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Modification of the existing maximum residue levels for difenoconazole in various crops

European Food Safety Authority (EFSA),
Alba Brancato, Daniela Brocca, Chloe De Lentdecker, Zoltan Erdos, Lucien Ferreira, Luna Greco,
Judith Janossy, Samira Jarrah, Dimitra Kardassi, Renata Leuschner, Christopher Lythgo,
Paula Medina, Ileana Miron, Tunde Molnar, Alexandre Nougadere, Ragnor Pedersen,
Hermine Reich, Angela Sacchi, Miguel Santos, Alois Stanek, Juergen Sturma, Jose Tarazona,
Anne Theobald, Benedicte Vagenende, Alessia Verani and Laura Villamar-Bouza

Abstract

In accordance with Article 6 of Regulation (EC) No 396/2005, the applicant BASF SE submitted a request to the competent national authority in the United Kingdom to modify the existing maximum residue levels (MRLs) for the active substance difenoconazole in various crops. The data submitted in support of the request were found to be sufficient to derive MRL proposals for all crops under consideration. Adequate analytical methods for enforcement are available to control the residues of difenoconazole in plant matrices under consideration. The estimated long-term and short-term intake to residues of difenoconazole resulting from the existing and the intended uses did not exceed the toxicological reference values established for the active substance difenoconazole. The consumer exposure assessment has to be considered provisional as the impact of a potentially different isomer composition in the residues of difenoconazole on this risk assessment is currently unknown and has to be reconsidered when data on possible preferential metabolism/degradation of the four stereo isomers of difenoconazole in plants is available and guidance on a risk assessment approach for residues containing isomers is implemented.

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Keywords: difenoconazole, flowering brassica, Brussel sprouts, escarole, broad leaved endive, Roman rocket, rucola, spinaches, purslanes, other spinaches and similar leaves, witloof, Belgian endive, rhubarb, pesticide, MRL, consumer risk assessment

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Correspondence: pesticides.mrl@efsa.europa.eu

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Summary

In accordance with Article 6 of Regulation (EC) No 396/2005, BASF SE submitted an application to the competent national authority in the United Kingdom (evaluating Member State, EMS) to modify the existing maximum residue levels (MRLs) for the active substance difenoconazole in various crops. The EMS 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 7 April 2017. To accommodate for the intended uses of difenoconazole in Europe, the EMS proposed to raise the existing MRLs for a wide range of food commodities, major part of them being already covered by a parallel MRL application which was assessed by EFSA in June 2017 with MRL proposals now implemented by the European Commission in the draft Regulation. These crops were excluded from the current assessment. EFSA assessed the proposal of the EMS to modify the existing MRLs for difenoconazole in other flowering brassica, Brussel sprouts, escarole/broad-leaved endive, Roman rocket/rucola, spinaches, purslanes, other spinaches and similar leaves, witloof/Belgian endive and rhubarb.

EFSA based its assessment on the updated evaluation report submitted by the EMS, the draft assessment report (DAR) prepared under Council Directive 91/414/EEC, the conclusion on the peer review of the pesticide risk assessment of the active substance difenoconazole as well as the conclusions from previous EFSA opinions on difenoconazole.

The metabolism of difenoconazole was investigated in fruit, root, cereals/grass and pulses/oilseed crop groups following foliar treatment and in cereals/grass following seed treatment. During the peer review, a data gap on information investigating the possible preferential metabolism/degradation of the four stereo isomers of difenoconazole in plants was identified and is still open. Once the specific guidance and the confirmatory data are available, the residue definitions may have to be revised.

Studies investigating the effect of processing on the nature of difenoconazole (hydrolysis studies) demonstrated that the active substance is stable.

In rotational crops, the major residues identified were the triazole derivative metabolites (TDMs).

Based on the metabolic pattern identified in metabolism studies, hydrolysis studies and the toxicological significance of metabolites, the residue definitions for plant products were proposed as difenoconazole for enforcement and difenoconazole and, provisionally, TDMs for the risk assessment. These residue definitions are applicable to primary crops, rotational crops and processed products. EFSA concluded that for the crops assessed in this application, metabolism of difenoconazole in primary and in rotational crops and the possible degradation in processed products has been investigated, and that the previously derived residue definitions are applicable.

Sufficiently validated analytical methods are available to quantify residues in the crops assessed in this application according to the enforcement residue definition. The methods enable quantification of difenoconazole residues at or above 0.01 mg/kg (limit of quantification (LOQ)) in the crops assessed.

The available residue trials are sufficient to derive MRL proposals for difenoconazole in all crops under consideration.

Specific studies investigating the magnitude of difenoconazole residues in processed commodities have not been submitted. It is unlikely that major processing types for the crops under consideration (cooking in water or steaming) will result in a concentration of difenoconazole in processed vegetable commodities. A refinement of the consumer dietary intake estimates is currently not necessary. Processing studies might become relevant once the data gap related to isomeric composition of difenoconazole in crops, and the relative toxicity of different isomers is addressed.

The occurrence of difenoconazole residues in rotational crops was investigated in the framework of the European Union (EU) pesticides peer review, which noted some limitations of the available studies regarding magnitude of TDMs in rotational crops. Since the maximum annual application rate on the crops under consideration is lower than the application rate tested in the limited rotational crop field trials and very similar to the application rate used in the confined rotational crop studies, it is concluded that significant difenoconazole residues in rotational crops are not expected, provided that the active substance is applied according to the proposed Good Agricultural Practices (GAP).

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

The toxicological profile of difenoconazole was assessed in the framework of the EU pesticides peer review under Directive 91/414/EEC where an acceptable daily intake (ADI) value of 0.01 mg/kg body weight (bw) per day and an acute reference dose (ARfD) of 0.16 mg/kg bw was derived. For the TDMs which are included in the provisional risk assessment residue definition for plant commodities, separate toxicological reference values are applicable as derived by EFSA in the framework of the peer review.

The consumer risk assessment was performed with revision 2 of the EFSA Pesticide Residues Intake Model (PRIMO). The consumer exposure assessment has to be considered provisional as the impact of a potentially different isomer composition in the residues of difenoconazole on this risk assessment is currently unknown and has to be reconsidered when data on possible preferential metabolism/degradation of the four stereo isomers of difenoconazole in plants are available, and guidance on a risk assessment approach for residues containing isomers is implemented.

The short-term exposure assessment was performed for the commodities assessed in this application using the highest residue (HR) values derived from supervised field trials. The short-term exposure did not exceed the ARfD for any of the crops assessed.

The long-term exposure assessment was calculated using the supervised trials median residue (STMR) values derived from the residue trials conducted with the crops under consideration. For other commodities, where available, the STMR values reported in the previous EFSA reasoned opinions were used as input values. For the remaining commodities of plant and animal origin, the existing MRLs as established in Regulation (EU) No 2017/626 were used as input values. The estimated long-term dietary intake was in the range of 13–87% of the ADI.

Based on the provisional risk assessment results, EFSA concluded that the long-term and short-term intake of residues of difenoconazole resulting from the existing and the intended uses did not exceed the toxicological reference values established for the active substance difenoconazole.

EFSA emphasises that the above assessment does not yet take into consideration TDMs. As these metabolites may be generated by several pesticides belonging to the group of triazole fungicides, EFSA recommends that a separate risk assessment should be performed for TDMs as soon as the confirmatory data requested for triazole compounds in the framework of Regulation (EC) No 1107/2009 have been evaluated and a general methodology on the risk assessment of triazole compounds and their TDMs are available.

EFSA proposes to amend the existing MRLs as reported in the summary table below.

