**Modification of the existing maximum residue levels for etridiazole in various crops**

In accordance with Article 6 of Regulation (EC) No 396/2005, the evaluating Member State (EMS), the Netherlands, received an application from Arysta LifeScience Great Britain Limited to modify the existing maximum residue levels (MRLs) for the active substance etridiazole in various crops. To accommodate for the intended uses of etridiazole, the Netherlands proposed to raise the existing MRLs from the limit of quantification (LOQ) of 0.05* mg/kg to 0.4 mg/kg in gherkin, courgette and other cucurbits with edible peel, and to raise the existing MRL value of 0.1 mg/kg to 0.4 mg/kg in cucumber. The Netherlands drafted an evaluation report in accordance with Article 8 of Regulation (EC) No 396/2005, which was submitted to the European Commission and forwarded to EFSA. Although the intended uses on gherkin, courgette and other cucurbits with edible peel are supported by residue trials, EFSA did not derive MRL proposals because appropriate information on the toxicological profile and on the relevance of the major plant metabolites 5-hydroxyethoxyetridiazole acid and 3-hydroxymethyletridiazole has not been provided. Thus, the tentative risk assessment is affected by a high degree of uncertainty.

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**Keywords:** etridiazole, cucumber, gherkin, courgette, cucurbits with edible peel, MRL application, consumer risk assessment

**Requestor:** European Commission

**Question number:** EFSA-Q-2016-00123

**Correspondence:** pesticides.mrl@efsa.europa.eu
Suggested citation: EFSA (European Food Safety Authority), Brancato A, Brocca D, De Lentdecker C, Erdos Z, Ferreira L, Greco L, Jarrah S, Kardassi D, Leuschner R, Lythgo C, Medina P, Miron I, Molnar T, Nougadere A, Pedersen R, Reich H, Sacchi A, Santos M, Stanek A, Sturma J, Tarazona J, Theobald A, Vagenende B, Verani A and Villamar-Bouza L, 2017. Reasoned opinion on the modification of the existing maximum residue levels for etridiazole in various crops. EFSA Journal 2017;15(3):4736, 19 pp. doi:10.2903/j.efsa.2017.4736

ISSN: 1831-4732

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

In accordance with Article 6 of Regulation (EC) No 396/2005, the evaluating Member State (EMS), the Netherlands, received an application from Arysta LifeScience Great Britain Limited to modify the existing maximum residue levels (MRLs) for the active substance etridiazole in various crops. To accommodate for the intended uses of etridiazole, the Netherlands proposed to raise the existing MRLs from the limit of quantification (LOQ) of 0.05* mg/kg to 0.4 mg/kg in gherkin, courgette and other cucurbits with edible peel, to raise the existing MRL value of 0.1 mg/kg to 0.4 mg/kg in cucumber.

The Netherlands drafted an evaluation report in accordance with Article 8 of Regulation (EC) No 396/2005, which was submitted to the European Commission and forwarded to the European Food Safety Authority (EFSA) on 5 February 2016.

EFSA bases its assessment on the evaluation report submitted by the EMS, the draft assessment report (DAR) (its additional report and its final addendum) prepared under Council Directive 91/414/EEC, the Commission review report on etridiazole, as well as the conclusion on the peer review of the pesticide risk assessment of the active substance etridiazole and the consultation on the pesticide risk assessment of confirmatory data for the active substance etridiazole.

The toxicological profile of etridiazole was assessed in the framework of the peer review under Directive 91/414/EEC and the data were sufficient to derive an acceptable daily intake (ADI) of 0.015 mg/kg body weight (bw) per day and an acute reference dose (ARfD) of 0.15 mg/kg bw. The consumer risk assessment could not be performed during the EU pesticides peer review of etridiazole because appropriate information on the toxicological profile and relevance of the major plant metabolites 5-hydroxyethoxyetridiazole acid and 3-hydroxymethyletridiazole was not available.

Etridiazole was included in Annex I to Directive 91/414/EEC on 1 June 2014 by Commission Directive 2011/29/EU, and has been deemed to be approved under Regulation (EC) No 1107/2009, in accordance with Commission Implementing Regulation (EU) No 540/2011, as amended by Commission Implementing Regulation (EU) No 541/2011. It was a specific provision of the approval that the applicant was required to submit further studies, including on the relevance of the major plant metabolites 5-hydroxyethoxyetridiazole acid and 3-hydroxymethyletridiazole.

The confirmatory data included new toxicological studies on 5-hydroxyethoxyetridiazole acid and the RMS evaluation in the Post Inclusion Addendum to the DAR concluded that 5-hydroxyethoxyetridiazole acid is mutagenic in the mouse lymphoma test system. In vitro or in vivo toxicological studies were not provided for the metabolite 3-hydroxymethyletridiazole. EFSA concluded in its technical report that insufficient toxicological information was provided on the major plant metabolites 5-hydroxyethoxyetridiazole acid and 3-hydroxymethyletridiazole. Regarding 5-hydroxyethoxyetridiazole acid, the genotoxic potential could not be concluded since positive results were obtained in an in vitro gene mutation test, which are supported by a quantitative structure–activity relationship (QSAR) analysis. With regard to 3-hydroxymethyletridiazole, no toxicological information has been submitted; the genotoxicity alerts found with 5-hydroxyethoxyetridiazole acid would be relevant to 3-hydroxymethyletridiazole based on the structural similarity between the two metabolites. Additionally, information regarding the repeated-dose toxicity, relevant to consumer exposure, is not available for either of the two metabolites, and thus, it cannot be established whether these metabolites would be of similar, lower or higher toxicity than the parent etridiazole.

