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Modification of the existing maximum residue levels for difenoconazole in leafy brassica

European Food Safety Authority (EFSA),
Maria Anastassiadou, Giovanni Bernasconi, Alba Brancato, Luis Carrasco Cabrera, Lucien Ferreira, Luna Greco, Samira Jarrah, Aija Kazocina, Renata Leuschner, Jose Oriol Magrans, Ileana Miron, Stefanie Nave, Ragnor Pedersen, Hermine Reich, Alejandro Rojas, Angela Sacchi, Miguel Santos, Alessia Pia Scarlato, Anne Theobald, Benedicte Vagenende and Alessia Verani

Abstract

In accordance with Article 6 of Regulation (EC) No 396/2005, the applicant Syngenta Crop Protection AG submitted a request to the competent national authority in the Netherlands to modify the existing maximum residue levels (MRLs) for the active substance difenoconazole in commodities belonging to the group of leafy brassica. The data submitted in support of the request were found to be sufficient to derive MRL proposals for leafy brassica. Adequate analytical methods for enforcement are available to control the residues of difenoconazole in plant matrices under consideration at the validated LOQ of 0.01 mg/kg and for difenoconazole and metabolite CGA205375 in animal matrices at the validated LOQ of 0.01 mg/kg for meat muscle, fat, liver, kidney and eggs and at the validated LOQ of 0.005 mg/kg for milk. Based on the risk assessment results, EFSA concluded that for the crops assessed in this application the short-term intake of residues resulting from the use of difenoconazole according to the reported agricultural practices is unlikely to present a risk to consumer health. Long-term consumer intake concerns cannot be excluded for the intended and existing difenoconazole uses as they are affected by uncertainties associated with the toxicity of metabolite CGA205375 and the lack of information on all existing difenoconazole uses in the EU. Overall, this 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 and has to be re-considered when the missing data become available. Additionally, this assessment does not take into consideration triazole derivative metabolites (TDMs) which may be generated by several pesticides belonging to the group of triazole fungicides as this application was submitted before September 2019 which is the date of application of the new strategy endorsed by the risk managers for the assessment of TDMs.

Keywords: difenoconazole, leafy brassica, kale, 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, Syngenta Crop Protection AG submitted an application to the competent national authority in the Netherlands (evaluating Member State, EMS) to modify the existing maximum residue levels (MRLs) for the active substance difenoconazole in commodities belonging to the group of leafy brassica. 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 19 July 2020. To accommodate for the intended uses of difenoconazole, the EMS proposed to raise the existing MRLs in leafy brassica (Chinese cabbage and kale) from 2 to 6 mg/kg.

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 28 October 2020, the EMS submitted the requested information in a revised evaluation report, which replaced the previously submitted evaluation report. EFSA emphasises that the present assessment does not take into consideration triazole derivative metabolites (TDMs), which are generated by difenoconazole and by several other pesticides belonging to the group of triazole fungicides. It is noted that in June 2019, the Standing Committee on Plants, Animals, Food and Feed (Pesticide residues) endorsed the EFSA recommendation to perform a separate risk assessment for TDMs and to apply the clock-stop mechanism in case data are missing that are needed in order to perform a comprehensive assessment for the TDMs. Risk managers agreed that such comprehensive risk assessment should be conducted for applications submitted from September 2019 onwards. As the present application was submitted before September 2019 (21 August 2019), the risk assessment for TDMs was not performed.

Based on the conclusions derived by EFSA in the framework of Directive 91/414/EEC, the data evaluated under previous MRL assessment and the additional data provided by the EMS in the framework of this application, the following conclusions are derived.

The metabolism of difenoconazole following foliar applications was investigated in crops belonging to the groups of fruit crops (tomatoes and grapes), cereals (wheat), root crops (potatoes) and pulses/oilseed crops (rapeseed). Difenoconazole and triazole derivative metabolites (TDMs) were main metabolites in all plants. In rotational crops, the major residues identified in cereal/grasses, leafy and root crops were the parent compound, difenoconazole alcohol (CGA205375) and triazole metabolites. It was noted that CGA205375 was also minor metabolite in primary crops (< 5% total radioactive residue (TRR)). Studies investigating the effect of processing on the nature of difenoconazole (hydrolysis studies) demonstrated that difenoconazole is hydrolytically stable.

Based on the metabolic pattern identified in metabolism studies and considering the results of hydrolysis studies, the residue definitions for plant products were proposed as difenoconazole for enforcement and risk assessment and, additionally, triazole derivative metabolites (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 sufficiently addressed and that the previously derived residue definitions are applicable. During the peer review, a data gap on information investigating the possible preferential metabolism/degradation of the four stereoisomers of difenoconazole in plants was identified and it is still open. Once the confirmatory data are available, the residue definitions may have to be revised.

Sufficiently validated analytical methods based on high-performance liquid chromatography with tandem mass spectroscopy (HPLC-MS/MS) are available to quantify residues in the crops assessed in this application according to the residue definition for enforcement. The methods enable quantification of residues at or above the LOQ of 0.01 mg/kg in the crops under assessment.

In support of the NEU authorisations of difenoconazole in leafy brassica, the applicant submitted six residue trials on kale which were performed in various northern EU member states during the growing seasons of 2002, 2003 and 2018. The available residue trials are sufficient to derive an MRL proposal of 6 mg/kg for all commodities belonging to the group of leafy brassica.

The occurrence of difenoconazole residues in rotational crops was investigated in the framework of the EU pesticides peer review, which noted some limitations of the available studies regarding magnitude of TDMs in rotational crops. Regarding the magnitude of residues of the parent difenoconazole and metabolite CGA205375 in rotational crops EFSA concluded that since the maximum annual application rate on the crops under consideration is lower (i.e. 375 g a.s./ha) than the

application rate tested in the limited rotational crop field trials and the more recent confined rotational crop study, significant levels of difenoconazole and CGA205375 in rotational crops are not expected, provided that the active substance is applied according to the proposed good agricultural practice (GAP).

Specific studies investigating the magnitude of difenoconazole residues in processed commodities have not been submitted. According to previously assessed studies on the magnitude of difenoconazole residues in cooked carrots, a reduction of difenoconazole residues is expected under cooking of vegetables, including processed (cooked/boiled) leafy brassica. It was noted that processing studies might become relevant once the data gap related to the isomeric composition of difenoconazole in crops and the relative toxicity of different isomers is addressed.

Kale is fed to livestock and is the main contributor to the estimated livestock dietary burdens which exceeded the trigger value of 0.1 mg/kg DM for all relevant animal species. Therefore, the possible occurrence of difenoconazole residues in commodities of animal origin was further investigated. Studies on the nature of residues in lactating goats and laying hens showed that difenoconazole was extensively metabolised to difenoconazole alcohol CGA205375 which was found to be the major metabolite in goat and hen liver, kidney, fat, muscle, milk and eggs whereas the 1,2,4-triazole was transported preferentially to eggs and milk. Two separate residue definitions for risk assessment were proposed in products of animal origin: (1) Difenoconazole alcohol (CGA205375) expressed as difenoconazole, (2) Triazole derivative metabolites. In the peer review, the residue definition for enforcement was proposed as difenoconazole alcohol (CGA205375) expressed as difenoconazole. The currently in place residue definition for enforcement in Regulation (EC) No 396/2005 is difenoconazole alone. A revision of the residue definition for enforcement might be considered by the risk managers in order to reflect the proposal of the EU pesticides peer review.

Sufficiently validated analytical methods based on HPLC-MS/MS are available to quantify residues of difenoconazole and metabolite CGA205375 in the products of animal origin. The methods enable quantification of residues at or above the LOQ of 0.01 mg/kg per substance in fat, muscle, eggs, kidney and liver and an LOQ of 0.005 mg/kg per substance in milk.

It is noted that the currently applicable MRLs for animal products are based on the Codex Maximum Limits (CXLs) derived by the JMPR in 2010, reflecting the residues of difenoconazole and its alcohol metabolite CGA205375. Based on the newly calculated livestock dietary burdens, the existing EU MRLs would need to be raised in mammalian fat, milk and liver. However, EFSA is of the opinion that the modification of the existing MRLs in products of animal origin at this stage is not required as long as metabolite CGA205375 is not included in the residue definition for enforcement according to Regulation (EC) No 396/2005.

The toxicological profile of difenoconazole was assessed in the framework of the EU pesticides peer review under Directive 91/414/EEC and the data were sufficient to derive an acceptable daily intake (ADI) of 0.1 mg/kg body weight (bw) per day and an acute reference dose (ARfD) of 0.16 mg/kg bw. For the metabolite CGA205375, which is the risk assessment residue definition for commodities of animal origin, no toxicological reference values were derived in the peer review from 2011 and no conclusions on its toxicity was derived.

The consumer risk assessment was performed with revision 3.1 of the EFSA Pesticide Residues Intake Model (PRIMo) The short-term exposure did not exceed the ARfD for any of the crops assessed in this application and accounted for kale (84% of ARfD) and Chinese cabbage (62% of ARfD).

The long-term exposure assessment which was performed in the most recent EFSA reasoned opinion on difenoconazole was updated using the supervised trial median residue (STMR) values for leafy brassica, as derived from the residue trials submitted in this application. For the remaining plant commodities, the input values were the STMRs as available from previous EFSA assessments or the MRLs as set in the Commission Regulation (EU) No 2019/552. For animal commodities (except poultry), the STMR values as derived for the calculated dietary burdens were used; these STMRs correspond to residues of metabolite CGA205375 expressed as difenoconazole assuming that parent and metabolite have a similar toxicological profile.

Based on this assumption, the calculated long-term exposure accounted for a maximum of 102% of the ADI (NL toddler). The contribution from commodities with MRLs at the LOQ is 5% of the ADI, from which 3.5% accounts for consumption of maize (NL toddler). It was noted that Dutch toddlers consume at least 5.5 times more maize-based products than all other European populations for which no ADI exceedance was observed. Considering that most of these commodities are consumed processed, the availability of processing factors would allow to refine the long-term assessment but these are not currently available.

Regarding the commodities evaluated in this application, the contribution of residues to the long-term exposure is lower than 2% of the ADI per commodity.

EFSA concludes that for the crops assessed in this application, the short-term intake of residues resulting from the use of difenoconazole according to the reported agricultural practices is unlikely to present a risk to consumer health. Long-term consumer intake concerns cannot be excluded for the intended and existing difenoconazole uses as they are affected by uncertainties associated with the toxicity of metabolite CGA205375 and the lack of information on all existing difenoconazole uses in the EU.