Code ^(a)	Commodity	Existing EU MRL (mg/kg)	Proposed EU MRL (mg/kg)	Comment/justification
Enforcement residue definition: Difenoconazole				
0241990	Others (flowering brassica)	0.05*	0.08	The MRL proposal was derived from residue trials performed in the NEU. According to the provisional dietary risk assessment, the toxicological reference values were not exceeded.
0242010	Brussels sprouts	0.3	0.4	The submitted data are sufficient to derive a MRL proposal for the NEU use. According to the provisional dietary risk assessment, the toxicological reference values were not exceeded.
0251030	Escaroles/broad leaved endives	0.8	3	The MRL proposal reflects the NEU outdoor use. According to the provisional dietary risk assessment, the toxicological reference values were not exceeded.
0251060	Roman rocket/rucola	2	3	
0252010	Spinaches	2	3	
0252020	Purslanes	2	3	
0252990	Other (spinaches and similar leaves)	0.05*	3	
0255000	Witloof/Belgian endives	0.08	4	The MRL proposal reflects the NEU outdoor use (in combination with indoor treatment) and indoor use. For SEU uses, the data were not submitted. According to the provisional dietary risk assessment, the toxicological reference values were not exceeded.

Code ^(a)	Commodity	Existing EU MRL (mg/kg)	Proposed EU MRL (mg/kg)	Comment/justification
0270070	Rhubarbs	0.5	5	The submitted data are sufficient to derive a MRL proposal for the SEU use. For the NEU use, no data were submitted. According to the provisional dietary risk assessment, the toxicological reference values were not exceeded

*: 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.

Table of contents

Abstract.....	1
Summary.....	3
Background.....	7
Terms of Reference.....	7
The active substance and its use pattern.....	8
Assessment.....	8
1. Residues in plants.....	9
1.1. Nature of residues and methods of analysis in plants.....	9
1.1.1. Nature of residues in primary crops.....	9
1.1.2. Nature of residues in rotational crops.....	9
1.1.3. Nature of residues in processed commodities.....	9
1.1.4. Methods of analysis in plants.....	9
1.1.5. Stability of residues in plants.....	9
1.1.6. Proposed residue definitions.....	10
1.2. Magnitude of residues in plants.....	10
1.2.1. Magnitude of residues in primary crops.....	10
1.2.1.1. Flowering brassica.....	10
1.2.1.2. Brussels sprouts.....	11
1.2.1.3. Escarole/broad-leaved endives, Roman rocket/rucola, spinach, purslanes and other spinaches and similar leaves.....	11
1.2.1.4. Witloof/Belgian endive.....	11
1.2.1.5. Rhubarb.....	11
1.2.2. Magnitude of residues in rotational crops.....	11
1.2.3. Magnitude of residues in processed commodities.....	12
1.2.4. Proposed MRLs.....	12
2. Residues in livestock.....	12
3. Consumer risk assessment.....	12
3.1. Short-term (acute) dietary risk assessment.....	12
3.2. Long-term (chronic) dietary risk assessment.....	12
Conclusions and recommendations.....	13
References.....	13
Abbreviations.....	14
Appendix A – Summary of intended GAP triggering the amendment of existing EU MRLs.....	16
Appendix B – List of end points.....	19
Appendix C – Pesticide Residue Intake Model (PRIMo).....	25
Appendix D – Input values for the exposure calculations.....	27
Appendix E – Used compound codes.....	28

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/EEC², repealed by Regulation (EC) No 1107/2009³, shall submit an application to a Member State to modify a MRL in accordance with the provisions of Article 7 of the MRL regulation.

The applicant BASF SE⁴ submitted an application to the competent national authority in the United Kingdom, hereafter referred to as the evaluating Member State (EMS), to modify the existing MRLs for the active substance difenoconazole 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 MRL regulation.

The EMS summarised the data provided by the applicant in an evaluation report which was submitted to the European Commission and forwarded to EFSA on 7 April 2017. The application was included in the EFSA Register of Questions with the reference number EFSA-Q-2017-00283 and the following subject:

Difenoconazole – MRLs in various crops

The United Kingdom proposed to raise the existing MRLs of difenoconazole as follows: from the limit of quantification (LOQ) 0.05 to 0.08 mg/kg for other flowering brassica, from the existing MRL 0.2 to 0.4 mg/kg for Brussel sprouts, from 0.7 to 3 mg/kg for escarole/broad leaves endive, from 2 to 3 mg/kg for roman rocket/rucola, for spinaches and for purslanes; from the LOQ 0.05 to 3 mg/kg for other spinaches and similar leaves, from the existing MRL 0.08 to 4 mg/kg for witloof/Belgian endive and finally from 0.3 to 5 mg/kg for rhubarb.

EFSA assessed the application and the evaluation report as required by Article 10 of the MRL regulation. EFSA identified points which needed further clarification, which were requested from the EMS. On October 2017, the EMS submitted a revised evaluation report (United Kingdom, 2017) which replaced the previously submitted evaluation report.

Terms of Reference

In accordance with Article 10 of Regulation (EC) No 396/2005, EFSA shall assess the application and the evaluation report and give a reasoned opinion on the risks to the consumer and, where relevant, to animals associated with the setting of the requested MRLs. The opinion shall include:

- An assessment of whether the analytical method for routine monitoring proposed in the application is appropriate for the intended control purposes;
- The anticipated LOQ for the pesticide/product combination;
- An assessment of the risks of the acceptable daily intake (ADI) and acute reference dose (ARfD) being exceeded as a result of the modification of the MRL;
- The contribution to the intake due to the residues in the product for which the MRLs was requested;
- Any other element relevant to the risk assessment.

In accordance with Article 11 of the MRL regulation, EFSA shall give its reasoned opinion as soon as possible and at the latest within 3 months from the date of receipt of the application.

The evaluation report submitted by the EMS (United Kingdom, 2017) 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 as background documents to this reasoned opinion.

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 BASF SE, Speyerer Strasse 2, 67114, Limburgerhof, Germany.

The active substance and its use pattern

The detailed description of the intended uses of difenoconazole in the crops under consideration which are the basis for the current MRL application is reported in Appendix A.

Difenoconazole is the ISO common name for 3-chloro-4-[(2*RS*,4*RS*;2*RS*,4*SR*)-4-methyl-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]phenyl 4-chlorophenyl ether (IUPAC). Difenoconazole consists of two diastereoisomers. The chemical structures of the active substance and its main metabolites are reported in Appendix E.

Difenoconazole was evaluated in the framework of Directive 91/414/EEC with Sweden designated as rapporteur Member State (RMS) for the representative uses as foliar applications on pome fruits and carrots and as seed treatment on cereals. Difenoconazole was approved⁵ for the use as fungicide on 1 January 2009. In 2011, the draft assessment report (DAR) prepared by the RMS, Sweden, has been peer reviewed by EFSA (EFSA, 2011a). Following the findings of the peer review, the conditions of approval were amended,⁶ requesting further confirmatory information that had to be submitted by specified deadlines in 2012 and 2013. One of the confirmatory data is still open (i.e. submission of confirmatory data as regards the possible impact of the variable isomer ratio in the technical material and of the preferential degradation and/or conversion of the mixture of isomers on the worker risk assessment, the consumer risk assessment and on the environment); the requested information has to be submitted within 2 years from the adoption of specific guidance. Pending the development of this guidance document, the data gap identified during the peer review (EFSA, 2011a) could not yet be addressed.

The EU MRLs for difenoconazole are established in Annex III A of Regulation (EC) No 396/2005. The review of existing MRLs according to Article 12 of Regulation (EC) No 396/2005 (MRL review) has not yet been completed. EFSA has issued several reasoned opinions on the modification of MRLs for difenoconazole (EFSA, 2009, 2010, 2011b, 2012, 2013, 2014a,b, 2017). The proposals from these reasoned opinions except the last one have been considered in the EU MRL legislation.⁷

Assessment

EFSA has based its assessment on the evaluation report submitted by the EMS (United Kingdom, 2017), the DAR prepared under Directive 91/414/EEC (Sweden, 2006), the conclusion on the peer review of the pesticide risk assessment of the active substance difenoconazole (EFSA, 2011a) as well as the conclusions from previous EFSA opinions and scientific reports on difenoconazole (EFSA, 2009, 2010, 2011b, 2012, 2013, 2014a,b, 2017).