The Standing Committee on the Plants, Animals, Food and Feed decided that the plant metabolites 5-hydroxyethoxyetridiazole acid and 3-hydroxymethyletridiazole are not considered toxicologically relevant and therefore should not be included in the residues definition for plants.

The metabolism of etridiazole in primary crops was investigated in the fruit crop group (cucumber; substrate grown, drip application) and in the oilseed crop group (cotton, soil treatment, informative only). From these studies, the peer review established the residue definition for enforcement and for risk assessment as: sum of etridiazole, 3-hydroxymethyletridiazole (and its conjugates) and 5-hydroxyethoxyetridiazole acid (provisional, pending conclusion on the toxicological profile of these two metabolites) (fruit crops only). For the uses on cucumber, gherkin, courgette and other cucurbits with edible peel, EFSA concludes that the metabolism of etridiazole in primary crops has been sufficiently addressed.

EFSA concludes that the submitted residue trials are sufficient to calculate a theoretical MRL of 0.40 mg/kg on cucumber; this proposal refers to the current residue definition established in Regulation (EC) No 396/2005 which covers only parent etridiazole. Adequate analytical enforcement methods are available to monitor the residues of etridiazole in plant matrices on the commodities under consideration at the validated LOQ of 0.01 mg/kg.
Studies investigating the nature and magnitude of etridiazole residues in processed commodities are not available. Considering that the total theoretical maximum daily intake (TMDI) from etridiazole in commodities that can be cooked (courgette) is below the trigger value of 10% of the ADI, this information is not required according to the data requirements.

As the proposed uses of etridiazole are on crops grown on artificial substrate, investigations of residues in rotational crops are not required.

Residues of etridiazole in commodities of animal origin were not assessed since the crops under consideration in this MRL application are normally not fed to livestock.

The consumer risk assessment was performed with revision 2 of the EFSA Pesticide Residues Intake Model (PRIMo). The risk assessment is affected by a higher degree of uncertainty due to the provisional residue definition for risk assessment and since the toxicological relevance of the plant metabolites 5-hydroxyethoxyetridiazole acid and 3-hydroxymethyletridiazole was not sufficiently addressed. A tentative risk assessment has been performed which is based on the risk management conclusion that the metabolites are considered not genotoxic and the approach postulates the metabolites being of similar toxicity as the parent compound. Based on the tentative risk assessment performed according to the assumptions described, the intended use of etridiazole on cucumber, gherkin, courgette and other cucurbits with edible peel did not result in a consumer exposure exceeding the toxicological reference values.

EFSA considers that the intended uses of etridiazole on cucumber, gherkin, courgette and other cucurbits with edible peel in the current MRL application are not adequately supported by appropriate information on the toxicological profile and on the relevance of the major plant metabolites 5-hydroxyethoxyetridiazole acid and 3-hydroxymethyletridiazole that is required to conduct a consumer risk assessment, and therefore, on the basis of the available information, a MRL is not proposed for these crops.

| Code(a) | Commodity                  | Existing EU MRL (mg/kg) | Proposed EU MRL (mg/kg) | Comment/justification                                                                 |
|---------|----------------------------|------------------------|------------------------|---------------------------------------------------------------------------------------|
| 232010  | Cucumbers                  | 0.10                   | Further risk management consideration is needed |
| 232020  | Gherkins                   | 0.05*                  | Further risk management consideration is needed |
| 232030  | Courgettes                 | 0.05*                  | Further risk management consideration is needed |
| 232990  | Other cucurbits – edible peel | 0.05*                  | Further risk management consideration is needed |

**Enforcement residue definition**: etridiazole (only)

MRL: maximum residue level.

*: Indicates that the MRL is set at the limit of analytical quantification (LOQ).

(a): Commodity code number according to Annex I of Regulation (EC) No 396/2005.
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Background

Regulation (EC) No 396/20051 (hereinafter referred to as 'the MRL regulation') establishes the rules governing the setting of pesticide maximum residue levels (MRLs) at European Union (EU) level. Article 6 of the MRL regulation lays down that any party having a legitimate interest or requesting an authorisation for the use of a plant protection product in accordance with Council Directive 91/414/EEC,2 repealed by Regulation (EC) No 1107/20093, shall submit to a Member State, when appropriate, an application to modify a MRL in accordance with the provisions of Article 7 of the MRL regulation.

The Netherlands, hereafter referred to as the evaluating Member State (EMS), received an application from the company Arysta LifeScience Great Britain Limited4 to modify the existing MRLs for the active substance etridiazole in various crops. This application was notified to the European Commission and the European Food Safety Authority (EFSA) and was subsequently evaluated by the EMS in accordance with Article 8 of the Regulation.

After completion, the evaluation report was submitted to the European Commission and to EFSA on 5 February 2016.

The application was included in the EFSA Register of Questions with the reference number EFSA-Q-2016-00123 and the following subject:

Etridiazole – Modification of existing MRLs in various crops

The Netherlands proposed to raise the existing MRLs of etridiazole from the limit of quantification (LOQ) of 0.05* kg/mg to 0.4 mg/kg in gherkin, courgette and other cucurbits with edible peel, and from the existing MRL value of 0.1 mg/kg to 0.4 mg/kg in cucumber.

EFSA proceeded with the assessment of the application and the evaluation report as required by Article 10 of the Regulation.

In accordance with Article 10 of Regulation (EC) No 396/2005, EFSA shall, based on the evaluation report provided by the EMS, provide a reasoned opinion on the risks to the consumer associated with the application.

The evaluation report submitted by the EMS (Netherlands, 2016) and the exposure calculations using the EFSA Pesticide Residues Intake Model (PRIMo) are considered as supporting documents to this reasoned opinion and, thus, are made publicly available.

