BCF	bioconcentration factor
bw	body weight
DAR	draft assessment report
DT_{50}	period required for 50% dissipation (define method of estimation)
DT_{90}	period required for 90% dissipation (define method of estimation)
ECHA	European Chemicals Agency
FAO	Food and Agriculture Organization of the United Nations
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
GAP	Good Agricultural Practice
GC–MS	gas chromatography with mass spectrometry
GC-NPD	gas chromatography with nitrogen–phosphorus detector
HPG	hypopharyngeal glands
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
JMPR	Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
K_{Foc}	Freundlich organic carbon adsorption coefficient
LC_{50}	lethal concentration, median
LC–MS/MS	liquid chromatography with tandem mass spectrometry
LOQ	limit of quantification
MRL	maximum residue level

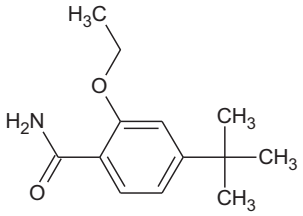
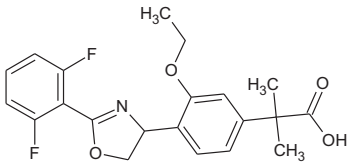
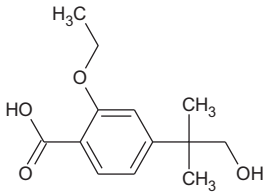
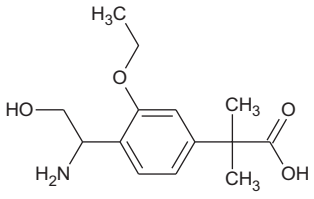
MS	mass spectrometry
MWHC	maximum water-holding capacity
NOAEL	no observed adverse effect level
NRU-PT	Neutral Red Uptake Phototoxicity Test
OECD	Organisation for Economic Co-operation and Development
PBI	plant back interval
PBT	persistent, bioaccumulative and toxic
PEC	predicted environmental concentration
PEC_{sw}	predicted environmental concentration in surface water
PPE	personal protective equipment
QSAR	quantitative structure–activity relationship
QuEChERS	Quick, Easy, Cheap, Effective, Rugged and Safe method
RAR	Renewal Assessment Report
REACH	Registration, Evaluation, Authorisation of Chemicals Regulation
RMS	rapporteur Member State
SC	suspension concentrate
SFO	single first order
SMILES	simplified molecular-input line-entry system
TMDI	theoretical maximum daily intake
TRR	total radioactive residue
UF	uncertainty factor
UVB	ultraviolet B
WHO	World Health Organization

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

Appendix A can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2017.4988

Appendix B – Used compound codes

Code/trivial name[a]	Chemical name/SMILES notation	Structural formula
2,6-Difluorobenzamide	2,6-difluorobenzamide O=C(N)c1c(F)cccc1F	
R-3	4-*tert*-butyl-*N*-(2,6-difluorobenzoyl)-2-ethoxybenzamide CCOc2cc(ccc2C(=O)NC(=O)c1c(F)cccc1F)C(C)(C)C	
R-4	*N*-[(1*RS*)-1-(4-*tert*-butyl-2-ethoxyphenyl)-2-hydroxyethyl]-2,6-difluorobenzamide CCOc2cc(ccc2C(CO)NC(=O)c1c(F)cccc1F)C(C)(C)C	
R-7	(2*RS*)-2-amino-2-(4-*tert*-butyl-2-ethoxyphenyl)ethyl 2,6-difluorobenzoate CCOc2cc(ccc2C(N)COC(=O)c1c(F)cccc1F)C(C)(C)C	
R-8	(2*RS*)-2-amino-2-(4-*tert*-butyl-2-ethoxyphenyl)ethanol CCOc1cc(ccc1C(N)CO)C(C)(C)C	
R-11	2,6-difluorobenzoic acid OC(=O)c1c(F)cccc1F	
R-12	4-*tert*-butyl-2-ethoxybenzoic acid CCOc1cc(ccc1C(=O)O)C(C)(C)C	
R-13	(4*RS*)-4-(4-*tert*-butyl-2-ethoxyphenyl)-2-(2,6-difluorophenyl)-4,5-dihydro-1,3-oxazole CC(C)(C)c1cc(OCC)c(cc1)C2N=C(OC2)c3c(F)cccc3F	

Code/trivial name[(a)]	Chemical name/SMILES notation	Structural formula
R-15	4-*tert*-butyl-2-ethoxybenzamide CCOc1cc(ccc1C(N)=O)C(C)(C)C	
R-16	2-{4-[(4*RS*)-2-(2,6-difluorophenyl)-4,5-dihydro-1,3-oxazol-4-yl]-3-ethoxyphenyl}-2-methylpropanoic acid O=C(O)C(C)(C)c1cc(OCC)c(cc1)C2N=C(OC2)c3c(F)cccc3F	
R-20	2-ethoxy-4-(1-hydroxy-2-methylpropan-2-yl) benzoic acid CCOc1cc(ccc1C(=O)O)C(C)(C)CO	
Metabolite 1	2-{4-[(1*RS*)-1-amino-2-hydroxyethyl]-3-ethoxyphenyl}-2-methylpropanoic acid CCOc1cc(ccc1C(N)CO)C(C)(C)C(=O)O	

SMILES: simplified molecular-input line-entry system.
(a): The compound name in bold is the name used in the conclusion.