For this application, the data requirements established in Regulation (EU) No 544/2011⁸ and the guidance documents applicable at the date of submission of the MRL application to the EMS are applicable (European Commission, 1997a–g, 2000, 2010a,b, 2017; OECD, 2011, 2013). 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 546/2011⁹.

A selected list of end points of the studies assessed by EFSA in the framework of the MRL review, including the end points of studies submitted in support of the current MRL application, are presented in Appendix B.

⁵ Commission Directive 2008/69/EC of 1 July 2008 amending Council Directive 91/414/EEC to include clofentezine, dicamba, difenoconazole, diflubenzuron, imazaquin, lenacil, oxadiazon, picloram and pyriproxyfen as active substances, OJ L 172 , 2.7.2008, p. 9–14.

⁶ Commission Implementing Regulation (EU) No 1100/2011 of 31 October 2011 amending Implementing Regulation (EU) No 540/2011 as regards the conditions of approval of the active substances dicamba, difenoconazole and imazaquin. OJ L 285, 1.11.2011, p. 10–14.

⁷ For an overview of all MRL Regulations on this active substance, please consult: <http://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/public/?event=pesticide.residue.selection&language=EN>

⁸ Commission Regulation (EU) No 544/2011 of 10 June 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards the data requirements for active substances Text with EEA relevance. OJ L 155, 11.6.2011, p. 1–66.

⁹ 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. Residues in plants

1.1. Nature of residues and methods of analysis in plants

1.1.1. Nature of residues in primary crops

The metabolism of difenoconazole in primary crops was investigated in the framework of the peer review under Directive 91/414/EEC following foliar applications in fruit, root and pulses/oilseed crop groups and following foliar and seed treatment in cereals/grass crop group (Sweden, 2006; EFSA, 2011a). Basically, the metabolism was comparable in all four crop groups. Difenoconazole was the major component of the residues in the major plant parts, with the exception of the cereal grains, potato tubers and rape seeds, where total radioactive residue (TRR) was mainly composed of triazole derivative metabolites (TDM): triazole alanine, triazole acetic acid and 1,2,4-triazole. The data gap identified during the peer review (EFSA, 2011a) on information investigating the possible preferential metabolism/degradation of the four stereo isomers of difenoconazole in plants has not yet been addressed (see also Section on 'the active substance and its use pattern').

1.1.2. Nature of residues in rotational crops

Difenoconazole is proposed to be used on several crops that can be grown in a crop rotation. According to the soil degradation studies evaluated in the framework of the peer review, the DT_{90} value of difenoconazole is 879 days (EFSA, 2011a). The trigger value of 100 days is exceeded and therefore further studies investigating the nature and magnitude of residues in rotational crops are required.

Metabolism of difenoconazole in rotational crops has been investigated in the framework of the peer review in two studies with [^{14}C -triazole-] and [^{14}C -phenyl-] difenoconazole (Sweden, 2006; EFSA, 2011a). Bare soil was treated with difenoconazole at either 32.4 g/ha (study 1) or 125 g/ha (study 2) and rotational crops belonging to cereal/grasses, leafy and root crop groups were planted/sown 30 days (study 1) or 98, 126, 342 and 369 days (study 2) after the soil treatment.

In mature turnip, wheat and mustard from study 1 (performed only with [^{14}C -phenyl] difenoconazole), the total TRR was below 0.01 mg eq/kg and was not further characterized.

The TRR in mature crops from the study 2 when treated with [^{14}C -triazole] difenoconazole accounted for up to 0.02 mg eq/kg in lettuce, 0.34 mg eq/kg wheat grain, 0.11 mg eq/kg in straw, 0.005 mg eq/kg sugar beet roots, 0.03 mg eq/kg in sugar beet tops and 0.21 mg eq/kg in maize grain and was mainly composed of the TDMs. The TRR in crops treated with [^{14}C -phenyl-] difenoconazole was too low to be characterized.

The peer review concluded that the metabolic pathway in primary and rotational crops is partially similar. Pending the outcome of the evaluation of confirmatory data (according to Regulation (EC) No 1100/2011) on the formation of TDMs in rotational crops, the same residue definitions as established in primary crops are currently applicable.

1.1.3. Nature of residues in processed commodities

The effect of processing on the nature of difenoconazole (hydrolysis study) was investigated in the framework of the EU pesticides peer review under Directive 91/414/EEC and showed that difenoconazole is hydrolytically stable (Sweden, 2006; EFSA, 2011a).

1.1.4. Methods of analysis in plants

Analytical method for the determination of difenoconazole residues was assessed during the EU pesticides peer review under Directive 91/414/EEC (Sweden, 2006; EFSA, 2011a). Additionally, a QuEChERS method as reported in the European Standard EN 15662:2008 (CEN, 2008) is validated for the determination of difenoconazole residues.

It is concluded that sufficiently validated analytical enforcement methods are available for the determination of difenoconazole residues at or above the LOQ of 0.01 mg/kg in crops belonging to the commodity groups of high water and high acid content.

1.1.5. Stability of residues in plants

The storage stability of difenoconazole in plants stored under frozen conditions was investigated in the framework of the EU pesticides peer review under Directive 91/414/EEC (Sweden, 2006; EFSA,

2011a) and under the previous MRL applications (EFSA, 2017). It was demonstrated that in crops assessed in the framework of this application, residues were stable for at least 12 months when stored at -18°C .

1.1.6. Proposed residue definitions

Based on the metabolic pattern identified in metabolism studies, the results of hydrolysis studies, the toxicological significance of metabolites and the capabilities of enforcement analytical methods, the following residue definitions were proposed

- residue for risk assessment: (1) difenoconazole; (2) TDMs (provisionally, pending the definition of a common and harmonised approach for all the active substances of the triazole class)
- residue definition for enforcement: difenoconazole

Since difenoconazole consists of four stereo isomers, and since the available analytical methods are not stereo selective, the proposed residue definitions for enforcement and risk assessment are derived for the sum of the *R*- and *S*-isomers.

The same residue definitions are applicable to rotational crops and processed products.

The residue definition for enforcement set in Regulation (EC) No 396/2005 is identical with the above-mentioned residue definition.

For the uses on the crops under consideration, EFSA concludes that the metabolism of difenoconazole is addressed and the residue definitions for enforcement and risk assessment agreed in the peer review are applicable.

The data gap identified during the peer review on information investigating the possible preferential metabolism/degradation of the four stereo isomers of difenoconazole in plants is still open (EFSA, 2011a). Once the specific guidance and the confirmatory data are available, the residue definitions may have to be revised.

EFSA emphasises that the current assessment does not yet take into consideration TDMs. As these metabolites may be generated by several pesticides belonging to the group of triazole fungicides, EFSA recommends that a separate risk assessment is performed for TDMs as soon as the confirmatory data requested for triazole compounds in the framework of Regulation (EC) No 1107/2009 have been evaluated, and a general methodology on the risk assessment of triazole compounds and their TDMs is available.

1.2. Magnitude of residues in plants

1.2.1. Magnitude of residues in primary crops

In support of the MRL application, the applicant submitted residue trials on cauliflower, broccoli, Brussels sprouts, lettuce, lamb's lettuce, witloof and celery. Samples of treated crops were analysed for the parent compound difenoconazole; residue data on TDMs have not been provided. According to the assessment of the EMS, the methods used were sufficiently validated and fit for purpose.

The samples of residue trials were stored under conditions, for which integrity of the samples has been demonstrated.