In accordance with Article 11 of the Regulation, the reasoned opinion shall be provided as soon as possible and at the latest within 3 months (which may be extended to 6 months if more detailed evaluations need to be carried out) from the date of receipt of the application. If EFSA requests supplementary information, the time limit laid down shall be suspended until that information has been provided.

The active substance and its use pattern

Etridiazole is the ISO common name for ethyl 3-trichloromethyl-1,2,4-thiadiazol-5-yl ether (IUPAC). The chemical structures of the active substance and its main metabolites are reported in Appendix B.

The details of the intended Good Agricultural Practices (GAPs) for etridiazole which are the basis for this MRL application are given in Appendix A.

Etridiazole was evaluated in the framework of Directive 91/414/EEC with the Netherlands designated as rapporteur Member State (RMS). It was initially not included in Annex I of this Directive by Decision 2008/934 following the withdrawal of the support for the inclusion by the applicant. After resubmission of an application according to Reg. 33/2008, the draft assessment report (DAR) and the

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1 Regulation (EC) No 396/2005 of the 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.
2 Council Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products on the market. OJ L 230, 19.8.1991, p. 1–32.
3 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.
4 Arysta LifeScience Great Britain Limited, Brooklands Farm, Cheltenham Road, Evesham, WR11 2LS, United Kingdom.
5 Commission Decision of 5 December 2008 concerning the non-inclusion of certain active substances in Annex I to Council Directive 91/414/EEC and the withdrawal of authorisations for plant protection products containing these substances. OJ L 333, 11.12.2008, p. 11–14.
6 Commission Regulation (EC) No 33/2008 of 17 January 2008 laying down detailed rules for the application of Council Directive 91/414/EEC as regards a regular and an accelerated procedure for the assessment of active substances which were part of the programme of work referred to in Article 8 of that Directive but have not been included into its Annex I, OJ L 15, 18.1.2008, p. 5–12.
additional report to the DAR prepared by the Netherlands (Netherlands, 2007, 2009) were peer reviewed by EFSA (2010). The representative uses evaluated in the EU pesticides peer review were applications through drip-irrigation on tomatoes, peppers, cucumbers and ornamental crops. The consumer risk assessment could not be performed during the peer review of etridiazole because appropriate information on the toxicological profile and relevance of the major plant metabolites 5-hydroxyethoxyetridiazole acid and 3-hydroxymethyletridiazole was not available (EFSA, 2010).

Etridiazole was included in Annex I to Directive 91/414/EEC on 1 June 2014 by Commission Directive 2011/29/EU7, and has been deemed to be approved under Regulation (EC) No 1107/20098, in accordance with Commission Implementing Regulation (EU) No 540/20119, as amended by Commission Implementing Regulation (EU) No 541/20119 (European Commission, 2011). The inclusion in Annex I of Directive 91/414/EEC was restricted to uses as a fungicide in non-soil bound systems in greenhouse. It was a specific provision of the approval that the applicant was required to submit further studies, including studies on the relevance of the plant metabolites 5-hydroxyethoxyetridiazole acid and 3-hydroxymethyletridiazole to the European Commission. The applicant Arysta LifeScience Great Britain Limited submitted an updated dossier in May 2013 to address the confirmatory data. The updated dossier included new toxicological studies on 5-hydroxyethoxyetridiazole acid that were evaluated by the RMS in the form of a Post Inclusion Addendum to the DAR, which concluded that 5-hydroxyethoxyetridiazole acid is mutagenic in the mouse lymphoma test system (Netherlands, 2014). In vitro or in vivo toxicological studies were not provided for the metabolite 3-hydroxymethyletridiazole. The updated dossier and the Addendum to the DAR were subject to a Member State consultation organised by the RMS. The outcome of the consultation process and EFSA’s scientific views on the individual comments received were summarised by EFSA in a Technical Report (EFSA, 2014). EFSA concluded that the toxicological relevance of the plant metabolites 5-hydroxyethoxyetridiazole acid and 3-hydroxymethyletridiazole was not sufficiently addressed.

On 29 May 2015, the Standing Committee on Plants, Animals, Food and Feed took note of the revised review report of the active substance etridiazole; the Committee decided that the plant metabolites 5-hydroxyethoxyetridiazole acid and 3-hydroxymethyletridiazole are not considered toxicologically relevant and therefore should not be included in the residues definition for plants (European Commission, 2015a).

EU MRLs for etridiazole are established in Annex IIIA of Regulation (EC) No 396/2005. The MRL review under Article 12 of Regulation (EC) No 396/2005 has not yet been finalised. No CXLs are established for etridiazole.

Assessment

EFSA has based its assessment on the evaluation report submitted by the EMS (Netherlands, 2016), the DAR (its additional report and its final addendum) prepared under Directive 91/414/EEC (Netherlands, 2007, 2009, 2010), the Commission review report on etridiazole (European Commission, 2015a), as well as the conclusion on the peer review of the pesticide risk assessment of the active substance etridiazole (EFSA, 2010) and the technical report on the outcome of the consultation on the pesticide risk assessment of confirmatory data for the active substance etridiazole (EFSA, 2014). The assessment is performed in accordance with the legal provisions of the Uniform Principles for the Evaluation and the Authorisation of Plant Protection Products adopted by Commission Regulation (EU) No 546/201110 and the currently applicable guidance documents relevant for the consumer risk assessment of pesticide residues (European Commission, 1996, 1997a–g, 2000, 2010a,b, 2015b; OECD, 2011).