Overall, the present risk assessment is considered provisional pending the submission of confirmatory data on possible preferential metabolism/degradation of the four stereoisomers of difenoconazole in plants. Additionally, it does not take into consideration triazole derivative metabolites (TDMs). EFSA proposes to refine the consumer exposure assessment in the framework of the ongoing renewal of the approval of the active substance and subsequent comprehensive review of all existing uses under the MRL review.

The renewal of approval of the active substance in accordance with Regulation (EC) No 1107/2009 is ongoing, and therefore, the conclusions reported in this reasoned opinion might need to be reconsidered in the light of the outcome of the renewal.

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

Full details of all endpoints and the consumer risk assessment can be found in Appendices B–D.

Code[(a)]	Commodity	Existing EU MRL (mg/kg)	Proposed EU MRL (mg/kg)	Comment/justification
Enforcement residue definition: Difenoconazole				
0243010 0243010 0243090	– Chinese cabbages/ pe-tsai – Kales – Others	2	Further risk management considerations are required	The submitted data are sufficient to derive an MRL proposal of 6 mg/kg for the NEU use. Risk for consumers from short-term intake of residues of difenoconazole from leafy brassica is unlikely. Long-term consumer intake concerns cannot be excluded for the intended and existing difenoconazole uses as they are affected by uncertainties associated with the toxicity of metabolite CGA205375 and the lack of information on all existing difenoconazole uses in the EU.

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

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Assessment

The European Food Safety Authority (EFSA) received an application to modify the existing maximum residue level (MRL) for difenoconazole in commodities belonging to the group of leafy brassica. The detailed description of the intended NEU outdoor uses of difenoconazole in leafy brassica, 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). 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[1] 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. The draft assessment report (DAR) prepared by the RMS has been peer reviewed by EFSA (EFSA, 2011a). Difenoconazole was approved[2] for the use as fungicide on 1 January 2009.

The process of renewal of the first approval is currently ongoing.

The EU MRLs for difenoconazole are established in Annex III of Regulation (EC) No 396/2005.[3] To date, EFSA has issued several reasoned opinions on the modification of MRLs for difenoconazole. The proposals from these reasoned opinions have been considered in recent MRL regulations.[4] Certain Codex maximum residue limits (CXLs) have been taken over in the EU MRL legislation.[5,6,7,8]

In accordance with Article 6 of Regulation (EC) No 396/2005, Syngenta Crop Protection AG submitted an application to the competent national authority in the Netherlands (evaluating Member State, EMS) to modify the existing maximum residue levels (MRLs) for the active substance difenoconazole in leafy brassica. 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 19 July 2020. To accommodate for the intended uses of difenoconazole, the EMS proposed to raise the existing MRLs from 2 mg/kg to 6 mg/kg for the whole group of leafy brassicas (kale, Chinese cabbage/pe-tsai and others).

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 28 October 2020, the EMS submitted the requested information in a revised evaluation report (Netherlands, 2020), which replaced the previously submitted evaluation report.

EFSA based its assessment on the evaluation report submitted by the EMS (Netherlands, 2020), the draft assessment report (DAR) (Sweden, 2006) prepared under Council Directive 91/414/EEC, the

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1 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.

2 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.

3 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.

4 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

5 Commission Regulation (EU) No 441/2012 of 24 May 2012 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 bifenazate, bifenthrin, boscalid, cadusafos, chlorantraniliprole, chlorothalonil, clothianidin, cyproconazole, deltamethrin, dicamba, difenoconazole, dinocap, etoxazole, fenpyroximate, flubendiamide, fludioxonil, glyphosate, metalaxyl-M, meptyldinocap, novaluron, thiamethoxam and triazophos in or on certain products. OJ L 135, 25.5.2012, p. 4–56.

6 Commission Regulation (EU) 2015/845 of 27 May 2015 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 azoxystrobin, chlorantraniliprole, cyantraniliprole, dicamba, difenoconazole, fenpyroximate, fludioxonil, glufosinate-ammonium, imazapic, imazapyr, indoxacarb, isoxaflutole, mandipropamid, penthiopyrad, propiconazole, pyrimethanil, spirotetramat and trinexapac in or on certain products. OJ L 138, 4.6.2015, p. 1–69.

7 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, spirotetramat, tebuconazole, triazophos and trifloxystrobin in or on certain products C/2017/2035. OJ L 96, 7.4.2017, p. 1–43.

8 Commission Regulation (EU) 2019/552 of 4 April 2019 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 azoxystrobin, bicyclopyrone, chlormequat, cyprodinil, difenoconazole, fenpropimorph, fenpyroximate, fluopyram, fosetyl, isoprothiolane, isopyrazam, oxamyl, prothioconazole, spinetoram, trifloxystrobin and triflumezopyrim in or on certain products C/2019/2496. OJ L 96, 5.4.2019, p. 6–49.

Commission review report on difenoconazole (European Commission, 2008, 2020), 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 on difenoconazole (EFSA, 2009, 2010, 2011b, 2012, 2013, 2014a,b, 2017, 2018a).

For this application, the data requirements established in Regulation (EU) No 544/2011[9] and the guidance documents applicable at the date of submission of the application to the EMS are applicable (European Commission, 1997a–g, 2000, 2010a,b, 2017a,b; 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 546/2011.[10]

Since the review of the existing MRLs under Article 12 of Regulation 396/2005 is not yet initiated and the renewal of the first approval has not yet been finalised, the conclusions reported in this reasoned opinion are provisional and may need to be reconsidered in the light of the outcome of the renewal of the approval of difenoconazole and the future MRL review.

A selected list of end points of the studies assessed by EFSA in the framework of this MRL application including the end points of relevant studies assessed previously are presented in Appendix B.

The evaluation report submitted by the EMS (Netherlands, 2020) 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. 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 has been investigated in the framework of the EU pesticides peer review following foliar applications in fruit crops (tomatoes and grapes), cereals/grass crops (wheat), root crops (potatoes) and pulses/oilseed crops (rapeseed). Studies in cereals following seed application were also considered (Sweden, 2006; EFSA, 2011a). The metabolism was found comparable in the four crop groups. Difenoconazole was the major component of the residues in the major plant parts, except for cereal grains, potato tubers and rape seeds, where the major components of the residues were the triazole derivative metabolites (TDMs) triazole alanine, triazole acetic acid and 1,2,4-triazole. Metabolites CGA205374 (ketone), CGA205375 (alcohol) and CGA189138 (benzoic acid) were also identified in low proportions (below 5% TRR).

The data gap on the investigation of the possible preferential metabolism/degradation of the four stereoisomers of difenoconazole in plants that was identified in the framework of the peer review (EFSA, 2011a) has not yet been addressed.

It was concluded that for the intended use, the metabolic behaviour of difenoconazole in primary crops is sufficiently addressed.

1.1.2. Nature of residues in rotational crops

Difenoconazole is proposed to be used on kale and other leafy brassica which can be grown in rotation with other crops. According to the soil degradation studies evaluated in the framework of the peer review, the DT90 value of difenoconazole is 879 days (EFSA, 2011a) which exceeds the value of 100 days triggering the need for studies investigating the nature and magnitude of residues in rotational crops.

Metabolism of difenoconazole in rotational crops has been investigated in the framework of the peer review in two studies with ^{14}C-labelled difenoconazole (Sweden, 2006; EFSA, 2011a). In the first study, bare soil was treated with [^{14}C-phenyl-] difenoconazole at 32.4 g/ha and rotational crops belonging to cereal/grasses (wheat), leafy crop (mustard) and root crop (turnip) groups were planted/sown 30–33

[9] 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. OJ L 155, 11.6.2011, p. 1–66.

[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.

days after the soil treatment. In this study, the total TRR was below 0.01 mg eq/kg and was not further characterised.

In the second study, bare soil was treated with [^{14}C-triazole-] and [^{14}C-phenyl-] difenoconazole at 125 g/ha and rotational crops belonging to cereal/grasses (maize and wheat), leafy crop (lettuces) and root crop (sugar beet) groups were planted/sown 98, 126, 342 and 369 days after the soil treatment. In this study, the TRR in mature crops treated with [^{14}C-triazole] difenoconazole accounted for up to 0.02 mg eq/kg in lettuces (at 126 and 151 days after application), 0.34 mg eq/kg wheat grain (at 418 days after application), 0.11 mg eq/kg in straw (at 418 days after application), 0.005 mg eq/kg sugar beet roots (at 488 days after application), 0.03 mg eq/kg in sugar beet tops (at 488 days after application) and 0.21 mg eq/kg in maize grain (at 488 days after application) and was mainly composed of the triazole derivative metabolites. The TRR in crops treated with [^{14}C-phenyl-] difenoconazole was at levels below 0.01 mg eq/kg and was not further characterised. The EU pesticides peer review concluded that the metabolism of difenoconazole in primary and rotational crops is partially similar (EFSA, 2011a).

A new rotational crop metabolism study has been submitted with the present application (Netherlands, 2020). Bare soil was treated with difenoconazole ^{14}C-labelled on the phenyl ring at 516 g/ha (1.4N intended use on leafy brassica). EFSA noted that the study covers the metabolic pathway of the *p*-chloro-phenoxy ring which has not been elucidated in the previously submitted studies because of the very low TRR in the treated crops. The new study was performed on rotational crops belonging to cereal/grasses (wheat and sorghum), leafy crop (lettuces) and root crop (radishes) groups, planted into the treated soil at intervals of 30, 60, 120, and 270 days after treatment.

Very low radioactive residues were found in rotational crops. Parent difenoconazole was the highest residue observed in immature lettuces (42.0–81.5% TRR, from 0.005 mg eq/kg at 270 days after treatment (DAT) to 0.026 mg eq/kg at 30 DAT), mature lettuces (48.5–68.7% TRR, 0.012 mg eq/kg at 120 DAT to 0.040 mg eq/kg at 30 DAT), radish leaves (27.9–72.0% TRR, from 0.008 mg eq/kg at 30 DAT to 0.060 mg eq/kg at 120 DAT), radish roots (31.1–60.3% TRR, from 0.008 mg eq/kg at 30 and 270 DAT to 0.017 mg eq/kg at 120 DAT) and sorghum forage (9.9% TRR, 0.001 mg eq/kg at 30 DAT). In wheat straw difenoconazole was a minor residue (6.6–12.3% TRR, from 0.002 mg eq/kg at 270 DAT to 0.006 mg eq/kg at 120 DAT).