1.2.1.1. Flowering brassica

In support of the northern Europe (NEU) Good Agricultural Practices (GAP), the applicant submitted eight GAP compliant residue trials on cauliflower (4) and broccoli (4). In support of the southern Europe (SEU), the applicant provided eight GAP-compliant residue trials on cauliflower (4) and broccoli (4). Trials were performed in various NEU and sEU Member states in the growing seasons of 2013–2014. The applicant proposes to extrapolate the combined residue data set of cauliflower and broccoli to a group of 'other flowering brassica' (crop code 0241990 in Annex I of Regulation (EC) No 396/2005).

According to an EU guidance document, the number of trials is sufficient to set a group MRL for the whole group of flowering brassica (European Commission, 2017). Considering that the existing MRLs for cauliflower and broccoli are higher than the MRL proposal derived in this assessment (i.e. 0.08 mg/kg), there is no need to modify the MRLs for these two crops. Thus, the MRL proposal of 0.08 mg/kg would be relevant only for the crop code 0241990.¹⁰

¹⁰ Since no specific crops are listed under this crop code in Part B of Annex I to Regulation (EC) No 396/2009, risk managers need to decide if it is necessary to amend the existing MRL set at the limit of quantification of 0.05 mg/kg.

1.2.1.2. Brussels sprouts

In support of the NEU GAP, the applicant submitted four GAP compliant residue trials on Brussels sprouts which were performed in France and Germany over growing seasons of 2013–2014. The number and quality of residue trials are sufficient to propose an MRL of 0.4 mg/kg for difenoconazole in Brussels sprouts.

1.2.1.3. Escarole/broad-leaved endives, Roman rocket/rucola, spinach, purslanes and other spinaches and similar leaves

In support of the indoor GAP and the SEU outdoor GAP, the applicant submitted eight GAP-compliant residue trials on open leaf lettuce, respectively. In support of the NEU use, the applicant submitted seven GAP-compliant residue trials on open leaf lettuce and three trials on lamb's lettuce. Trials were performed over growing seasons of 2013–2014 in various European Member states.

According to the EU guidance document on extrapolation (European Commission, 2017), the indoor trials, the SEU and the NEU residue trials are sufficient to derive a MRL proposal of 3 mg/kg for escarole/broad-leaved endives, Roman rocket/rucola and the whole group of spinaches and similar leaves, including spinach and purslane.

1.2.1.4. Witloof/Belgian endive

For witloof, several intended GAPs were submitted by the applicant, which cover field treatments of the roots before harvest in NEU and SEU (GAP 2a/2b) with or without subsequent spraying or dipping/drenching treatment of the roots before forcing (GAP 1a/1b, GAP 3a/3b) or only dipping/drenching of roots before forcing (without field treatment, GAP 4) (details of the different GAPs can be found in Appendix A).

The applicant submitted residue trials on witloof reflecting different treatment patterns. Trials were performed in growing seasons of 2013–2014. Of all treatments, the most critical GAPs with regard to the residues in witloof were the indoor treatments of roots (GAP 4) and the outdoor treatment in the NEU combined with spray indoor treatment (GAP 1a). Both uses result in a MRL proposal of 4 mg/kg, which is supported by a sufficient number of residue trials. Trials reflecting the SEU use have not been submitted (GAP 1b, 2b and 3b) and, as the outdoor use is intended only in France, where witloof is grown mostly in northern part, this is not considered a data gap.

1.2.1.5. Rhubarb

In support of the intended SEU GAP, the applicant submitted nine GAP compliant residue trials on celery, which were performed in various southern EU Member states over growing seasons of 2013–2014. Trials representing the NEU use have not been submitted. Based on the available residue data set, a MRL of 5 mg/kg is derived, extrapolated to rhubarb, as proposed by the applicant and the EMS and supported by the EU guidance document (European Commission, 2017).

1.2.2. Magnitude of residues in rotational crops

The possible transfer of difenoconazole residues to crops that are grown in a crop rotation has been assessed in EU pesticides peer review under Directive 91/414/EEC (Sweden, 2006; EFSA, 2011a).

The available rotational crop field study investigated the uptake of difenoconazole and triazole alanine in carrot and spinaches being planted 30–31 days after the treatment of soil with 750 g difenoconazole/ha (Sweden, 2006). The results demonstrated that in mature crops, difenoconazole and triazole alanine residues were below the LOQs of 0.02 and 0.05 mg/kg, respectively. The peer review, however, noted that further information on TDM residues in rotational crops are still required since the study was limited to a single plant back interval and to two crops only (EFSA, 2011a). In the confined rotational crop studies conducted with three different plant back intervals and an application rate of 125 g a.s./ha, residues of difenoconazole were not detected in crops at maturity while significant TDM residues were found primarily in cereal grains at medium and long plant back intervals. It is noted that the magnitude of TDMs in rotational crops will be assessed once the overall assessment of the confirmatory data on the TDMs is finalised.

Since the maximum annual application rate on the crops under consideration is lower (i.e. 150 g a.s./ha) than the application rate tested in the limited rotational crop field trials and very similar to the application rate used in the confined rotational crop studies, it is concluded that significant difenoconazole residues in rotational crops are not expected, provided that the active substance is applied according to the proposed GAP.

1.2.3. Magnitude of residues in processed commodities

New studies investigating the effect of processing on the magnitude of difenoconazole residues in processed commodities under consideration have not been submitted. It is unlikely that major processing types for the crops under consideration (cooking in water, or steaming) will result in a concentration of difenoconazole in processed vegetable commodities. A refinement of the consumer dietary intake estimates is currently not necessary.

Processing studies might become relevant once the data gap related to isomeric composition of difenoconazole in crops and the relative toxicity of different isomers is addressed.

1.2.4. Proposed MRLs

The available data are considered sufficient to derive MRL proposals as well as risk assessment values for all the commodities under evaluation (see Appendix B.1.2.1). In Section 3, EFSA assessed whether residues on these crops resulting from the intended uses are likely to pose a consumer health risk.

2. Residues in livestock

Not relevant as the crops under consideration are not used for feed purposes.

3. Consumer risk assessment

EFSA performed a provisional dietary risk assessment using revision 2 of the EFSA PRIMo (EFSA, 2007). This exposure assessment model contains food consumption data for different subgroups of the EU population and allows the acute and chronic exposure assessment to be performed in accordance with the internationally agreed methodology for pesticide residues (FAO, 2016).

The risk assessment is considered provisional, pending the submission of confirmatory data on possible preferential metabolism/degradation of the four stereo isomers of difenoconazole in plants. Thus, the risk assessment has to be reconsidered when the missing data are available and the guidance on a risk assessment approach for residues containing isomers is implemented. In addition, the comprehensive risk assessment of TDMs is still pending.

The toxicological reference values for difenoconazole used in the risk assessment (i.e. ADI and ARfD values) were derived in the framework of the EU pesticides peer review (EFSA, 2011a).

3.1. Short-term (acute) dietary risk assessment

The short-term exposure assessment was performed for the commodities assessed in this application in accordance with the internationally agreed methodology (FAO, 2016). The calculations were based on the highest residue (HR) values derived from supervised field trials and the complete list of input values can be found in Appendix D.1.

The short-term exposure did not exceed the ARfD for any the crops assessed in this application (see Appendix C).

3.2. Long-term (chronic) dietary risk assessment

The long-term exposure assessment was performed taking into account the supervised trials median residue (STMR) values derived for the commodities assessed in this application; for the remaining commodities covered by the Commission Regulation (EU) No 2017/626¹¹, the existing EU MRLs and STMR values derived in previous MRL applications were selected as input values (EFSA, 2017). The complete list of input values is presented in Appendix D.1.

The estimated long-term dietary intake was in the range of 13–87% of the ADI. The contribution of residues expected in the commodities assessed in this application to the overall long-term exposure is low and is presented in more detail in Appendix C.