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7 Commission Directive 2011/29/EU of 7 March 2011 amending Council Directive 91/414/EEC to include etridiazole as active substance and amending Commission Decision 2008/934/EC. OJ L 61, 8.3.2011, p. 9–13.
8 Commission Implementing Regulation (EU) No 540/2011 of 25 May 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards the list of approved active substances. OJ L 153, 11.6.2011, p. 1–186.
9 Commission Implementing Regulation (EU) No 541/2011 of 1 June 2011 amending Implementing Regulation (EU) No 540/2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards the list of approved active substances. OJ L 153, 11.6.2011, p. 187–188.
10 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.
1. Method of analysis

1.1. Methods for enforcement of residues in food of plant origin

Analytical methods for the determination of etridiazole residues in plant commodities were assessed during the peer review under Directive 91/414/EEC (EFSA, 2010). An adequate analytical method is available for determination of etridiazole in food of plant origin with high water content by gas chromatography–mass spectrometry (GC–MS) with an LOQ of 0.01 mg/kg for monitoring purposes. This analytical method is appropriate to enforce MRLs in accordance with the current residue definition established in Regulation (EC) No 396/2005.

The peer review proposed a provisional plant residue definition for monitoring as the sum of etridiazole, 3-hydroxymethyletridiazole (and its conjugates) and 5-hydroxyethoxyetridiazole acid (pending conclusion on the toxicological profile of these two metabolites) and indicated that a data gap might be identified for adequate analytical methods in food of plant origin for these metabolites in plants. Following the submission and assessment of further studies, the Standing Committee on the Plants, Animals, Food and Feed concluded that the plant metabolites 5-hydroxyethoxyetridiazole acid and 3-hydroxymethyletridiazole are not considered toxicologically relevant and therefore should not be included in the residues definition for plants (European Commission, 2015a).

Additional analytical methods for enforcement of etridiazole related residues in food of plant origin were submitted in the MRL application and evaluated by the EMS in the evaluation report. The method based on liquid chromatography with tandem mass spectrometry (LC–MS/MS) was considered to be successfully validated with an LOQ of 0.01 mg/kg for the metabolites 3-hydroxymethyletridiazole (T-07) and 5-hydroxyethoxyetridiazole acid (T-30). However, the analytical method for the determination of the glucosidal conjugate of 3-hydroxymethyletridiazole (T-31) was not validated and recoveries from the enzymatic hydrolysis step were consistently below the acceptable range (Netherlands, 2016). The EMS proposed that the risk assessment calculations use a factor of 2.5 to compensate for low recoveries for the 3-hydroxymethyletridiazole glucoside conjugate (T-31).

Independent laboratory validation (ILV) data were not submitted.

The multiresidue QuEChERS method described in the European Standard EN 15662:2008 and using gas chromatography with tandem mass spectrometric (GC–MS/MS) detection is also applicable to analyse etridiazole residues (parent compound only) in high water content commodities at the LOQ of 0.01 mg/kg (CEN, 2008).

As the commodities under consideration belong to the high water commodity group, EFSA concludes that sufficiently validated analytical methods are available for enforcing the proposed MRLs for etridiazole (parent compound only) in cucumber, gherkin, courgette and other cucurbits with edible peel.

1.2. Methods for enforcement of residues in food of animal origin

Analytical methods for the determination of residues in food of animal origin are not assessed in the current application since cucumber, gherkin, courgette and other cucurbits with edible peel are normally not fed to livestock.

2. Mammalian toxicology

The toxicological profile of the active substance etridiazole was assessed in the framework of the peer review under Directive 91/414/EEC (EFSA, 2010). The data were sufficient to derive toxicological reference values compiled in Table 1.

| Source | Year | Value | Study | Safety factor |
|--------|------|-------|-------|--------------|
| ADI    | EFSA | 2010  | 0.015 mg/kg bw per day 2-year rat study | 300(a) |
| ARfD   | EFSA | 2010  | 0.15 mg/kg bw Rabbit, developmental toxicity study | 100 |

ADI: acceptable daily intake; ARfD: acute reference dose; bw: body weight.
(a): Additional safety factor as ADI based on a LOAEL.
During the EU peer review of the active substance etridiazole, insufficient toxicological information was provided on the major plant metabolites 5-hydroxyethoxyetridiazole acid and 3-hydroxymethyletridiazole. The confirmatory data included new toxicological studies on 5-hydroxyethoxyetridiazole acid and the RMS evaluation in the Post Inclusion Addendum to the DAR concluded that 5-hydroxyethoxyetridiazole acid is mutagenic in the mouse lymphoma test system (Netherlands, 2014). In vitro or in vivo toxicological studies were not provided for the metabolite 3-hydroxymethyletridiazole.

Regarding 5-hydroxyethoxyetridiazole acid, the genotoxic potential could not be concluded since positive results were obtained in an in vitro gene mutation test, which are supported by a quantitative structure–activity relationship (QSAR) analysis. With regard to 3-hydroxymethyletridiazole, no toxicological information has been submitted; the genotoxicity alerts found with 5-hydroxyethoxyetridiazole acid would be relevant to 3-hydroxymethyletridiazole based on the structural similarity between the two metabolites. Additionally, information regarding the repeated-dose toxicity, relevant to consumer exposure, is not available for either of the two metabolites, and thus, it cannot be established whether these metabolites would be of similar, lower or higher toxicity than the parent etridiazole (EFSA, 2014). Overall, the toxicological relevance of the plant metabolites 5-hydroxyethoxyetridiazole acid and 3-hydroxymethyletridiazole was not sufficiently addressed (EFSA, 2014).

The Standing Committee on the Plants, Animals, Food and Feed, after the assessment of the confirmatory data, decided that the plant metabolites 5-hydroxyethoxyetridiazole acid and 3-hydroxymethyletridiazole are not considered toxicologically relevant and therefore should not be included in the residues definition for plants (European Commission, 2015a).