Metabolite CGA205375 was also found but in lower levels in radish leaves (7.9–22.6% TRR, from 0.004 mg eq/kg at 270 DAT to 0.007 mg eq/kg at 120 DAT), radish roots (7.6–23.7% TRR, from 0.002 mg eq/kg at DAT 30 DAT to 0.005 mg eq/kg at 60 DAT), immature lettuces (2.8–11.3% TRR, from $<$ 0.001 mg eq/kg at 270 DAT to 0.003 mg eq/kg at 30 DAT), mature lettuces (4.8–6.6% TRR, from 0.001 mg eq/kg at 120 DAT to 0.004 mg eq/kg at 30 DAT) and sorghum forage (2.6% TRR, $<$ 0.001 mg eq/kg at 30 DAT).

Difenoconazole was the main residue in wheat straw (37.9–39.9% TRR, from 0.011 mg eq/kg at 270 DAT to 0.021 mg eq/kg at 60 DAT).

Metabolite CGA189138 was detected in immature, mature lettuces and radish roots and metabolite CGA205374 in radish roots (levels $\leq$ 0.001 mg eq/kg). In leafy and root/tuber vegetables, residues were found to decline as plant back intervals became longer (Netherlands, 2020).

In wheat forage and hay, residues were extracted but not analysed due to the low levels of extractable residues. In sorghum, two components in forage (60.1% TRR) and four in stover (59.2% TRR) remained unidentified. These could be further investigated in the framework of the ongoing renewal of the approval of difenoconazole. In wheat grain, residues were below 0.01 mg eq/kg and in sorghum grain the radioactivity in the plant tissue was also very low; therefore, characterisation of residues in cereal grain was not possible (Netherlands, 2020).

The extraction efficiency and storage stability have been investigated in the context of the study. According to the EMS, difenoconazole was quantitatively extracted from mature lettuces (60 days plant back) fortified with ^{14}C-difenoconazole; approximately 99% of the applied radioactivity was recovered by extraction. HPLC-RAD analysis of the sample extracts showed that the parent and CGA205375 were stable when the samples were immediately extracted after fortification. Analysis by HPLC of radish leaf extract (120-day plant back interval) after 230 days storage in freezer, showed a stable distribution of radioactive components under storage conditions (Netherlands, 2020).

The results of the new study suggest little uptake of difenoconazole and soil metabolites by cereal grains, leafy and root crops from the treated soil. The metabolic pathway for the difenoconazole phenyl ring in primary and rotational crops is similar: degradation of the dioxolane ring to CGA205374 which would further reduce to CGA205375 or oxidatively cleaved to CGA189138 (Netherlands, 2020). The study also indicates that apart from parent difenoconazole and TDMs, plant metabolite

CGA205375 occurs above 10% of the TRR in several plant matrices but the actual levels of this metabolite in crops were below the trigger values of 0.01 mg/kg in food and 0.05 mg/kg in feed. It is proposed that the relevance of this metabolite in rotational crops is investigated in the framework of the renewal of the approval process.

EFSA concludes that the metabolic pathway of difenoconazole in rotational crops is similar to that in primary crops.

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 (Sweden, 2006; EFSA, 2011a). These studies showed that difenoconazole is hydrolytically stable.

1.1.4. Methods of analysis in plants

Analytical methods for the determination of difenoconazole residues were assessed in the framework of the EU pesticides peer review (Sweden, 2006; EFSA, 2011a). They are based on liquid chromatography with tandem mass spectrometry (LC–MS/MS) and were validated in high water content commodities (apples, lettuces) at the LOQ of 0.02 mg/kg, in dry commodities (wheat grain) at the LOQ of 0.05 mg/kg and in high oil content commodities (rapeseed) at the LOQ of 0.05 mg/kg. A QuEChERS method as reported in the European Standard EN 15662:2008 (CEN, 2008) is also available for the analysis of difenoconazole residues in high water, acidic and dry/high starch content commodities with an LOQ of 0.01 mg/kg (EFSA, 2017, 2018a).

New validation data for a multiresidue method QuEChERS based on EN15662:2009-02 (CEN, 2008) were submitted with the present application (Netherlands, 2020). The method quantifies residues of difenoconazole by HPLC-MS/MS in tomatoes (high water content), oilseed rape (high oil content), dried broad bean (high protein content), wheat grain (high starch content), grapes (high acid content) and herbal infusion (difficult to analyse) at an LOQ of 0.01 mg/kg. It is a highly specific method validated at one primary transition (m/z 406 ≥ 251) and one confirmatory transition (m/z 406 ≥ 188), therefore, a confirmatory method is not required. An ILV in tomatoes, oilseed rape, dried broad bean and herbal infusion matrix was also provided.

For the purpose of the present assessment, the analytical method for the determination of difenoconazole in high water content commodities can be considered to be fully validated as enforcement method in terms of specificity, linearity, accuracy and precision based on the provisions of the SANCO/825/00 rev 8.1 guidance document (European Commission, 2010a,b). See also Appendix B.1.1.1.

The efficiency of the extraction process was investigated in a cross-validation study using incurred residues from lettuces, olives, dry beans, wheat grain and strawberry in Northern and Southern Europe in 2017, based on SANTE/2017/10632 rev.3 (European Commission, 2017b). The method compares amounts of difenoconazole residues extracted from samples with incurred residues using the solvent system of the monitoring method and the solvent system under the conditions applied during the metabolism studies (European Commission, 2017a,b). With regard to the efficiency of the extraction in high water content commodities, the study results in lettuces suggest that the residues determined by the QuEChERS method using an extraction system of methanol/water (50/50 v/v) do not differ by more than 30% when compared to the residues obtained with the solvent used in the metabolism study (i.e. methanol/water (80/20 v/v)). EFSA would recommend that all data on extraction efficiency which were submitted for all types of crops in the framework of this application are further considered and confirmed in the framework of the ongoing peer review for the renewal of the active substance.

EFSA concludes that the methods available are sufficiently validated for the determination of residues of difenoconazole in the crops under consideration. The methods allow quantifying residues at or above the LOQ of 0.01 mg/kg in high water content commodities.

1.1.5. Storage stability of residues in plants

The storage stability of difenoconazole in plants 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, 2018a). In high water content crops (relevant for leafy brassica), residues are 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 for primary, rotational crops and processed commodities (EFSA, 2011a, 2018b):

- residue definition for risk assessment:
  1) difenoconazole;
  2) triazole derivative metabolites (TDM) (a new residue definition established for TDMs in the peer review of the pesticide risk assessment for the triazole derivative metabolites in light of confirmatory data submitted but not assessed in the present application (EFSA, 2018b))
- residue definition for enforcement: difenoconazole

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

Since difenoconazole consists of four stereoisomers, and since the available analytical methods are not stereoselective, the proposed residue definitions for enforcement and risk assessment are derived for the sum of the *R*- and *S*-isomers. EFSA noted that the data gap identified during the peer review on the possible preferential metabolism/degradation of the four stereoisomers of difenoconazole in plants is still open (EFSA, 2011a).

EFSA recommends that the existing residue definitions are reconsidered in the renewal of the approval process considering the data of the new metabolism study in rotational crops and the new EFSA guidance document on stereoisomers (EFSA, 2019b).

Furthermore, EFSA would like to emphasise that the present assessment does not take into consideration triazole derivative metabolites (TDMs) which may be generated by several pesticides belonging to the group of triazole fungicides. It is noted that in June 2019, the Standing Committee on Plants, Animals, Food and Feed (Pesticide residues)[11] endorsed the EFSA recommendation to perform a separate risk assessment for TDMs, as provided in the peer review of the pesticide risk assessment for TDMs in light of confirmatory data (EFSA, 2018b); and to apply the clock-stop mechanism in case data are missing that are needed in order to perform a comprehensive assessment for the TDMs. Risk managers agreed that such comprehensive risk assessment should be conducted for applications submitted from September 2019 onwards. As the present application was submitted before September 2019 (21 August 2019), the risk assessment for TDMs was not performed.

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 (EFSA, 2011a) are applicable.

1.2. Magnitude of residues in plants

1.2.1. Magnitude of residues in primary crops

In support of the intended NEU authorisations of difenoconazole in leafy brassica, the applicant submitted six residue trials on kale which were performed in various northern EU member states during the growing seasons of 2002, 2003 and 2018.

The trials concerned foliar applications of 3 × 125 g difenoconazole/ha on kale at growth stages BBCH 19–47 and application intervals of 6–10 days. Samples were taken 14/15 days after the last application (PHI of the intended GAP) and, in the decline trials, 0, 7, 10/11 and 21/22 days after the last application. EFSA noted that the reported critical Dutch GAP as summarised in Appendix A, refers to a less critical application interval of 14 days instead of the 7 days interval used in the context of the trials. The applicant/EMS claimed that the interval between applications varies between 7 and 14 days in the GAPs among various northern European countries and, therefore, residue trials were designed to reflect the worst-case scenario. EFSA accepted the argumentation of the applicant/EMS. Additionally, the results from the decline trials show considerable decline of residues after 21 days of treatment and suggest that the application interval is not a critical parameter of the GAP when the

[11] Standing Committee on Plants, Animals, Food and Feed Section Phytopharmaceuticals – Residues, held on 13–14 June 2019. sante.ddg2.g.5(2019)4475145.

harvest is done 14 days after the last application. Based on this information, the deviation of 7 days interval between applications was considered acceptable.

Differences were noted between the kale growth stages at the time of application in the trials (BBCH 19-47) and the critical Dutch GAP (BBCH 50-55). The growth stage in the Dutch label suggests that difenoconazole is applied on the crop after harvest. In its evaluation report, the EMS clarified that the growth stage in the Dutch GAP has not been established nor been evaluated from a residue perspective but was included in order to protect mammals and anticipate that the use of the substance in outdoor crops (such as leafy brassica) is only allowed if the crop sufficiently covers the soil. Overall, EFSA agrees with the EMS that with regard to the application timing, the critical part of the GAP is the PHI of 14 days: *In case of crops from which leafy parts are harvested, a significant part of the consumable crop is present if 6 true leaves, leaf pairs or whorls are unfolded (BBCH 16). This implies that from BBCH 16 onwards the PHI should be used in the crop field trials as a component of the cGAP, whereas the growth stage at application is of minor importance*. Based on the above, the growth stage of the trials was not further considered as essential parameter in the assessment of the trials.