¹¹ Commission Regulation (EU) 2017/626 of 31 March 2017 amending Annexes II and III to Regulation (EC) No 396/2005 of the European Parliament and of the Council as regards maximum residue levels for acetamiprid, cyantraniliprole, cypermethrin, cyprodinil, difenoconazole, ethephon, fluopyram, flutriafol, fluxapyroxad, imazapic, imazapyr, lambda-cyhalothrin, mesotrione, profenofos, propiconazole, pyrimethanil, spirotriamat, tebuconazole, triazophos and trifloxystrobin in or on certain products. OJ L 96, 7.4.2017, p. 1–43.

EFSA concluded that the long-term intake of residues of difenoconazole resulting from the existing and the intended uses do not exceed the toxicological reference value established for the active substance difenoconazole.

Conclusions and recommendations

The data submitted in support of this MRL application were found to be sufficient to derive MRL proposals for all crops under consideration.

Adequate analytical methods for enforcement are available to control the residues of difenoconazole in plant commodities under consideration.

Based on the risk assessment results, EFSA concluded that the long-term and short-term intake of residues of difenoconazole resulting from the existing and the intended uses do not exceed the toxicological reference values established for the active substance difenoconazole. The consumer exposure assessment has to be considered provisional as the impact of a potentially different isomer composition in the residues of difenoconazole on this risk assessment is currently unknown and has to be reconsidered when data on possible preferential metabolism/degradation of the four stereo isomers of difenoconazole in plants are available and guidance on a risk assessment approach for residues containing isomers is implemented. In addition, the comprehensive risk assessment of TDMs is still pending.

The MRL recommendations are summarised in Appendix B.4.

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Abbreviations

a.s.	active substance
ADI	acceptable daily intake
ARfD	acute reference dose
AT	Austria
BBCH	growth stages of mono- and dicotyledonous plants
BE	Belgium
bw	body weight
CEN	European Committee for Standardisation (Comité Européen de Normalisation)
CZ	Czech Republic
DALA	days after last application
DAR	draft assessment report
DAT	days after treatment
DE	Germany
DK	Denmark
DT _{90 field}	period required for 90% dissipation (field method of estimation)
EL	Greece
EMS	evaluating Member State
ES	Spain
eq	residue expressed as a.s. equivalent
FAO	Food and Agriculture Organization of the United Nations
FR	France
GAP	Good Agricultural Practice
GC	gas chromatography
HPLC-MS/MS	high performance liquid chromatography with tandem mass spectrometry
HR	highest residue
IEDI	international estimated daily intake
IESTI	international estimated short-term intake

ILV	independent laboratory validation
ISO	International Organisation for Standardisation
IT	Italy
IUPAC	International Union of Pure and Applied Chemistry
LC	liquid chromatography
LOQ	limit of quantification
MRL	maximum residue level
MS	Member States
MS	mass spectrometry detector
MS/MS	tandem mass spectrometry detector
NEU	northern Europe
NL	The Netherlands
OECD	Organisation for Economic Co-operation and Development
PBI	plant back interval
PHI	preharvest interval
PL	Poland
PRIMo	(EFSA) Pesticide Residues Intake Model
PT	Portugal
QuEChERS	Quick, Easy, Cheap, Effective, Rugged and Safe (analytical method)
RMS	rappporteur Member State
RO	Romania
SC	suspension concentrate
SEU	southern Europe
SI	Slovenia
STMR	supervised trials median residue
TDMs	triazole derivative metabolites
TRR	total radioactive residue
UK	The United Kingdom
WHO	World Health Organization

Appendix A – Summary of intended GAP triggering the amendment of existing EU MRLs

Crop and/or situation	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
				Type ^(b)	Conc. a.s.	Method kind	Range of growth stages and season ^(c)	Number min–max	Int. between appl. (min)	g a.s./hL min–max	Water L/ha min–max	g a.s./ha min–max		
Other flowering brassica	NEU/SEU (AT, BE, CZ, NL, PL, RO, SI, UK, DE, ES, FR, EL, IT, PT)	F	<i>Alternaria</i> spp., <i>Mycosphaerella brassicicola</i> , <i>Stemphylium</i> spp., <i>Rust*</i> (<i>Albugo candida</i>)	SC	50 g/L	Spray	BBCH 41–91	3	7	6.25–25	200–1,000	50	14	*Rust: Registration under Article 51 (2)(a) and (c) of the Regulation (EC) No 1107/2009
Brussels sprouts	NEU (BE, CZ, NL, PL, RO, SI, UK)	F	<i>Alternaria</i> spp., <i>Mycosphaerella brassicicola</i>	SC	50 g/L	Spray	BBCH 41–91	3	7	6.25–25	200–800	50	14	
Escarole/broad-leaved endives, Roman rocket/rucola	NEU/SEU (UK, CZ, PL, RO, SI, ES, FR, EL, IT, PT)	I	<i>Sclerotinia sclerotiorum</i> , <i>Sclerotinia minor</i> , <i>Rhizoctonia solani*</i>	SC	50 g/L	Spray	BBCH 12–49	2	7	6–30	200–1,000	60	14	<i>Rhizoctonia solani*</i> Registration under Article 51 (2)(a) and (c) of the Regulation (EC) No 1107/2009
	NEU/SEU (AT, BE, CZ, DE, NL, PL, RO, SI, UK, ES, FR, EL, IT, PT)	F	<i>Rhizoctonia solani*</i>	SC	50 g/L	Spray	BBCH 12–49	1	–	10–50	200–1,000	100	14	
Spinaches and similar leaves	NEU/SEU (ES, FR, GR, IT, PT, UK, AT, BE, CZ, DE, NL, PL, RO, SI)	F	<i>Sclerotinia sclerotiorum</i> , <i>Sclerotinia minor</i> , <i>Rhizoctonia solani*</i>	SC	50 g/L	Spray	BBCH 12–49	1	–	10–50	200–1,000	100	14	<i>Rhizoctonia solani*</i> Registration under Article 51 (2)(a) and (c) of the Regulation (EC) No 1107/2009

Crop and/or situation	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
				Type ^(b)	Conc. a.s.	Method kind	Range of growth stages and season ^(c)	Number min–max	Int. between appl. (min)	g a.s./hL min–max	Water L/ha min–max	g a.s./ha min–max		
Witloof/ Belgian Endive	NEU/SEU (FR)	F	Rust* (<i>Puccinia cichorii</i>), <i>Alternaria spp.</i> *	SC	50 g/L	Spraying Spraying	BBCH 13–49	2	7	5–25	200–1,000	50	14	GAP 1a (NEU), 1b (SEU) Critical GAP 1a *Registration under Article 51 (2)(a) and (c) of the Regulation (EC) No 1107/2009
							BBCH 49 after harvest (shortly after preparation for forcing)	1		15 mL product m (spraying) ²	Spray 5 L/m ²	21		
	NEU/SEU (FR)	F	Rust* (<i>Puccinia cichorii</i>), <i>Alternaria spp.</i> *	SC	50 g/L	Spraying	BBCH 13–49	2	7	5–25	200–1,000	50	42**	
NEU/SEU (FR)	F	I	Rust* (<i>Puccinia cichorii</i>), <i>Alternaria spp.</i> *	SC	50 g/L	Spraying	BBCH 13–49	2	7	5–25	200–1,000	50	14	GAP 3a (NEU), 3b (SEU) *Registration under Article 51 (2)(a) and (c) of the Regulation (EC) No 1107/2009
						Drenching/ dipping	BBCH 49 after harvest, before storage	1		0.25 product L/hL	30–40 L/t tubers	21		

Crop and/or situation	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
				Type ^(b)	Conc. a.s.	Method kind	Range of growth stages and season ^(c)	Number min–max	Int. between appl. (min)	g a.s./hL min–max	Water L/ha min–max	g a.s./ha min–max		
	NEU/SEU (BE, NL, UK, ES, FR, EL, IT, PT)	I	<i>Sclerotinia spp.</i> , <i>Thielaviopsis spp.</i>	SC	50 g/L	Dipping/drenching	BBCH 49 after harvest before storage (dipping/drenching) and shortly after preparation for forcing (spray)	1–2	–	0.25 product L/hL (dipping/drenching) 15 mL product m ² (spraying)	Dipping/drenching 30–40 L/t tubers Spray 5 L/m ²		21	GAP 4
Rhubarb	NEU/SEU (ES, FR, GR, IT, PT)	F	<i>Septoria spp.*</i> , <i>Sclerotonia spp.*</i>	SC	50 g/L	Spraying	BBCH 41–91	1	–	16.7–25	400–600	100	7	*Registration under Article 51 (2)(a) and (c) of the Regulation (EC) No 1107/2009

NEU: northern European Union; SEU: southern European Union; MS: Member State.