3. Residues

3.1. Nature and magnitude of residues in plant

3.1.1. Primary crops

3.1.1.1. Nature of residues

The metabolism of etridiazole in primary crops was evaluated in the framework of the peer review under Directive 91/414/EEC (EFSA, 2010) in the fruit crops group (cucumber, substrate grown, drip application) and in the oilseed crop group (cotton, soil treatment, informative only). An overview of the available metabolism studies is presented in Table 2.

Table 2: Summary of available metabolism studies in plants

| Crop groups | Crop(s) | Application(s) | Sampling (DAT) | Comments |
|-------------|---------|----------------|----------------|----------|
| Fruit       | Cucumber (Corona F1) | Hydroponic culture: 2 x 21.3; 114 and 229 mg/plant (2 x 1.1 N; 5.7 N & 11.5 N, respectively) | 3, 5, 11, 15, 21, 26, 39, 46 | Cucumbers of 25 cm or longer of the low dose were harvested at 3, 5, 11, 15, 21, 26, 39 and 46 days after the first treatment (DAT1). A limited number of samples were taken for the middle and high dose treatment. Study 1999–2004, reviewed by EFSA (2010) |
| Pulses/oilseeds | Cotton (Stoneville 825) | Soil: 0.94, 9.8, and 78 mg/kg (equivalent to 0.71, 7.4 and 59 kg/ha assuming a soil depth of 5 cm and a bulk density of 1,500 kg/m²) | 5 months after treatment | Whole plants harvested and separated into cotton seeds, foliage and fluff. Study 1993–1996, reviewed by EFSA (2010) |

DAT: days after treatment.

Metabolism study in cucumber: Parent etridiazole was only detected in the samples collected shortly after treatment, within 6 days after application, accounting for 2–23% total radioactive residue (TRR) (EFSA, 2010). For later intervals (> 11 days), the residues were mainly composed of the metabolites 5-hydroxyethoxyetridiazole acid (14–33% TRR) and 3-hydroxymethyletridiazole, free (3–12% TRR) or
glucose conjugated (5–17% TRR), the remaining radioactivity (28–59% TRR) being characterised as a large number of polar components associated with natural plant constituents.

The second metabolism study conducted on cotton was submitted but considered as informative only. The information submitted on the toxicity of etridiazole acid has shown this metabolite to be of lower acute and semichronic toxicity than the parent (EFSA, 2010) and its inclusion in the plant residue definition is therefore not necessary.

In contrast, data provided during the EU pesticide peer review and the confirmatory data were insufficient to conclude on the toxicity of the metabolites 5-hydroxyethoxyetridiazole acid and 3-hydroxymethyleneetridiazole (free and conjugated), although these two compounds were seen to represent a large part of the residues at some harvest points (up to ca 30% TRR and 0.18 mg/kg). Therefore, as the toxicity of these two major metabolites was not addressed, EFSA was of the opinion in the conclusion of the pesticide peer review that the residue in plant for monitoring and for risk assessment was provisionally to be defined as the sum of etridiazole, 5-hydroxyethoxyetridiazole acid and 3-hydroxymethyleneetridiazole (and its conjugates), pending conclusion on the toxicological profile of these two metabolites (EFSA, 2010). The current EU MRLs for etridiazole established in Annex IIIA of Regulation (EC) No 396/2005 are based on the residue definition: etridiazole (only).

For the uses on cucumber, gherkin, courgette and other cucurbits with edible peel, EFSA concludes that the metabolism of etridiazole is sufficiently addressed.

In this reasoned opinion for modification of the existing MRLs for etridiazole in cucumber, gherkin, courgette and other cucurbits with edible peel, residues for monitoring and enforcement were assessed according to the residue definitions under the Regulation (EC) No 396/2005 which is etridiazole (only). For risk assessment, EFSA followed the proposal of the EMS to assess the residues according to the provisional residue definition derived during the EU pesticide peer review, which is: sum of etridiazole, 3-hydroxymethyleneetridiazole and 5-hydroxyethoxyetridiazole acid.

In the framework of the MRL review under Article 12 of Regulation (EC) No 396/2005, the residue definitions should be reconsidered, taking into account the following aspects:

- the parent compound etridiazole is not a reliable marker substance for the treatment since it is quickly metabolised;
- additional metabolism studies representative for other crop groups (e.g. oilseeds);
- toxicological relevance of 5-hydroxyethoxyetridiazole acid: the genotoxic potential could not be concluded since positive results were obtained in an in vitro gene mutation test, which are supported by a QSAR analysis, and it cannot be established whether this metabolite would be of similar, lower or higher toxicity than the parent etridiazole;
- toxicological relevance of 3-hydroxymethyleneetridiazole and its conjugate: no toxicological information has been submitted, the genotoxicity alerts found with 5-hydroxyethoxyetridiazole acid would be relevant to 3-hydroxymethyleneetridiazole based on the structural similarity between the two metabolites;
- the analytical method for the determination of the 3-hydroxymethyleneetridiazole glucoside conjugate was not validated and recoveries were consistently below the acceptable range.

### 3.1.1.2. Magnitude of residues

In support of the MRL application, eight GAP-compliant trials (four decline studies with preharvest interval (PHI) of 0, 1, 3, 7 and 14 days and four trials reflecting the critical GAP (PHI 0 and 1 day)) were conducted on indoor cucumbers in eight different locations in northern Europe (the Netherlands) in 2012. The trials were performed using substrate-grown medium. Treated cucumber crops received two applications with an application rate of 288 g a.s./ha and an interval of 14 days.