An additional clarification was requested with regard to the high residue value of 3.07 mg/kg reported for one residue trial on kale performed in France in 2018. As no significant deviations from the study plan, or analytical errors were recorded during the conduct of this trial which could account for this result, the result from the trial was considered acceptable and included in the OECD MRL calculator.

Samples were analysed for parent difenoconazole only. Residue data on TDMs have not been provided and are not required for applications submitted before September 2019.[11] It was noted that in one of the two French trials on kale from 2002, the samples were stored for 15 instead of 12 months, corresponding to the period for which storage stability was investigated for difenoconazole in lettuces. Considering, however, that (i) during the 12-month period of the lettuces study, difenoconazole residues were stable and (ii) the storage stability for difenoconazole in another high water content matrix (tomato) was demonstrated for up to 24 months (Sweden, 2006; EFSA 2011a), the result derived after 15 months of storage was considered acceptable. It was concluded that all samples taken in the context of the residue trials were stored under conditions for which their integrity has been demonstrated.

Samples from the 2002 and 2003 residue trials were analysed with a method based on GC-NPD. The method was validated at an LOQ of 0.01 mg/kg in high water content matrices (apples, pears and carrots). A new method of analysis was developed and performed in the context of the 2018 residue trials based on HPLC-MS/MS. The method was validated at an LOQ of 0.01 mg/kg. The extraction efficiency of methanol/ammonium hydroxide (8/2) which was the extraction medium used in both old and new methods of analysis in the context of the trials was investigated based on the procedure detailed in Section 1.1.4. EFSA recommends that the submitted data on extraction efficiency for all crops are further considered and confirmed in the framework of the ongoing peer review for the renewal of the active substance.

EFSA concluded that the methods of analysis in the context of the trials were sufficiently validated and fit-for-purpose.

The EMS proposed to extrapolate the residue data set from kale to the entire group of 'leafy brassica' (crop code 0243000 in Annex I of Regulation (EC) No 396/2005), containing Chinese cabbage and kale. As kale belongs to the group of leafy brassica, a group which contains only minor crops, the extrapolation proposal and number of trials are sufficient to propose an MRL of 6 mg/kg for difenoconazole in the whole group of leafy brassica for which a minimum set of four trials are required for MRL setting in line with the applicable EU guidance document on crop extrapolation (European Commission, 2017a,b).

1.2.2. Magnitude of residues in rotational crops

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

The uptake of difenoconazole and triazole alanine was investigated in carrots and spinaches planted 30–31 days after soil treatment with 750 g difenoconazole/ha (2 N the intended use) (Sweden, 2006). The results showed that in mature crops, difenoconazole and triazole alanine residues were below the LOQs of 0.02 mg/kg and 0.05 mg/kg, respectively. Regarding TDM residues, further information in rotational crops was requested by the EU pesticides peer review as the study was limited to two crops only and a single plant back interval (EFSA, 2011a).

Additional rotational crop field trials on cereals small grain, carrots and lettuces were submitted for the peer review on TDMs investigating the magnitude of TDMs at different plant back intervals. The maximum storage interval of the residue trial samples was not provided to conclude on the validity of these trials (EFSA, 2018b). Nevertheless, the magnitude of TDMs in rotational crops is out of the scope of the present assessment (see Section 1.1.6).

In the confined rotational crop study (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 (EFSA, 2011a). The confined rotational crop study performed with 516 g a.s./ha (1.4N intended use) suggests little uptake of the active substance and soil metabolites in cereal grains, leafy and root/tuber crops from the treated soil (See Section 1.1.2) (Netherlands, 2020).

Overall, since the maximum annual application rate on the crops under consideration is lower (i.e. 375 g a.s./ha) than the application rate tested in the limited rotational crop field trials and the more recent confined rotational crop study, it is concluded that significant levels of difenoconazole and CGA205375 in rotational crops are not expected, provided that the active substance is applied according to the proposed GAPs. Regarding triazole metabolites, the data are currently not sufficient to conclude on the magnitude of TDMs in rotational crops. These conclusions might be subject of revision following the outcome of the renewal of the approval of difenoconazole.

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. According to four previously assessed studies on the magnitude of difenoconazole residues in peeled, washed and 15 min cooked carrots (treated with 3 $\times$ 500 g a.s./ha at a PHI of 14 days), no concentration of difenoconazole residues was observed (EFSA, 2010). The derived processing factor of 0.05 in carrots suggests that concentration of difenoconazole residues is not expected under cooking of vegetables, which is expected to be also applicable for processed (cooked/boiled) leafy brassica.

1.2.4. Proposed MRLs

The available data are considered sufficient to derive an MRL proposal as well as risk assessment values for 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

Among the crops under assessment kale may be used for feed purposes. Hence, it was necessary to update the previous livestock dietary burden calculation (EFSA, 2017, 2018a) to estimate whether residues in kale from the intended use of difenoconazole would have an impact on the residues expected in food of animal origin.

The input values for the exposure calculations for livestock are presented in Appendix D. EFSA notes that the review of existing difenoconazole MRLs under Article 12 of Regulation (EC) No 396/2005 (MRL review) has not been performed yet; therefore, a comprehensive overview of all authorised difenoconazole uses is not available and the calculated livestock dietary exposure might be under- or overestimated.

The results of the dietary burden calculation are presented in Appendix B.2 and show that the trigger value of 0.1 mg/kg DM is exceeded for all livestock species. Kale is a significant contributor to all except poultry diets. Thus, the nature and magnitude of difenoconazole residues in livestock were investigated further.

2.1. Nature of residues and methods of analysis in livestock

The metabolism and distribution of difenoconazole has been investigated in lactating goats and laying hens in the framework of the peer review where animals were fed with ^{14}C-difenoconazole labelled on the phenyl and triazole ring (EFSA, 2011a). The test compound was administered orally in the diet at a concentration of 5 and 100 mg/kg feed to the lactating goats and 5, 68 and 121 mg/kg feed to the laying hens.

Residues of parent difenoconazole were detected in the liver and fat of the lactating goats and laying hens, at concentrations up to 0.891 mg/kg (9.1% of the TRR) and 1.912 mg/kg (18.4% of the TRR), respectively. In other edible tissues, residues of parent difenoconazole were $\leq$ 0.107 mg/kg (2.2% of the TRR). In milk, residues of parent difenoconazole were up to 0.028 mg/kg (8.8% of the TRR) and up to 0.236 mg/kg (5.3% of the TRR) in egg yolk.

CGA205375 was found to be the major metabolite in goats and hens, occurring at levels up to 7.127 mg/kg (72.8% TRR) in liver, 1.180 mg/kg (43.2% TRR) in kidney, 0.949 mg/kg (91.7% TRR) in fat, 0.423 mg/kg (91.4% TRR) in muscle and up to 0.130 mg/kg (34.4% TRR) in milk, egg white and egg yolk.

1,2,4-triazole (CGA71019) was transported preferentially to eggs and milk, occurring at levels of 0.182 mg/kg (67.7% TRR) and 0.043 mg/kg (32.3% TRR) in egg white and yolk, respectively, and levels up to 0.022 mg/kg (5.8% TRR) in milk.

Ring hydroxylated difenoconazole, hydroxylated CGA205374 and hydroxylated CGA205375 were observed at levels up to 0.235 mg/kg (3.9% TRR) in goat liver and 0.021 mg/kg (15.2% TRR) in milk.

These studies showed that difenoconazole was extensively metabolised (less than 10% TRR was found in nearly all matrices). Difenoconazole alcohol CGA205375 was found to be the major metabolite in goat and hen liver, kidney, fat, muscle, milk and eggs whereas the 1,2,4-triazole (CGA71019) was transported preferentially to eggs and milk (Sweden, 2006, EFSA, 2011a).

Based on these studies, the residue definition for enforcement proposed in the peer review was limited to the metabolite difenoconazole-alcohol (CGA205375) only. For risk assessment, the following residue definitions were proposed in the peer review of difenoconazole (EFSA, 2011a) and TDMs (EFSA, 2018b):

1) Difenoconazole alcohol (CGA205375), expressed as difenoconazole
2) Triazole derivative metabolites (a new residue definition was established for TDMs in the peer review of the pesticide risk assessment for the triazole derivative metabolites in light of confirmatory data submitted but not assessed in the present application (EFSA, 2018b)). As discussed previously, TDMs were not considered in the present assessment (see Section 1.1.6).

It was noted that although metabolite CGA205375 was found to be the main residue in products of animal origin, the existing residue definition for enforcement as set in Regulation (EC) No 396/2005 is difenoconazole alone. A revision of the residue definition for enforcement might be considered by the risk managers in order to reflect the proposal of the EU pesticides peer review.

Methods of analysis in livestock

Analytical methods for the determination of difenoconazole and CGA205375 in commodities of animal origin were evaluated during the peer review under Directive 91/414/EEC (Sweden, 2006; EFSA, 2011a). They are based on LC–MS/MS and are validated at an LOQ of 0.01 mg/kg in tissues, fat and eggs, and with an LOQ of 0.005 mg/kg in milk. A multiresidue QuEChERS method based on LC–MS/MS for difenoconazole and CGA205375 with an LOQ of 0.01 mg/kg in tissues, fat and eggs, and an LOQ of 0.005 mg/kg in milk per each analyte is also applicable (CEN, 2008, EFSA, 2017, 2018a).

A new method of analysis for difenoconazole and metabolite CGA205375 in animal matrices was submitted with the present application (Netherlands, 2020). The method is based on HPLC-MS/MS and validated at an LOQ of 0.01 mg/kg per substance in fat, muscle, eggs, kidney and liver and an LOQ of 0.005 mg/kg per substance in milk. An ILV is available for fat, liver, eggs and milk. No ILV was submitted for muscle and kidney but is not required as for primary methods identical for all animal matrices, a validated ILV for two matrices is considered sufficient (European Commission, 2010b). No confirmatory method is needed as the method is highly selective. The extraction efficiency of acetonitrile/water, which is the extraction media used to extract difenoconazole and CGA205375 from animal products, was investigated using incurred ^{14}C residues from poultry metabolism study according to the requirements of SANTE/2017/10632 rev. 3 (European Commission, 2017b). EFSA recommends that the submitted data on extraction efficiency for all animal matrices are further considered and confirmed in the framework of the ongoing peer review for the renewal of the active substance.

EFSA concluded that the new analytical method can be considered fully validated as enforcement method in terms of specificity, linearity, accuracy and precision based on the provisions of the SANCO/825/00 rev 8.1 guidance document (European Commission, 2010b).