(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 formulation types and international coding system.

(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 – List of end points

B.1. Residues in plants

B.1.1. Nature of residues and methods of analysis in plants

B.1.1.1. Metabolism studies, methods of analysis and residue definitions in plants

Primary crops (available studies)	Crop groups	Crop(s)	Application(s)	Sampling (DALA)
	Fruit crops	Tomatoes	Foliar (indoor), 6 × 123 g/ha	34
			Foliar (indoor), 6 × 123 g/ha, 7 days interval	7
			Foliar (field), 3 × 247 g/ha, 14 days interval	40
		Grapes	Foliar, 5 × 247 g/ha	20
	Root crops	Potatoes	Foliar, 6 × 123 g/ha, 7 days interval	11
	Cereals/grass	Spring wheat	Foliar, 4 × 247 g/ha, 7–8 days interval	29
			Seed treatment, 20–30 g/100 kg seed	At harvest
Pulses/oilseeds	Rape seed	Foliar 2 × 125 g/ha, 14 days interval	39	
Radiolabelled active substance: [phenyl- ¹⁴ C]- and [triazole- ¹⁴ C]-labelled difenoconazole (Sweden, 2006, EFSA, 2011a)				
Rotational crops (available studies)	Crop groups	Crop(s)	Application(s)	PBI (DAT)
	Root/tuber crops	Turnip*	Soil, 1 × 32.4 g/ha	30–33 days
		Sugar beet	Soil, 1 × 125 g/ha	98, 126, 342, 369 days
	Leafy crops	Mustard*	Soil, 1 × 32.4 g/ha	30–33 days
		Lettuce	Soil, 1 × 125 g/ha	98, 126, 342, 369 days
Cereal	Wheat	Soil, 1 × 125 g/ha	98, 126, 342, 369 days	
	Maize			
	Wheat*	Soil, 1 × 32.4 g/ha	30–33 days	
Radiolabelled active substance: [phenyl- ¹⁴ C]- and [triazole- ¹⁴ C]-labelled difenoconazole *Study performed with [phenyl- ¹⁴ C]difenoconazole only (Sweden, 2006)				
Processed commodities (hydrolysis study)	Conditions			Stable?
	Pasteurisation (20 min, 90°C, pH 4)			Yes
	Baking, brewing and boiling (60 min, 100°C, pH 5)			Yes
	Sterilisation (20 min, 120°C, pH 6)			Yes
Hydrolysis studies performed with [triazole- ¹⁴ C]-labelled difenoconazole identify no degradation of difenoconazole (Sweden, 2006; EFSA, 2011a)				

DALA: days after last application; DAT: days after treatment.

Can a general residue definition be proposed for primary crops?	Yes
Rotational crop and primary crop metabolism similar?	Partially. No residues of difenoconazole were found in rotational crops, while parent compound was present in primary crops. Residues in rotational crops mainly composed of TDM metabolites, triazole alanine (TA), triazole acetic acid (TAA) and triazole lactic acid (TLA)
Residue pattern in processed commodities similar to residue pattern in raw commodities?	Yes
Plant residue definition for monitoring (RD-Mo)	Difenoconazole
Plant residue definition for risk assessment (RD-RA)	1) Difenoconazole 2) Triazole derivative metabolites (TDM) (provisional, pending the definition of a common and harmonised approach for all the active substances of the triazole class)
Conversion factor (monitoring to risk assessment)	None
Methods of analysis for monitoring of residues (analytical technique, crop groups, LOQs)	LC–MS/MS: -high water content 0.02 mg/kg (lettuce, apple) -high oil content 0.05 mg/kg (oilseed rape) -high starch content 0.05 mg/kg (wheat) ILV available for all matrices (EFSA, 2011a) HPLC–MS/MS (QuEChERS) - high acid content 0.01 mg/kg - high water content 0.01 mg/kg - high starch content (cereals) 0.01 mg/kg (EFSA, 2017)

B.1.1.2. Stability of residues in plants

Plant products (available studies)	Category	Commodity	T (°C)	Stability (months)
High water content		Tomatoes	–20	24
		Lettuce	–20	12
		Banana	–20	12
		Sugar beet	–18	12
High oil content		Soybean	–20	12
		Cotton seed	–20	24
		Rape seed	–18	12
High starch content		Potatoes	–20	24
		Wheat grain	–20	24
High protein content		–		
High acid content		Grapes	–18	12
In all studies the demonstrated storage stability period is equal with the overall duration of the study. All studies assessed in the DAR (Sweden, 2006), except those on rape seed, sugar beet root and grapes (Austria, 2017; EFSA, 2017).				

DAR: draft assessment report.

B.1.2. Magnitude of residues in plants

B.1.2.1. Summary of residues data from the supervised residue trials

Crop (GAP)	Region/indoor ^(a)	Residue levels observed in the supervised residue trials (mg/kg)	Comments (OECD calculations)	MRL proposals (mg/kg)	HR _{Mo} ^(b) (mg/kg)	STMR _{Mo} ^(c) (mg/kg)
Other flowering brassica	NEU	Broccoli, cauliflower: 5 × < 0.01; 0.026; 0.03; 0.047 ^(e)	MRL _{OECD} = 0.07/0.08	0.08	0.04	0.01
	SEU	Broccoli, cauliflower: 6 × < 0.01; 0.022; 0.024	MRL _{OECD} = 0.04/0.04	0.04	0.02	0.01
Brussels sprouts	NEU	0.012; 0.018; 0.12; 0.14	MRL _{OECD} = 0.34/0.40	0.4	0.14	0.07
Escaroles/broad-leaved endives; Roman rocket/rucola, spinach, purslane and other spinach and similar leaves	Indoor	Open leaf lettuce: 2 × < 0.01; 0.038; 2 × 0.10; 0.24; 0.28; 0.43; 0.72; 1.1 ^(e)	MRL _{OECD} = 1.74/2.0	2.0	1.10	0.17
	NEU	Open leaf lettuce: < 0.01; 0.047; 0.056; 0.09; 0.33; 0.45; 0.86 Lamb`s lettuce: 0.32; 0.55; 1.50	Residue trials on lettuce and lamb`s lettuce combined. Extrapolation to escaroles/ broad-leaved endives, Roman rocket/rucola, spinach, purslanes and other spinach and similar leaves MRL _{OECD} = 2.28/3.0	3.0	1.50	0.33
	SEU	Open leaf lettuce: 0.012; 0.018; 0.042; 0.087; 0.10; 0.48; 0.87; 1.0 ^(e)	MRL _{OECD} = 1.95/2.0	2.0	1.00	0.09
Witloof/Belgian Endive	NEU (2 field treatments)	4 × < 0.01	MRL _{OECD} = 0.01/0.01	0.01*	0.01	0.01
	NEU + Indoor (two field treatments+ indoor dip/drench)	0.11; 0.14; 0.16; 0.19 ^(f) ; 0.28; 0.60 ^(f) ; 0.85 ^(f)	MRL _{OECD} = 1.46/1.50	1.50	0.85	0.19

Crop (GAP)	Region/indoor ^(a)	Residue levels observed in the supervised residue trials (mg/kg)	Comments (OECD calculations)	MRL proposals (mg/kg)	HR _{Mo} ^(b) (mg/kg)	STMR _{Mo} ^(c) (mg/kg)
	NEU + Indoor (two field treatments + indoor spray)	0.046; 0.18; 0.23; 0.36; 0.43; 0.47; 0.90; 2.20	MRL _{OECD} = 3.38/4.0	4.0	2.2	0.4
	Indoor (dip + spray)	0.39; 1.1; 1.5; 1.8	MRL _{OECD} = 3.64/4.0	4.0	1.80	1.30
Rhubarb	SEU	Celery: 0.11; 0.12; 0.19; 0.31; 0.70; 1.10; 1.65; 1.99; 2.59 ^(g)	Residue data on celery extrapolated to rhubarb MRL _{OECD} = 4.64/5.0	5.0	2.59	0.70
	NEU	–	Residue trials supporting the use not submitted	–	–	–

*: Indicates that the MRL is proposed at the limit of quantification.