All samples were analysed for etridiazole and for the metabolites etridiazole acid, 5-hydroxyethoxyetridiazole acid, 3-hydroxymethyleneetridiazole and its glucoside conjugate. The results of the residue trials, the related risk assessment input values (highest residue, median residue) and the theoretical MRL derived with the OECD calculator are summarised in Table 3.

Robust conversion factors for risk assessment could not be derived from the submitted trials as the residue levels for metabolites were at or below the LOQ in all trials and therefore disregarded from the calculation.

The stability of etridiazole residues in plant matrices under storage conditions prior to analysis was assessed during the EU pesticides peer review under Directive 91/414/EEC (EFSA, 2010). Residues of etridiazole were found to be stable at ≤ −18°C for up to 14 months in high water matrix (tomato).
the trial samples were stored within the period and conditions for which integrity of the samples was demonstrated, it is concluded that the residue data are valid with regard to storage stability.

According to the EMS, the analytical methods used to analyse the residue trial samples have been sufficiently validated for etridiazole and for the metabolites etridiazole acid, 5-hydroxyethoxyetridiazole acid, 3-hydroxymethyletridiazole (Netherlands, 2016). However, the analytical method for the glucosidal conjugate of 3-hydroxymethyletridiazole was not validated and recoveries from the enzymatic hydrolysis step were consistently below the acceptable range (Netherlands, 2016). The EMS proposed that the risk assessment calculations use a factor of 2.5 to compensate for low recoveries for the glucosidal conjugate of 3-hydroxymethyletridiazole. It is noted that the glucosidal conjugate of 3-hydroxymethyletridiazole was not detected at the LOQ in all eight residue trials. For risk assessment, residues of 3-hydroxymethyletridiazole glucoside conjugate were calculated based on the LOQ multiplied with the proposed factor 2.5 to compensate the low recoveries in the method.
Table 3: Overview of the available residues trials data

| Crop (GAPs) | Region/indoor(a) | Residue levels observed in the supervised residue trials(b) (mg/kg) | Recommendations/comments(c) | Theoretical MRL (mg/kg) | HR(d) (mg/kg) | STMR(e) (mg/kg) |
|-------------|------------------|------------------------------------------------------------------|----------------------------|------------------------|--------------|---------------|
| Cucumber    | Indoor           | Mo: 0.02; 0.02; 0.03; 0.04; 0.05; 0.08; 0.1; 0.13; 0.14; 0.17; 0.19; 0.34 | Proposed extrapolation to gherkin, courgette, and other cucurbits with edible peel | 0.40 | (HR<sub>Mo</sub>: 0.25) | (STMR<sub>Mo</sub>: 0.05) | 0.13 |
| GAP: 2x 288 g a.s./ha | PHI 1 day | RA: 0.11; 0.11; 0.12; 0.13; 0.14; 0.17; 0.19; 0.34 | | | | | |

GAP: Good Agricultural Practice; a.s.: active substance; MRL: maximum residue level.
(a): NEU: Outdoor trials conducted in northern Europe; SEU: Outdoor trials conducted in southern Europe; Indoor: indoor EU trials or Country code: if non-EU trials.
(b): Individual residue levels considered for MRL calculation are reported in ascending order (2 × < 0.01, 0.01, 6 × 0.02, 0.04, 0.08, 2 × 0.10, 0.15, 0.17).
Mo: residue level according to the monitoring residue definition.
RA: residue level according to the residue definition for risk assessment.
Underlined values: samples taken at a PHI longer than the intended PHI.
(c): Any information/comment supporting the decision and OECD MRL calculation (unrounded/rounded values).
(d): HR: Highest residue level according to the residue definition for risk assessment.
HR<sub>Mo</sub>: Highest residue level according to residue definition for monitoring.
(e): STMR: Median residue level according to residue definition for monitoring.
STMR<sub>Mo</sub>: Median residue level according to residue definition for monitoring.
3.1.1.3. Effect of industrial processing and/or household preparation

Standard hydrolysis studies were not submitted during the EU peer review and were not required for the representative use on non-edible crop (ornamentals) (EFSA, 2010). Specific studies to assess the magnitude of etridiazole residues during the processing of cucumber and other cucurbits with edible peel are not required because these products are mostly eaten raw (European Commission, 1997d). The residue levels in raw agricultural commodities (RAC) that can be cooked (courgette) exceeded the trigger value of 0.1 mg/kg (extrapolation from cucumber HR_{RAC}, 0.25 mg/kg); however, processing studies addressing the nature (standard hydrolysis study) and the magnitude of residues in cooked vegetables are not required since the theoretical maximum daily intake (TMDI) for etridiazole in courgette is below the trigger value of 10% of the acceptable daily intake (ADI).

3.1.2. Rotational crops

As the proposed uses of etridiazole are on crops grown on artificial substrate, the investigation of residues in rotational crops is not required and is therefore not considered in this reasoned opinion.

3.2. Nature and magnitude of residues in livestock

As crops under consideration and their by-products are not normally fed to livestock, the nature and magnitude of etridiazole residues in livestock is not assessed in the framework of this application (European Commission, 1996).

4. Consumer risk assessment

A tentative consumer risk assessment was performed with revision 2 of the EFSA PRIMo. This exposure assessment model contains the relevant European food consumption data for different subgroups of the EU population\(^{11}\) (EFSA, 2007).

To calculate the chronic exposure, EFSA used median residue value (STMR) derived from the residue trials conducted for the crop under consideration in this MRL application and reported in Table 3. For the remaining commodities of plant and animal origin, the existing MRLs as established in Regulation (EU) No 396/2005 were used as input values.