2.2. Magnitude of residues in livestock

A feeding study on dairy cows (animals dosed with difenoconazole at the levels of 1, 3 and 10 mg/kg DM) was considered in the peer review where samples were analysed for difenoconazole and metabolite CGA205375 (EFSA, 2011a). Difenoconazole was not detected at any dose in any of the animal matrices, except in liver (highest residue 0.02 mg/kg) (EFSA, 2011a). When animals were fed with the highest dose of 15 mg difenoconazole/kg dry matter, being the closest to the updated dietary burden for cattle of 11.88 mg/kg DM (see Appendix B.2), metabolite CGA205375 (expressed as difenoconazole) was found at levels up to 0.02 mg/kg in muscle, 0.08 mg/kg in fat tissue, 0.35 mg/kg in liver and 0.05 mg/kg in kidney.

The metabolism and feeding studies indicate that in animal matrices, the relevant residue is metabolite CGA205375, suggesting that the parent difenoconazole, although defined as enforcement residue in Regulation (EC) No 396/2005, is not a sufficient marker for enforcement.

It was noted that the existing EU MRLs for animal products are based on the implementation of Codex MRLs in the EU legislation from the 2010 JMPR evaluation (FAO, 2010, EFSA, 2011a). These MRLs cover the residue definition 'sum of difenoconazole and CGA205375 (1-[2-chloro-4-(4-chloro-phenoxy)-phenyl]-2-(1,2,4-triazol)-1-yl-ethanol), expressed as difenoconazole' and, therefore, take into consideration also metabolite CGA205375.[12] Additionally, the currently applicable MRLs are sufficient to account for residues of difenoconazole and its alcohol metabolite in mammalian muscle and kidney, based on the newly calculated EU livestock dietary burdens. On the other hand, they are not sufficient to account for residues of difenoconazole and its alcohol metabolite in mammalian fat, milk and liver, where higher MRL proposals have currently been estimated (see Appendix B.2). Although this suggests that the MRLs for difenoconazole residues in fat tissues, liver and milk would need to be raised, EFSA is of the opinion that the modification of the existing MRLs in products of animal origin at this stage is not required as long as metabolite CGA205375 is not included in the residue definition for enforcement, legally implemented under Regulation (EC) No 396/2005.

Moreover, the calculated EU dietary burden might not reflect all existing authorised uses of difenoconazole, and, therefore, EFSA is of the opinion that a full assessment of the magnitude of the residues in livestock should be performed in the framework of the MRL review under Article 12 of the Regulation (EC) No 396/2005.

3. Consumer risk assessment

EFSA performed a provisional dietary risk assessment using revision 3.1 of the EFSA PRIMo (EFSA, 2018c, 2019a). 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 toxicological reference values for difenoconazole used in the risk assessment (i.e. ADI of 0.01 mg/kg bw and ARfD value of 0.16 mg/kg bw) were derived in the framework of the EU pesticides peer review (EFSA, 2011a). The risk assessment residue definition in plant commodities refers to difenoconazole alone, whereas in animal commodities, it refers only to metabolite CGA205375, expressed as difenoconazole. For metabolite CGA205375, no toxicological reference values were derived in the 2011 peer review and no conclusion on its toxicity was derived (EFSA, 2011a).

3.1. Short-term (acute) dietary risk assessment

The short-term exposure assessment was performed only for the crops under consideration and was based on the HR values derived from supervised residue field trials on kale. The complete list of input values can be found in Appendix D.2.

The short-term exposure did not exceed the ARfD for any of the crops assessed in this application and accounted for kale (84% of ARfD) and for Chinese cabbage (62% of ARfD) (see Appendix C).

[12] Commission Regulation (EU) No 441/2012 of 24 May 2012 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 bifenazate, bifenthrin, boscalid, cadusafos, chlorantraniliprole, chlorothalonil, clothianidin, cyproconazole, deltamethrin, dicamba, difenoconazole, dinocap, etoxazole, fenpyroximate, flubendiamide, fludioxonil, glyphosate, metalaxyl-M, meptyldinocap, novaluron, thiamethoxam, and triazophos in or on certain products. OJ L 135, 25.5.2012, p. 4–56.

3.2. Long-term (chronic) dietary risk assessment

The long-term exposure assessment which was performed in the most recent EFSA opinion (EFSA, 2018a) was updated using the STMR values for leafy brassica, as derived from the residue trials submitted in this application. For the remaining plant commodities, the input values were the STMRs as available from previous EFSA assessments or the MRLs as set in the Commission Regulation (EU) No 2019/552[13]. For animal commodities (except poultry), the STMR values as derived for the calculated dietary burdens were used as input values, since these were higher than the values calculated by the JMPR for the existing MRLs. It is highlighted that the STMR values for animal commodities correspond to residues of metabolite CGA205375 expressed as difenoconazole and, therefore, assume that parent and metabolite have a similar toxicological profile.

Based on this assumption, the calculated long-term exposure accounted for a maximum of 102% of the ADI (NL toddler). The contribution from commodities with MRLs at the LOQ is 5% of the ADI, from which 3.5% accounts for consumption of maize (NL toddler). It was noted that Dutch toddlers consume at least 5.5 times more maize-based products than all other European populations for which no ADI exceedance was observed. Considering that most of these commodities are consumed processed, the availability of processing factors would allow to refine the long-term exposure assessment, but are not currently available (EFSA, 2019a,b).

Regarding the commodities assessed in this application, the long-term exposure is lower than 2% of the ADI per commodity.

EFSA concludes that for the crops assessed in this application, the short-term intake of residues resulting from the use of difenoconazole according to the reported agricultural practices is unlikely to present a risk to consumer health. Long-term consumer intake concerns cannot be excluded for the intended and existing difenoconazole uses as they are affected by uncertainties associated with the toxicity of metabolite CGA205375 and the lack of information on all existing difenoconazole uses in the EU.

Overall, the present risk assessment is considered provisional pending the submission of confirmatory data on possible preferential metabolism/degradation of the four stereoisomers of difenoconazole in plants. Additionally, it does not take into consideration triazole derivative metabolites (TDMs). EFSA proposes to refine the consumer exposure assessment in the framework of the renewal of the approval of the active substance and subsequent comprehensive review of all existing uses under the MRL review.

The complete list of input values is presented in Appendix D.2. For further details on the exposure calculations, a screenshot of the Report sheet of the PRIMo is presented in Appendix C.

4. Conclusion and Recommendations

The data submitted in support of this MRL application were found to be sufficient to derive an MRL proposal for leafy brassica (Chinese cabbage and kale). The calculated livestock exposure to difenoconazole residues indicates that the existing MRLs, which reflect CXLs for the residues of difenoconazole and its metabolite CGA20537, might need to be raised for mammalian fat, liver and milk. However, as long as the existing enforcement residue definition in Regulation (EC) No 396/2005 refers to difenoconazole alone, EFSA is of the opinion that the modification of the existing MRLs in products of animal origin at this stage is not required. It is also noted that due to the lack of information on the existing difenoconazole EU uses, the calculated livestock dietary exposure might be under- or overestimated.

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

EFSA concludes that for the crops assessed in this application, the short-term intake of residues resulting from the use of difenoconazole according to the reported agricultural practices is unlikely to present a risk to consumer health. Long-term consumer intake concerns cannot be excluded for the intended and existing difenoconazole uses as they are affected by uncertainties associated with the toxicity of metabolite CGA205375 and the lack of information on all existing difenoconazole uses in the EU.

[13] Commission Regulation (EU) 2019/552 of 4 April 2019 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 azoxystrobin, bicyclopyrone, chlormequat, cyprodinil, difenoconazole, fenpropimorph, fenpyroximate, fluopyram, fosetyl, isoprothiolane, isopyrazam, oxamyl, prothioconazole, spinetoram, trifloxystrobin and triflumezopyrim in or on certain products. OJ L 96, 5.4.2019, p. 6–49.

Overall, this risk assessment is considered provisional, pending the submission of confirmatory data on possible preferential metabolism/degradation of the four stereoisomers of difenoconazole in plants. Additionally, it does not take into consideration triazole derivative metabolites (TDMs) which may be generated by several pesticides belonging to the group of triazole fungicides as this application was submitted before the date of application of the new strategy endorsed by the risk managers for the assessment of TDMs (i.e. September 2019). EFSA proposes to refine the consumer exposure assessment in the framework of the renewal of the approval and subsequent comprehensive review of all existing uses under the MRL review.

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
BBCH	growth stages of mono- and dicotyledonous plants
bw	body weight
CAS	Chemical Abstract Service
CEN	European Committee for Standardisation (Comité Européen de Normalisation)
CF	conversion factor for enforcement to risk assessment residue definition
cGAP	critical GAP
CIRCA	(EU) Communication & Information Resource Centre Administrator
CS	capsule suspension
CV	coefficient of variation (relative standard deviation)
CXL	Codex maximum residue limit
DALA	days after last application
DAR	draft assessment report
DAT	days after treatment
DM	dry matter
DS	powder for dry seed treatment
DT_{90}	period required for 90% dissipation (define method of estimation)
eq	residue expressed as a.s. equivalent
FAO	Food and Agriculture Organization of the United Nations
GAP	Good Agricultural Practice
GC	gas chromatography
GC-NPD	gas chromatography with nitrogen/phosphorous detector
GS	growth stage
HPLC	high-performance liquid chromatography
HPLC-MS	high-performance liquid chromatography with mass spectrometry
HPLC-MS/MS	high-performance liquid chromatography with tandem mass spectrometry
IEDI	international estimated daily intake
IESTI	international estimated short-term intake
ILV	independent laboratory validation
ISO	International Organisation for Standardisation
IUPAC	International Union of Pure and Applied Chemistry
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LOQ	limit of quantification
MRL	maximum residue level
MS	Member States
MS	mass spectrometry detector
MS/MS	tandem mass spectrometry detector
MW	molecular weight
NEU	northern Europe
NPD	nitrogen/phosphorous detector
OECD	Organisation for Economic Co-operation and Development
PBI	plant back interval
PF	processing factor
PHI	preharvest interval
PRIMo	(EFSA) Pesticide Residues Intake Model
QuEChERS	Quick, Easy, Cheap, Effective, Rugged, and Safe (analytical method)
RA	risk assessment
RD	residue definition
RMS	rapporteur Member State
SANCO	Directorate-General for Health and Consumers
SC	suspension concentrate