(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): Highest residue according to the residue definition for monitoring.

(c): Supervised trials median residue according to the residue definition for monitoring.

(d): Conversion factor to recalculate residues according to the residue definition for monitoring to the residue definition for risk assessment.

(e): Residues higher at a longer PHI interval of 21 days.

(f): Residues higher at a longer PHI interval of 36 days.

(g): Residues higher at a longer PHI interval of 14 days.

B.1.2.2. Residues in succeeding crops

Confined rotational crop study (quantitative aspect)	In studies with [¹⁴ C-phenyl] difenoconazole (appl. of 32.4 g/ha and 125 g/ha) the TRR too low to be characterised. In a study with [¹⁴ C-triazole] difenoconazole, the TRR in mature crops accounted for up to 0.02 mg eq/kg in lettuce, 0.34 mg eq/kg in wheat grain, 0.11 mg eq/kg in straw, 0.005 mg eq/kg in sugar beet roots, 0.03 mg eq/kg in sugar beet tops and 0.21 mg eq/kg in maize grain (Sweden, 2006)
Field rotational crop study	Field study available with difenoconazole applied on a bare soil at a rate of 750 g/ha. Mature rotational crops carrot and spinach, planted at 30-and 31-day PBI, did not contain difenoconazole and triazole alanine residues above the respective LOQs (Sweden, 2006). Study limitations: single plant back interval and two crops only (EFSA, 2011a)

B.2. Residues in livestock

Not relevant for the current MRL application.

B.3. Consumer risk assessment

ARfD	0.16 mg/kg bw Comments: The isomer ratio in the tested compound was not reported; no information available on the relative toxicity of different isomers (EFSA, 2011a)
Highest IESTI, according to EFSA PRIMo	Escaroles/broad leaved endives: 82% of ARfD Witloof/Belgian endive: 64% of ARfD Rhubarb: 60% of ARfD Spinach: 21% of ARfD Purslane: 14% of ARfD Other commodities under consideration: < 10% of ARfD
Assumptions made for the calculations	The calculation is performed only for the crops under assessment, considering the highest residue levels derived from the supervised field trials performed for the intended GAPs The calculation shall be considered provisional as the contribution of TDMS and the isomeric composition of active substance has not been considered
ADI	0.01 mg/kg bw per day Comments: The isomer ratio in the tested compound was not reported; no information available on the relative toxicity of different isomers (EFSA, 2011a)
Highest IEDI, according to EFSA PRIMo	87% ADI (WHO Cluster diet B) Contribution of crops assessed: Brussels sprouts : 0.14% of ADI (IE adult) Escaroles/broad leaved endives: 0.67% of ADI (NL child) Roman rocket/rucola: 0.02% of ADI (DE child) Spinach: 2.3% ADI (FR toddler) Purslane: 0.02% ADI (DE child diet) Other spinaches and similar leaves: 0.2% ADI (IT adult) Witloof/Belgian endive: 2.4% ADI (NL child) Rhubarb: 1.7% ADI (IE adult)

Assumptions made for the calculations

The calculation is based on the median residue levels derived from the residue trials on raw agricultural commodities under consideration. Where available, STMR values were used for other commodities of plant origin previously assessed by EFSA (2017). For the remaining commodities, the existing EU MRLs were used as input values. The calculation shall be considered provisional as the contribution of TDMs and the isomeric composition of active substance has not been considered.

B.4. Recommended MRLs

Code ^(a)	Commodity	Existing EU MRL (mg/kg)	Proposed EU MRL (mg/kg)	Comment/justification
Enforcement residue definition: Difenoconazole				
0241990	Others (flowering brassica)	0.05*	0.08	The MRL proposal was derived from residue trials performed in the NEU. According to the provisional dietary risk assessment, the toxicological reference values were not exceeded.
0242010	Brussels sprouts	0.3	0.4	The submitted data are sufficient to derive a MRL proposal for the NEU use. According to the provisional dietary risk assessment, the toxicological reference values were not exceeded.
0251030	Escaroles/broad-leaved endives	0.8	3	The MRL proposal reflects the NEU outdoor use. According to the provisional dietary risk assessment, the toxicological reference values were not exceeded.
0251060	Roman rocket/rucola	2	3	
0252010	Spinaches	2	3	
0252020	Purslanes	2	3	
0252990	Other (spinaches and similar leaves)	0.05*	3	
0255000	Witloofs/Belgian endives	0.08	4	The MRL proposal reflects the NEU outdoor use (in combination with indoor treatment) and indoor use. For SEU uses, the data were not submitted. According to the provisional dietary risk assessment, the toxicological reference values were not exceeded.
0270070	Rhubarbs	0.5	5	The submitted data are sufficient to derive a MRL proposal for the SEU use. For the NEU use, no data were submitted. According to the provisional dietary risk assessment, the toxicological reference values were not exceeded.

*: 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.

Appendix C – Pesticide Residue Intake Model (PRIMo)

Difenoconazole			
Status of the active substance:		Code no.	
LOQ (mg/kg bw):		Proposed LOQ:	
Toxicological end points			
ADI (mg/kg bw per day):	0.01	ARfD (mg/kg bw):	0.16
Source of ADI:	EFSA	Source of ARfD:	EFSA
Year of evaluation:	2011	Year of evaluation:	2011

Chronic risk assessment – refined calculations									
		TMDI (range) in % of ADI minimum – maximum 13 – 87							
		No of diets exceeding ADI:		---					
Highest calculated TMDI values in % of ADI	MS Diet	Highest contributor to MS diet (in % of ADI)	Commodity/ group of commodities	2nd contributor to MS diet (in % of ADI)	Commodity/ group of commodities	3rd contributor to MS diet (in % of ADI)	Commodity/ group of commodities	pTMRLs at LOQ (in % of ADI)	
87	WHO Cluster diet B	22	Tomatoes	9	Wine grapes	9	Olives for oil production		
74	DE child	20	Pome fruit	9	Herbal infusions (dried)	7	Citrus fruit		
67	NL child	11	Pome fruit	6	Citrus fruit	6	Potatoes		
62	IE adult	7	Wine grapes	4	Citrus fruit	4	Other leafy brassica		
54	FR toddler	11	Beans (with pods)	6	Tomatoes	5	Potatoes		
48	WHO cluster diet E	8	Wine grapes	4	Potatoes	4	Tomatoes		
46	PT General population	13	Wine grapes	7	Rice	6	Tomatoes		
42	WHO cluster diet D	7	Tomatoes	5	Rice	4	Potatoes		
40	WHO regional European diet	8	Tomatoes	4	Potatoes	2	Peas (with pods)		
40	FR all population	21	Wine grapes	3	Tomatoes	2	Witloof		
38	ES child	7	Tomatoes	4	Rice	4	Citrus fruit		
37	FR infant	8	Beans (with pods)	5	Pome fruit	4	Potatoes		
35	SE general population 90th percentile	6	Tomatoes	4	Potatoes	4	Chinese cabbage		
35	UK Toddler	5	Rice	5	Sugar beet (root)	4	Tomatoes		
33	NL general	3	Wine grapes	3	Tomatoes	3	Citrus fruit		
32	UK Infant	6	Peas (without pods)	6	Rice	3	Potatoes		
32	WHO Cluster diet F	5	Tomatoes	3	Potatoes	3	Wine grapes		
30	ES adult	6	Tomatoes	3	Lettuce	2	Beans (with pods)		
29	IT kids/toddler	10	Tomatoes	2	Pome fruit	2	Rice		
27	IT adult	8	Tomatoes	2	Lettuce	2	Pome fruit		
24	UK vegetarian	4	Tomatoes	4	Wine grapes	3	Rice		
22	DK child	5	Pome fruit	4	Tomatoes	2	Potatoes		
21	UK Adult	6	Wine grapes	3	Rice	3	Tomatoes		
20	PL general population	6	Tomatoes	4	Pome fruit	3	Potatoes		
20	DK adult	7	Wine grapes	3	Tomatoes	2	Pome fruit		
17	LT adult	4	Tomatoes	3	Pome fruit	3	Potatoes		
13	FI adult	3	Tomatoes	2	Citrus fruit	2	Wine grapes		