The acute exposure assessment was performed only with regard to the commodities under consideration assuming the consumption of a large portion of the food item(s) as reported in the national food surveys and that these items contained residues at the highest residue level (HR) as observed in supervised field trials (Table 4). A variability factor accounting for the inhomogeneous distribution on the individual items consumed was included in the calculation, when required (EFSA, 2007).

The input values used for the dietary exposure calculation are summarised in Table 4.

Table 4: Input values for the consumer dietary exposure assessment

| Commodity                        | Chronic exposure assessment | Acute exposure assessment |
|----------------------------------|-----------------------------|---------------------------|
|                                  | Input (mg/kg) | Comment | Input (mg/kg) | Comment |
|----------------------------------|---------------|---------|---------------|---------|
| **Risk assessment residue definition:** sum of etridiazole, 5-hydroxyethoxyetridiazole acid and 3-hydroxymethyletridiazole (and its conjugates) (provisional RD for fruit crops only) |
| Cucumbers                        | 0.13 STMR     |         | 0.34 HR       |
| Gherkins                         | 0.13 STMR cucumbers | 0.34 HR cucumbers |
| Courgettes                       | 0.13 STMR cucumbers | 0.34 HR cucumbers |
| Other cucurbits – edible peel    | 0.13 STMR cucumbers | 0.34 HR cucumbers |
| Other plant and animal commodities | MRL | MRLs in Regulation (EU) 396/2005 | Not relevant for current application |

RD: residue definition; STMR: supervised trials median residue; HR: highest residue; MRL: maximum residue level.

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\(^{11}\) The calculation of the long-term exposure (chronic exposure) is based on the mean consumption data representative for 22 national diets collected from MS surveys plus 1 regional and 4 cluster diets from the WHO GEMS Food database; for the acute exposure assessment the most critical large portion consumption data from 19 national diets collected from Member States surveys are used. The complete list of diets incorporated in EFSA PRIMo is given in its reference section (EFSA, 2007).
The estimated exposure was then compared with the toxicological reference values derived for etridiazole (Table 1).

The tentative risk assessment is affected by a higher degree of uncertainty due to the provisional residue definition for risk assessment and since the toxicological relevance of the plant metabolites 5-hydroxyethoxyetridiazole acid and 3-hydroxymethyletridiazole was not sufficiently addressed. The risk assessment is based on the risk management decision that the metabolites are not genotoxic (European Commission, 2015a) and the approach postulates the metabolites being of similar toxicity as the parent compound. The results of the intake calculation using the EFSA PRIMo is a key supporting document and is made publicly available as a background document to this reasoned opinion.

A long-term consumer intake concern was not identified for any of the European diets incorporated in the EFSA PRIMo. The highest chronic intake was calculated to be 23% of the ADI (FR, toddler). The contribution of residues in cucumber to the total consumer exposure accounted for a maximum of 1.4% of the ADI (DK, child). The contribution of residues in gherkin to the total consumer exposure accounted for a maximum of 0.18% of the ADI (WHO Cluster diet B). The contribution of residues in courgette to the total consumer exposure accounted for a maximum of 0.58% of the ADI (FR, infant).

An acute consumer risk was not identified in relation to the MRL proposals for cucumber, gherkin, courgette and other cucurbits with edible peel. The highest acute consumer exposures were calculated to be 13.3% of the acute reference dose (ARfD) for cucumber; 10.5% of the ARfD for courgette; and 3.7% of the ARfD for gherkin.

Based on the tentative risk assessment performed according to the assumptions described in this section, the intended use of etridiazole on cucumber, gherkin, courgette and other cucurbits with edible peel did not result in a consumer exposure exceeding the toxicological reference values.

Conclusions and recommendations

The consumer risk assessment could not be performed during the EU pesticides peer review of etridiazole because appropriate information on the toxicological profile and relevance of the major plant metabolites 5-hydroxyethoxyetridiazole acid and 3-hydroxymethyletridiazole was not available (EFSA, 2010). The confirmatory data included new toxicological studies on 5-hydroxyethoxyetridiazole acid; however, the genotoxic potential could not be concluded since positive results were obtained in an in vitro gene mutation test, which are supported by a QSAR analysis. The genotoxicity alerts found with 5-hydroxyethoxyetridiazole acid would be relevant to 3-hydroxymethyletridiazole based on the structural similarity between the two metabolites. Additionally, it cannot be established whether these metabolites would be of similar, lower or higher toxicity than the parent etridiazole (EFSA, 2014). Overall, the toxicological relevance of the plant metabolites 5-hydroxyethoxyetridiazole acid and 3-hydroxymethyletridiazole was not sufficiently addressed (EFSA, 2014).

The tentative risk assessment in this reasoned opinion is affected by a higher degree of uncertainty due to the provisional residue definition for risk assessment, and since the toxicological relevance of the plant metabolites 5-hydroxyethoxyetridiazole acid and 3-hydroxymethyletridiazole was not sufficiently addressed. The tentative risk assessment is based on the risk management decision that the metabolites are not genotoxic (European Commission, 2015a) and the approach postulates the metabolites being of similar toxicity as the parent compound. Based on the tentative risk assessment performed according to the assumptions described, the intended use of etridiazole on cucumber, gherkin, courgette and other cucurbits with edible peel did not result in a consumer exposure exceeding the toxicological reference values.

EFSA considers that the intended uses of etridiazole on cucumber, gherkin, courgette and other cucurbits with edible peel in the current MRL application are not adequately supported by appropriate information on the toxicological profile and on the relevance of the major plant metabolites 5-hydroxyethoxyetridiazole acid and 3-hydroxymethyletridiazole that is required to conduct a consumer risk assessment, and therefore, on the basis of the available information, a MRL is not proposed for these crops.