SEU	southern Europe
SL	soluble concentrate
SP	water-soluble powder
STMR	supervised trials median residue
TAR	total applied radioactivity
TRR	total radioactive residue
UV	ultraviolet (detector)
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 & season[(c)]	Number max	Interval between application (min)	g a.s./hL min–max	Water L/ha min–max	Rate	Unit		
Chinese cabbages/petsai	NEU	F	Mycosphaerella brassicicola (MYCOBR); Alternaria sp. (ALTESP)	EC	250 g/L	Foliar treatment – broadcast spraying	*BBCH 50–55*[(e)]	3	14		200–800	125	g a.i./ha	14	
Kales	NEU	F	Mycosphaerella brassicicola (MYCOBR); Alternaria sp. (ALTESP)	EC	250 g/L	Foliar treatment – broadcast spraying	*BBCH 50–55*[(e)]	3	14		200–800	125	g a.i./ha	14	Refers to the Dutch GAP. A French GAP for kale is also submitted; French GAP reports different growth stage from the Dutch GAP (i.e. min. BBCH 19) and does not specify interval between applications.
Other leafy brassica	NEU	F	Mycosphaerella brassicicola (MYCOBR); Alternaria sp. (ALTESP)	EC	250 g/L	Foliar treatment – broadcast spraying	*BBCH 50–55*[(e)]	3	14		200–800	125	g a.i./ha	14	

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, 7th Edition. Revised March 2017. 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 pre-harvest interval.
(e): The EMS clarified that growth stage was included in the Dutch GAP in order to protect mammals. Uses in outdoor crops such as leafy brassica are only allowed if the crop sufficiently covers the soil. This was interpreted as growth stage BBCH 50–55 on the Dutch label. From a residues point of view, the PHI is considered as the critical part of the GAP with regard to the application timing.

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	Rapeseeds	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
		Radishes**	Soil, 1 × 516 g/ha	30, 60, 120 and 270 days
	Leafy crops	Mustard*	Soil, 1 × 32.4 g/ha	30–33 days
		Lettuces	Soil, 1 × 125 g/ha	98, 126, 342, 369 days
		Lettuces**	Soil, 1 × 516 g/ha	30, 60, 120 and 270 days
	Cereal	Maize	Soil, 1 × 125 g/ha	98, 126, 342, 369 days
		Wheat		
		Wheat *	Soil, 1 × 32.4 g/ha	30-33 days
		Wheat**	Soil, 1 × 516 g/ha	30, 60, 120 and 270 days
		Sorghum**	Soil, 1 × 516 g/ha	30, 60, 120 and 270 days
	Radiolabelled active substance: [phenyl-^{14}C]- and [triazole-^{14}C]-labelled difenoconazole *: Study performed with [phenyl-^{14}C] difenoconazole only (Sweden, 2006) **: Study performed with [phenyl-^{14}C] difenoconazole only (Netherlands, 2020)			

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)	

Can a general residue definition be proposed for primary crops?	Yes
Rotational crop and primary crop metabolism similar?	Yes Parent difenoconazole was present in primary (EFSA, 2011a) and rotational crops (main metabolite in leafy and root/tuber vegetables) (Netherlands, 2020). Residues of TDM metabolites- triazole alanine (TA), triazole acetic acid (TAA) and triazole lactic acid (TLA) were identified in primary and rotational crops. Metabolite CGA 205375 was major metabolite in radish and lettuces tissue grown in rotation with minor residues of CGA189138 and CGA205374 detected. CGA205375 (alcohol) was also identified in primary crops but in low proportions (below 5% TRR). Residues in wheat grain grown in rotation were < 0.01 mg/kg; in wheat straw, major radioactive component was CGA205375 with difenoconazole being the minor residue (Netherlands, 2020).
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) (new RD, EFSA, 2018b).* * Not considered in the present assessment as dossier submitted before the date of application of the new strategy for the assessment of TDMs (i.e. September 2019).
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, LOQ: 0.02 mg/kg (lettuces, apples) –high oil content, LOQ: 0.05 mg/kg (oilseed rape) –high starch content, LOQ: 0.05 mg/kg (wheat) ILV available for all matrices (EFSA, 2011a) HPLC–MS/MS (QuEChERS) – high acid content, LOQ: 0.01 mg/kg – high water content, LOQ: 0.01 mg/kg – high starch content (cereals), LOQ: 0.01 mg/kg (EFSA, 2017)

	HPLC–MS/MS (QuEChERS) – high water content, LOQ: 0.01 mg/kg – high acid content, LOQ: 0.01 mg/kg – high oil content, LOQ: 0.01 mg/kg – high starch content, LOQ: 0.01 mg/kg – high protein content, LOQ: 0.01 mg/kg – dry commodities, LOQ: 0.01 mg/kg – difficult matrices (herbal infusion), LOQ: 0.01 mg/kg Confirmatory method not necessary as primary method highly specific ILV available in high water, high oil, high protein content commodities and herbal infusion (Netherlands, 2020)

DAT: days after treatment; PBI: plant-back interval; LC–MS/MS: liquid chromatography with tandem mass spectrometry; HPLC–MS/MS: high-performance liquid chromatography with tandem mass spectrometry; LOQ: limit of quantification; ILV: independent laboratory validation

B.1.1.2. Storage stability of residues in plants

Plant products (available studies)	**Category**	**Commodity**	**T (°C)**	**Stability (months)**
	High water content	Tomatoes	–20	24
		Lettuces	–20	12
		Banana	–20	12
		Sugar beet	–18	12
	High oil content	Soybean	–20	12
		Cotton seed	–20	24
		Rapeseeds	–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 of parent difenoconazole is equal with the overall duration of the study. All studies assessed in the DAR (Sweden, 2006), except those on rapeseeds, sugar beet root and grapes (Austria, 2017; EFSA, 2017, 2018a)			

B.1.2. Magnitude of residues in plants

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

Commodity	Region/Indoor[(a)]	Residue levels observed in the supervised residue trials (mg/kg)	Comments/Source	Calculated MRL (mg/kg)	HR[(b)] (mg/kg)	STMR[(c)] (mg/kg)	CF[(d)]
Leafy brassica	NEU	0.19, 0.43, 0.74, 0.92, 1.07, 3.07	Residue trials on kale compliant with the GAP in terms of number of applications, application rate and PHI. Three trials were performed with an application interval of 7 instead of 14 days which might overestimate the overall residues. Extrapolation to the whole group of leafy brassica possible. The residue data of TDMs are not provided and not explicitly requested as the MRL application was submitted before the requirement for such data became applicable[11]	**6**	**3.07**	**0.83**	–

(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. The highest residue for risk assessment refers to the whole commodity and not to the edible portion.
(c): Supervised trials median residue. The median residue for risk assessment refers to the whole commodity and not to the edible portion.
(d): Conversion factor to recalculate residues according to the residue definition for monitoring to the residue definition for risk assessment.

B.1.2.2. Residues in rotational crops

Residues in rotational and succeeding crops expected based on confined rotational crop study?	Yes	In studies with [^{14}C-phenyl] difenoconazole (appl. of 32.4 g/ha and 125 g/ha), the TRR was too low to be characterised (Sweden, 2006). In a new study submitted under this assessment with [^{14}C-phenyl] difenoconazole (appl. of 516 g/ha) in lettuces, radishes and wheat, the TRR accounted for up to 0.04 mg eq/kg in lettuces and 0.06 mg eq/kg in radishes. In wheat grain, residues were below 0.01 mg eq/kg and, therefore, too low to be characterised (Netherlands, 2020). In a study with [^{14}C-triazole] difenoconazole (appl. 125 g/ha), the TRR in mature crops accounted for up to 0.02 mg eq/kg in lettuces, 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).
Residues in rotational and succeeding crops expected based on field rotational crop study?	Inconclusive	Field study available with difenoconazole applied on a bare soil at a rate of 750 g/ha. Mature rotational crops carrots and spinaches, 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).

TRR: total radioactive residue; PBI: plant-back interval; LOQ: limit of quantification.

B.2. Residues in livestock

Dietary burden calculation according to OECD (2013).

Relevant groups (sub groups)	Dietary burden expressed in				Most critical sub group[(a)]	Most critical commodity[(b)]	Trigger exceeded (Y/N)	Previous assessment (EFSA, 2017, 2018a)
	mg/kg bw per day		mg/kg DM					Max burden
	Median	Maximum	Median	Maximum				mg/kg DM
Cattle (all)	0.242	0.372	8.09	11.88	Dairy cattle	Kale	Yes	10.45
Cattle (dairy only)	0.242	0.372	6.29	9.68	Dairy cattle	Kale	Yes	8.25
Sheep (all)	0.249	0.319	7.48	9.58	Ram/Ewe	Kale	Yes	8.86
Sheep (ewe only)	0.249	0.319	7.48	9.58	Ram/Ewe	Kale	Yes	5.53
Swine (all)	0.098	0.151	4.23	6.52	Swine (breeding)	Kale	Yes	5.81
Poultry (all)	0.076	0.090	1.08	1.28	Poultry broiler	Rice	Yes	1.28
Poultry (layer only)	0.055	0.075	0.81	1.10	Poultry layer	Potato	Yes	1.10

(a): When one group of livestock includes several subgroups (e.g. poultry 'all' including broiler, layer and turkey), the result of the most critical subgroup is identified from the maximum dietary burdens expressed as 'mg/kg bw per day'.
(b): The most critical commodity is the major contributor identified from the maximum dietary burden expressed as 'mg/kg bw per day'.