Conclusion:
The estimated Theoretical Maximum Daily Intakes (TMDI), based on pTMRLs were below the ADI.
A long-term intake of residues of Difenoconazole is unlikely to present a public health concern.

Acute risk assessment/children – refined calculations	Acute risk assessment/adults/general population – refined calculations
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The acute risk assessment is based on the ARfD.

For each commodity, the calculation is based on the highest reported MS consumption per kg bw and the corresponding unit weight from the MS with the critical consumption. If no data on the unit weight was available from that MS, an average European unit weight was used for the IESTI calculation.

In the IESTI 1 calculation, the variability factors were 10, 7 or 5 (according to JMPR manual 2002); for lettuce, a variability factor of 5 was used.

In the IESTI 2 calculations, the variability factors of 10 and 7 were replaced by 5. For lettuce, the calculation was performed with a variability factor of 3.

Threshold MRL is the calculated residue level which would leads to an exposure equivalent to 100% of the ARfD.

Unprocessed commodities	No of commodities for which ARfD/ADI is exceeded (IESTI 1): ---			No of commodities for which ARfD/ADI is exceeded (IESTI 2): ---			No of commodities for which ARfD/ADI is exceeded (IESTI 1): ---			No of commodities for which ARfD/ADI is exceeded (IESTI 2): ---					
	IESTI 1 *)		**)	IESTI 2 *)		**)	IESTI 1 *)		**)	IESTI 2 *)		**)			
	Highest % of ARfD/ADI	Commodities	pTMRL/ threshold MRL (mg/kg)	Highest % of ARfD/ADI	Commodities	pTMRL/ threshold MRL (mg/kg)	Highest % of ARfD/ADI	Commodities	pTMRL/ threshold MRL (mg/kg)	Highest % of ARfD/ADI	Commodities	pTMRL/ threshold MRL (mg/kg)			
	82	Scarole (broad-leaf)	1.5/-	49.2	Scarole (broad-leaf)	1.5/-	22.7	Witloof	2.2/-	18.6	Witloof	2.2/-			
	64	Witloof	2.2/-	48.6	Witloof	2.2/-	15.9	Rhubarb	2.59/-	12.7	Rhubarb	2.59/-			
	60	Rhubarb	2.59/-	43.2	Rhubarb	2.59/-	9.7	Purslane	1.5/-	8.8	Purslane	1.5/-			
	21	Spinach	1.5/-	21.2	Spinach	1.5/-	8.4	Spinach	1.5/-	8.4	Spinach	1.5/-			
	14	Purslane	1.5/-	10.7	Purslane	1.5/-	8.3	Scarole (broad-leaf)	1.5/-	8.3	Scarole (broad-leaf endive)	1.5/-			
	3	Rocket, Rucola	1.5/-	2.9	Rocket, Rucola	1.5/-	0.4	Brussels sprouts	0.14/-	0.4	Brussels sprouts	0.14/-			
	1	Brussels sprouts	0.14/-	0.8	Brussels sprouts	0.14/-									
No of critical MRLs (IESTI 1)			---	No of critical MRLs (IESTI 2)			---	No of critical MRLs (IESTI 1)			---	No of critical MRLs (IESTI 2)			---

Processed commodities	No of commodities for which ARfD/ADI is exceeded: ---			No of commodities for which ARfD/ADI is exceeded: ---		
			***)			***)
	Highest % of ARfD/ADI	Processed commodities	pTMRL/ threshold MRL (mg/kg)	Highest % of ARfD/ADI	Processed commodities	pTMRL/ threshold MRL (mg/kg)

*) The results of the IESTI calculations are reported for at least 5 commodities. If the ARfD is exceeded for more than 5 commodities, all IESTI values > 90% of ARfD are reported.

**) pTMRL: provisional temporary MRL

***) pTMRL: provisional temporary MRL for unprocessed commodity.

Conclusion:

For Difenoconazole, IESTI 1 and IESTI 2 were calculated for food commodities for which pTMRLs were submitted and for which consumption data are available. No exceedance of the ARfD/ADI was identified for any unprocessed commodity.

For processed commodities, no exceedance of the ARfD/ADI was identified.

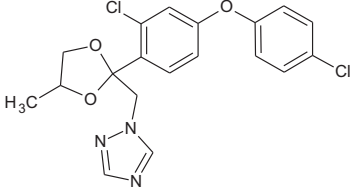

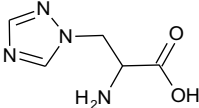
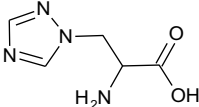
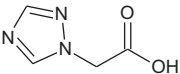
Appendix D – Input values for the exposure calculations

D.1. Consumer risk assessment

Commodity	Chronic risk assessment		Acute risk assessment	
	Input value (mg/kg)	Comment	Input value (mg/kg)	Comment
Other flowering brassica	0.01	STMR	0.04	HR
Brussels sprouts	0.07	STMR	0.14	HR
Escaroles/broad leaved endives, Roman rocket/ rucola, spinach, purslane, other spinach and similar leaves	0.33	STMR (NEU use)	1.50	HR (NEU use)
Witloofs/Belgian endives	1.30	STMR (indoor use)	2.20	HR (combined field and indoor use)
Rhubarb	0.70	STMR	2.59	HR
Other commodities of plant and animal origin	STMRs	EFSA (2017)	Acute risk assessment performed only for the crops under consideration	
	MRLs	Commission Regulation (EU) No 2017/626		

HR: highest residue; MRL: maximum residue levels; NEU: northern Europe; STMR: supervised trials median residue.

Appendix E – Used compound codes

Code/trivial name	Chemical name/SMILES notation	Structural formula
difenoconazole	3-chloro-4-[(2 <i>RS</i> ,4 <i>RS</i> ;2 <i>RS</i> ,4 <i>SR</i>)-4-methyl-2-(1 <i>H</i> -1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]phenyl 4-chlorophenyl ether	
Triazole derivative metabolites (TDMs)		
1,2,4-triazole	1 <i>H</i> -1,2,4-triazole	
Triazole alanine	3-(1 <i>H</i> -1,2,4-triazol-1-yl)-D,L-alanine	
Triazole acetic acid	1 <i>H</i> -1,2,4-triazol-1-ylacetic acid	
Triazole lactic acid or Triazole hydroxy propionic acid	(2 <i>RS</i>)-2-hydroxy-3-(1 <i>H</i> -1,2,4-triazol-1-yl)propanoic acid	

SMILES: simplified molecular-input line-entry system.