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**Abbreviations**

| Abbreviation | Description |
|--------------|-------------|
| a.s. | active substance |
| ADI | acceptable daily intake |
| ARfD | acute reference dose |
| BBCH | growth stages of mono- and dicotyledonous plants |
| bw | body weight |
| CEN | European Committee for Standardisation (Comité Européen de Normalisation) |
| CXL | Codex maximum residue limit |
| DAR | draft assessment report |
| DAT | days after treatment |
| EC | emulsiifiable concentrate |
| EMS | evaluating Member State |
Modification of existing MRLs for etridiazole in various crops

FAO Food and Agriculture Organization of the United Nations
GAP Good Agricultural Practice
GC-MS gas chromatography with mass spectrometry
GC-MS/MS gas chromatography with tandem mass spectrometry
HR highest residue
ILV independent laboratory validation
ISO International Organisation for Standardisation
IUPAC International Union of Pure and Applied Chemistry
LC-MS/MS liquid chromatography with tandem mass spectrometry
LOAEL lowest observed adverse effect level
LOQ limit of quantification
ME microemulsion
MRL maximum residue level
MS Member States
MW molecular weight
NEU northern Europe
OECD Organisation for Economic Co-operation and Development
PHI preharvest interval
PRIMo (EFSA) Pesticide Residues Intake Model
QSAR quantitative structure-activity relationship
QuEChERS Quick, Easy, Cheap, Effective, Rugged, and Safe (analytical method)
RA risk assessment
RAC raw agricultural commodity
RD residue definition
RMS rapporteur Member State
RPF relative potency factor
SANCO Directorate-General for Health and Consumers
SEU southern Europe
SMILES simplified molecular-input line-entry system
STMR supervised trials median residue
TMDI theoretical maximum daily intake
TRR total radioactive residue
UV ultraviolet (detector)
WHO World Health Organization
Appendix A – Good Agricultural Practice

| Crop | Preparation | Application | Remarks |
|------|-------------|-------------|---------|
| Cucurbitaceous edible peel (cucumber, gherkin, courgette, other), on artificial substrate, and root fungi (Pythium) | Substrate and root fungicide (Pythium) | 700 g/L Application through drip-irrigation | Min 14 days interval between applications. |
| | | | Non-soil bound applications per crop cycle. |
| Courgette | | | Max. 0.8 L product/ha per crop cycle. |
| | | | For risk assessment purposes, water L/ha can be estimated as 1,000-3,000 (min/max). |
| | | | Max. 0.56 kg a.s./ha per crop cycle. |

Modification of existing MRLs for etridiazole in various crops.
| Crop                        | NEU, SEU, MS or country | F G or I(a) | Pests or group of pests controlled | Preparation      | Application         | Application rate per treatment | PHI (days)(d) | Remarks                                                                 |
|-----------------------------|-------------------------|-------------|-----------------------------------|------------------|---------------------|-------------------------------|----------------|------------------------------------------------------------------------|
| Cucurbit-edible peel (cucumber, gherkin, courgette, other), grown on artificial substrate CUMSA CUUPG | EL, ES, IT | G | Substrate and root fungi (Pythium PYTHSP) | EC (emulsifiable concentrate) | 480 g/L | Application through drip-irrigation | BBCH 71-89, but not before first fruit harvest Jan–Dec | 2 per crop cycle | Min 14 days interval | n.a (drip irrigation) | n.a (drip irrigation) | 288–576 g a.s./ha per application | 1 | Non-soil bound Max. 2 applications per crop cycle Courgette 2 crop cycles per year Cucumber 3 crop cycles per year Max. 1.2 L product/ha per crop cycle Max. 0.576 kg a.s./ha per crop cycle For risk assessment purposes, water L/ha can be estimated as 1,000–3,000 (min/max) |

NEU: northern European Union; SEU: southern European Union; MS: Member State; a.s.: active substance.
(a): Outdoor or field use (F), greenhouse application (G) or indoor application (I).
(b): CropLife International Technical Monograph no 2, 6th Edition. Revised May 2008. Catalogue of pesticide.
(c): Growth stage range from first to last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including, where relevant, information on season at time of application.
(d): PHI: minimum preharvest interval.
## Appendix B – Used compound codes

| Code/trivial name | Chemical name/SMILES notation | Structural formula |
|------------------|--------------------------------|--------------------|
| Etridiazole      | Ethyl 3-trichloromethyl-1,2,4-thiadiazol-5-yl ether | ![Etridiazole](image) |
| Etridiazole acid (T-02) | 5-Ethoxy-1,2,4-thiadiazole-3-carboxylic acid O(-O)c1nc(OCC)sn1 | ![Etridiazole acid](image) |
| 3-Hydroxymethyl etridiazole (T-07) | (5-Ethoxy-1,2,4-thiadiazol-3-yl) methanol OCc1nc(OCC)sn1 | ![3-Hydroxymethyl etridiazole](image) |
| 5-Hydroxyethoxy etridiazole acid (T-30) | 5-(2-Hydroxyethoxy)-1,2,4-thiadiazole-3-carboxylic acid O(-O)c1nc(OCCO)sn1 | ![5-Hydroxyethoxy etridiazole acid](image) |
| 3-Hydroxymethyl etridiazole glucoside conjugate (T-31) | (5-Ethoxy-1,2,4-thiadiazol-3-yl)methyl D-glucopyranoside O[C@H]1C(O[C@H][CO][C@@H][O][C@@H][O]) [C@@H][O]) OCC2nc(OCC)sn2 | ![3-Hydroxymethyl etridiazole glucoside conjugate](image) |

**SMILES:** simplified molecular-input line-entry system; **MW:** molecular weight.