B.2.1. Nature of residues and methods of analysis in livestock

B.2.1.1. Metabolism studies, methods of analysis and residue definitions in livestock

Livestock (available studies)	**Animal**	**Dose (mg/kg bw/d)**	**Duration (days)**	**Comment/Source**
	Laying hen	0.36-0.38	14	Label position: phenyl-^{14}C and triazole-^{14}C (Sweden, 2010, EFSA, 2011a, Netherlands, 2020)
		5	3	Label position: phenyl-^{14}C and triazole-^{14}C (Sweden, 2010, EFSA, 2011a, Netherlands, 2020)
		7.7	4	Label position: triazole-^{14}C (Sweden, 2010, EFSA, 2011a, Netherlands, 2020)
	Lactating ruminants	0.23	10	Goat; label position: phenyl-^{14}C and triazole-^{14}C (Sweden, 2010, EFSA, 2011a, Netherlands, 2020)
		3.75	3	Goat; label position: phenyl-^{14}C and triazole-^{14}C (Sweden, 2010, EFSA, 2011a, Netherlands, 2020)
		3.10	4	Goat; label position: phenyl-^{14}C (Sweden, 2010, EFSA, 2011a,b, Netherlands, 2020)

Time needed to reach a plateau concentration in milk and eggs (days)	Milk:	1) 48 hours (phenyl-^{14}C labelled) 2) 144 hours (triazole-^{14}C labelled) (EFSA, 2011a)
	Eggs:	1) 168 hours in egg yolk (phenyl-^{14}C and triazole-^{14}C labelled) 2) 120 hours in egg white (triazole-^{14}C labelled) (EFSA, 2011a)
Metabolism in rat and ruminant similar	yes	(EFSA, 2011a)
Can a general residue definition be proposed for animals?	yes	(EFSA, 2011a)
Animal residue definition for monitoring (RD-Mo)	EFSA peer review (EFSA, 2011b): Difenoconazole alcohol (CGA-205375) expressed as difenoconazole Regulation (EC) No 396/2005: Difenoconazole	

Animal residue definition for risk assessment (RD-RA)	1) Difenoconazole alcohol (CGA-205375) expressed as difenoconazole 2) Triazole derivative metabolites (new RD, EFSA, 2018b)* * Not considered in the present assessment as dossier submitted before the date of application of the new strategy for the assessment of TDMs (i.e. September 2019).	
Fat soluble residues	Yes	(EFSA, 2011a)
Methods of analysis for monitoring of residues (analytical technique, matrix, LOQs)	Difenoconazole and CGA 205375: HPLC–MS/MS - Tissues, fat and eggs, LOQ: 0.01 mg/kg - Milk, LOQ: 0.005 mg/kg (EFSA, 2011a, Netherlands, 2020 and EFSA, 2017 (QuEChERS)). ILV available (EFSA, 2011a, Netherlands, 2020).	

HPLC–MS/MS: high-performance liquid chromatography with tandem mass spectrometry; QuEChERS: Quick, Easy, Cheap, Effective, Rugged, and Safe; LOQ: limit of quantification; ILV: independent laboratory validation.

B.2.1.2. Storage stability of residues in livestock

Animal products (available studies)	**Animal**	**Commodity**	**T (°C)**	**Stability period**		**Compounds covered**	**Comment/ Source**
				Value	**Unit**		
	Laying hen	Muscle (breast)	–20	12	Months	Parent	EFSA (2011a)
		Eggs	–20	12	Months	Parent	EFSA (2011a)
	Cattle	Liver	–20	12	Months	Parent	EFSA (2011a)
		Muscle	–18	10	Months	Parent and metabolite CGA-205375	EFSA (2011a)
		Fat	–18	10	Months	Parent and metabolite CGA-205375	EFSA (2011a)
		Liver	–18	10	Months	Parent and metabolite CGA-205375	EFSA (2011a)
		Kidney	–18	10	Months	Parent and metabolite CGA-205375	EFSA (2011a)
		Milk	–20	12	Months	Parent	EFSA (2011a)
			–18	10	Months	Parent and metabolite CGA-205375	EFSA (2011a)

B.2.2. Magnitude of residues in livestock

B.2.2.1. Summary of the residue data from livestock feeding studies

Calculations performed with Animal Burden 2017. Residues refer to metabolite CGA205375 expressed as difenoconazole.

Animal commodity	Residues at the closest feeding level (mg/kg)		Estimated value at 1N		MRL proposal (mg/kg)[(f)]	Current MRL
	Mean	Highest	STMR[(a)] (mg/kg)	HR[(b)] (mg/kg)		
Cattle (all) Closest feeding level (0.35 mg/kg bw; 0.9 N rate)[(c)]						
Muscle	0.02	0.03	0.02	0.03	0.03	0.05
Fat	0.08	0.10	0.06	0.11	0.15	0.05
Liver	0.35	0.41	0.25	0.43	0.5	0.2
Kidney	0.05	0.06	0.04	0.06	0.07	0.2
Cattle (dairy only) Closest feeding level (0.35 mg/kg bw; 0.9N rate)[(c)]						
Milk[(d)]	0.01	0.01	0.01	0.01	0.009	0.005
Sheep (all)[(e)] Closest feeding level (0.35 mg/kg bw; 1.1 N rate)[(c)]						
Muscle	0.02	0.03	0.02	0.03	0.03	0.05
Fat	0.08	0.10	0.06	0.09	0.1	0.05
Liver	0.35	0.41	0.27	0.37	0.4	0.2
Kidney	0.05	0.06	0.04	0.06	0.06	0.2
Sheep (ewe only)[(e)] Closest feeding level (0.35 mg/kg bw; 1.1 N rate)[(c)]						
Milk[(d)]	0.01	0.01	0.01	0.01	0.009	0.005
Swine (all)[(e)] Closest feeding level (0.11 mg/kg bw; 0.7 N rate)[(c)]						
Muscle	0.01	0.02	0.01	0.02	0.03	0.05
Fat	0.03	0.04	0.03	0.05	0.05	0.05
Liver	0.14	0.15	0.12	0.21	0.2	0.2
Kidney	0.02	0.02	0.02	0.03	0.03	0.2

(a): The mean residue level for milk and the mean residue levels for tissues were recalculated at the 1N rate for the median dietary burden.
(b): The mean residue level in milk and the highest residue levels in tissues were recalculated at the 1N rate for the maximum dietary burden.
(c): Closest feeding level and N dose rate related to the maximum dietary burden.
(d): Highest residue level from day 1 to day 29 or day 30 (daily mean of 3 cows).
(e): Since extrapolation from cattle to other ruminants and swine is acceptable, results of the livestock feeding study on ruminants were relied upon to derive the MRL and risk assessment values in sheep and swine (EFSA, 2010).
(f): Although these MRL proposals suggest that MRLs for difenoconazole residues in fat tissues, liver and milk would need to be raised, EFSA is of the opinion that the modification of the existing MRLs in products of animal origin at this stage is not required as long as metabolite CGA205375 is not included in the residue definition for enforcement, according to the Regulation (EC) No 396/2005.

B.3. Consumer risk assessment

ARfD	0.16 mg/kg bw (European Comission, 2008)
Highest IESTI, according to EFSA PRIMo	Kales: 84% of ARfD
	Chinese cabbages: 62% of ARfD
Assumptions made for the calculations	Calculations were performed with PRIMo revision 3.1. The calculation is based on the highest residue levels expected in commodities belonging to the group of leafy brassica according to the submitted residue trials.

ADI	0.01 mg/kg bw per day (European Commission, 2008)
Highest IEDI, according to EFSA PRIMo	102% ADI (NL Toddler) Contribution of crops assessed: Chinese cabbages: 1.7% of ADI Kales: 1.6% of ADI Other leafy brassica: 1.6% of ADI Commodities with MRLs set at the LOQ: 5 % of ADI
Assumptions made for the calculations	Calculations were performed with PRIMo revision 3.1 (EFSA, 2018a). For leafy brassica, the STMR values as derived from the residue trials submitted in this application were used. For the remaining plant commodities, the input values were the available STMRs from previous EFSA assessments or the MRLs as set in the Commission Regulation (EU) No 2019/552. For animal commodities (except poultry), the STMR values as derived for the calculated livestock dietary burden (See Section B.2.2.1) were used as input values to account for a worst-case exposure scenario, noting that these values are higher than the risk assessment values derived by the JMPR in 2010 and supporting the existing EU MRLs. Input values for animal commodities (except poultry) correspond to metabolite CGA205375 (expressed as difenoconazole) assuming that metabolite and parent have similar toxicological profile. A more realistic estimate of the exposure to residues of difenoconazole is recommended to be performed in the framework of the MRL review.

ARfD: acute reference dose; bw: body weight; IESTI: international estimated short-term intake; PRIMo: (EFSA) Pesticide Residues Intake Model; ADI: acceptable daily intake; IEDI: international estimated daily intake; STMR: supervised trials median residue; MRL: maximum residue level.

B.4. Recommended MRLs

Code[(a)]	Commodity	Existing EU MRL (mg/kg)	Proposed EU MRL (mg/kg)	Comment/justification
Enforcement residue definition: Difenoconazole				
0243010 0243010 0243090	– Chinese cabbages/ pe-tsai – Kales – Others	2	Further risk management considerations are required	The submitted data are sufficient to derive an MRL proposal of 6 mg/kg for the NEU use. Risk for consumers from short-term intake of residues of difenoconazole from leafy brassica is unlikely. Long-term consumer intake concerns cannot be excluded for the intended and existing difenoconazole uses as they are affected by uncertainties associated with the toxicity of metabolite CGA205375 and the lack of information on all existing difenoconazole uses in the EU.

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

Appendix C – Pesticide Residue Intake Model (PRIMo)

European Food Safety Authority

EFSA PRIMo revision 3.1; 2019/03/19

Difenoconazole

LOQs (mg/kg) range from:	0.005	to:	0.05
Toxicological reference values			
ADI (mg/kg bw per day):	0.01	ARfD (mg/kg bw):	0.16
Source of ADI:	EC	Source of ARfD:	EC
Year of evaluation:	2008	Year of evaluation:	2008

Input values

Details – chronic risk assessment

Supplementary results – chronic risk assessment

Details – acute risk assessment/children

Details – acute risk assessment/adults

Comments:

Normal mode

Chronic risk assessment: JMPR methodology (IEDI/TMDI)

No of diets exceeding the ADI : 1

TMDI/NEDI/IEDI calculation (based on average food consumption)

Calculated exposure (% of ADI)	MS Diet	Expsoure (µg/kg bw per day)	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	Exposure resulting from MRLs set at the LOQ (in % of ADI)	Exposure resulting from commodities not under assessment (in % of ADI)
102%	NL toddler	10.21	17%	Apples	8%	Beans (with pods)	8%	Table grapes	5%	
76%	DE child	7.64	20%	Apples	7%	Tomatoes	7%	Table grapes	1%	
71%	GEMS/Food G06	7.12	26%	Tomatoes	14%	Rice	5%	Table grapes	2%	
55%	GEMS/Food G11	5.54	7%	Tomatoes	6%	Celeriacs/turnip rooted celeries	5%	Wine grapes	2%	
55%	IE adult	5.50	7%	Wine grapes	4%	Sweet potatoes	3%	Tomatoes	1%	
53%	GEMS/Food G10	5.26	11%	Rice	10%	Tomatoes	3%	Potatoes	2%	
52%	NL child	5.21	9%	Apples	5%	Table grapes	4%	Tomatoes	2%	
52%	GEMS/Food G07	5.19	8%	Tomatoes	8%	Wine grapes	4%	Potatoes	2%	
49%	PT general	4.87	13%	Wine grapes	7%	Rice	6%	Tomatoes	0.4%	
48%	GEMS/Food G08	4.82	8%	Tomatoes	5%	Wine grapes	4%	Potatoes	2%	
47%	FR child 3 15 yr	4.68	6%	Tomatoes	5%	Oranges	5%	Beans (with pods)	2%	
46%	GEMS/Food G15	4.58	9%	Tomatoes	5%	Wine grapes	4%	Potatoes	2%	
44%	FR toddler 2 3 yr	4.37	8%	Beans (with pods)	5%	Rice	5%	Apples	0.9%	
43%	RO general	4.34	14%	Tomatoes	9%	Wine grapes	4%	Potatoes	1%	
38%	ES child	3.78	7%	Tomatoes	4%	Rice	3%	Oranges	0.9%	
37%	SE general	3.73	6%	Tomatoes	4%	Potatoes	4%	Rice	0.6%	
36%	UK infant	3.58	6%	Peas (without pods)	6%	Rice	4%	Milk: Cattle	1%	
36%	DE women 14-50 yr	3.56	5%	Tomatoes	4%	Wine grapes	4%	Apples	0.8%	
34%	UK toddler	3.40	5%	Rice	4%	Tomatoes	3%	Potatoes	0.6%	
33%	DE general	3.27	5%	Tomatoes	4%	Wine grapes	4%	Apples	0.7%	
33%	FR adult	3.25	12%	Wine grapes	3%	Tomatoes	2%	Beans (with pods)	0.8%	
30%	NL general	3.00	3%	Wine grapes	3%	Tomatoes	2%	Beans (with pods)	1%	
29%	ES adult	2.95	6%	Tomatoes	3%	Lettuces	2%	Beans (with pods)	0.5%	
29%	IT toddler	2.94	10%	Tomatoes	2%	Rice	2%	Lettuces	0.9%	
27%	DK child	2.69	4%	Tomatoes	4%	Apples	3%	Rice	0.7%	
27%	IT adult	2.69	8%	Tomatoes	2%	Lettuces	2%	Florence fennels	0.4%	
26%	FI 3 yr	2.61	5%	Rice	5%	Potatoes	4%	Tomatoes	0.5%	
24%	UK vegetarian	2.37	4%	Tomatoes	4%	Wine grapes	3%	Rice	0.4%	
22%	FR infant	2.15	5%	Beans (with pods)	3%	Apples	2%	Potatoes	0.2%	
22%	UK adult	2.15	6%	Wine grapes	3%	Rice	3%	Tomatoes	0.3%	
20%	DK adult	2.03	5%	Wine grapes	4%	Tomatoes	2%	Apples	0.2%	
20%	PL general	2.02	6%	Tomatoes	3%	Potatoes	3%	Apples	0.1%	
20%	FI 6 yr	2.02	4%	Potatoes	4%	Rice	3%	Tomatoes	0.4%	
17%	FI adult	1.68	4%	Tomatoes	3%	Coffee beans	2%	Wine grapes	3%	
17%	LT adult	1.66	4%	Tomatoes	3%	Potatoes	3%	Apples	0.4%	
8%	IE child	0.78	3%	Rice	0.9%	Beans (without pods)	0.6%	Potatoes	0.1%	

Conclusion:
The estimated TMDI/NEDI/IEDI was in the range of 0 % to 102.1 % of the ADI.
For 1 diet(s), the ADI is exceeded.

Acute risk assessment/children	Acute risk assessment/adults/general population
Details – acute risk assessment/children	Details – acute risk assessment/adults

The acute risk assessment is based on the ARfD.
The calculation is based on the large portion of the most critical consumer group.

Show results for all crops

Unprocessed commodities

Results for children
No. of commodities for which ARfD/ADI is exceeded (IESTI): ---

Results for adults
No. of commodities for which ARfD/ADI is exceeded (IESTI): ---

IESTI

Highest % of ARfD/ADI	Commodities	MRL/input for RA (mg/kg)	Exposure (µg/kg bw)	Highest % of ARfD/ADI	Commodities	MRL/input for RA (mg/kg)	Exposure (µg/kg bw)
88%	Spring onions/green onions	9/9	141	49%	Chinese cabbages/pe-tsai	6/3.07	78
84%	Kales	6/3.07	135	39%	Florence fennels	5/3.31	62
80%	Celeries	7/3.4	127	37%	Kales	6/3.07	59
73%	Tomatoes	2/2	116	34%	Celeries	7/3.4	54
69%	Celeriacs/turnip rooted	2/2	111	32%	Table grapes	3/1.5	51
68%	Table grapes	3/1.5	109	30%	Chards/beet leaves	4/2.51	47
62%	Chinese cabbages/pe-tsai	6/3.07	99	25%	Witloofs/Belgian endives	4/2.2	40
60%	Rhubarbs	5/2.59	96	25%	Spring onions/green onions	9/9	40
60%	Lettuces	4/2.51	96	22%	Wine grapes	3/1.5	36
55%	Witloofs/Belgian endives	4/2.2	87	22%	Cardoons	7/3.4	35
41%	Pears	0.8/0.47	65	20%	Tomatoes	2/2	32
41%	Oranges	0.6/0.49	65	19%	Lettuces	4/2.51	30
38%	Escaroles/broad-leaved	3/1.5	60	19%	Escaroles/broad-leaved	3/1.5	30
34%	Florence fennels	5/3.31	54	15%	Rhubarbs	5/2.59	24
32%	Apples	0.8/0.47	51	15%	Celeriacs/turnip rooted	2/2	24

Expand/collapse list

Total number of commodities exceeding the ARfD/ADI in children and adult diets (IESTI calculation)

Processed commodities

Results for children
No of processed commodities for which ARfD/ADI is exceeded (IESTI): 1

Results for adults
No of processed commodities for which ARfD/ADI is exceeded (IESTI): ---

IESTI

Highest % of ARfD/ADI	Processed commodities	MRL/input for RA (mg/kg)	Exposure (µg/kg bw)	Highest % of ARfD/ADI	Processed commodities	MRL/input for RA (mg/kg)	Exposure (µg/kg bw)
122%	Witloofs/boiled	4/2.2	195	72%	Celeries/boiled	7/3.4	115
94%	Florence fennels/boiled	5/3.31	150	40%	Florence fennels/boiled	5/3.31	64
62%	Escaroles/broad-leaved end	3/1.5	99	26%	Cardoons/boiled	7/3.4	41
60%	Rhubarbs/sauce/puree	5/2.59	97	25%	Witloofs/boiled	4/2.2	41
53%	Kales/boiled	6/3.07	85	24%	Rhubarbs/sauce/puree	5/2.59	38
49%	Chards/beet leaves/boiled	4/2.51	78	23%	Celeriacs/boiled	2/2	36
20%	Broccoli/boiled	1/0.41	32	20%	Chards/beet leaves/boiled	4/2.51	31
18%	Celeriacs/juice	2/2	29	19%	Escaroles/broad-leaved	3/1.5	31
14%	Leeks/boiled	0.6/0.4	23	9%	Wine grapes/wine	3/1.5	14
14%	Wine grapes/juice	3/0.52	23	8%	Spinaches/frozen; boiled	3/1.5	12
13%	Spinaches/frozen; boiled	3/1.5	21	7%	Beetroots/boiled	0.4/0.28	11
9%	Turnips/boiled	0.4/0.28	14	7%	Wine grapes/juice	3/0.52	11
9%	Parsnips/boiled	0.4/0.28	14	6%	Broccoli/boiled	1/0.41	9.9
9%	Cauliflowers/boiled	0.2/0.2	14	5%	Table grapes/raisins	3/7.05	8.6
9%	Tomatoes/juice	2/0.72	14	5%	Cauliflowers/boiled	0.2/0.2	8.3

Expand/collapse list

Conclusion:
No exceedance of the toxicological reference value was identified for any unprocessed commodity.
A short-term intake of residues of Difenoconazole is unlikely to present a public health risk.
For processed commodities, the toxicological reference value was exceeded in one or several cases.

Appendix D – Input values for the exposure calculations

D.1. Livestock dietary burden calculations

Feed commodity	Median dietary burden		Maximum dietary burden	
	Input value (mg/kg)	**Comment**	**Input value (mg/kg)**	**Comment**
Risk assessment residue definition: difenoconazole				
1. Forages				
Barley straw	0.31	STMR (EFSA, 2017, 2018a)	0.71	HR (EFSA, 2017, 2018a)
Beet sugar leaves	0.25	STMR (EFSA, 2010)	0.62	HR (EFSA, 2010)
Head cabbage leaves	0.02	STMR (EFSA, 2017, 2018a)	0.19	HR (EFSA, 2017, 2018a)
Kale leaves	**0.83**	**STMR**	**3.07**	**HR**
Rye straw	0.48	STMR (EFSA, 2010)	1.30	HR (EFSA, 2010)
Wheat straw	0.48	STMR (EFSA, 2010)	1.30	HR (EFSA, 2010)
2. Roots and tubers				
Carrot culls	0.1	STMR (EFSA, 2013)	0.28	HR (EFSA, 2013)
Cassave/ Tapioca roots	0.10	EU MRL	0.10	EU MRL
Potato culls	0.1	EU MRL	0.1	EU MRL
Swede roots	0.08	STMR (EFSA, 2010)	0.28	HR (EFSA, 2010)
Turnip roots	0.08	STMR (EFSA, 2010)	0.28	HR (EFSA, 2010)
3. Cereal grains/crop seeds				
Barley grain	0.02	STMR (EFSA, 2017, 2018a)	0.02	STMR (EFSA, 2017, 2018a)
Bean seed (dry)	0.02	STMR (EFSA, 2017, 2018a)	0.02	STMR (EFSA, 2017, 2018a)
Lupin seed	0.02	STMR (EFSA, 2017, 2018a)	0.02	STMR (EFSA, 2017, 2018a)
Pea (field) seed (dry)	0.03	STMR (FAO, 2017)	0.03	STMR (FAO, 2017)
Rye grain	0.02	STMR (EFSA, 2010)	0.02	STMR (EFSA, 2010)
Soya bean seed	0.01	STMR (FAO, 2015)	0.01	STMR (FAO, 2015)
Wheat grain	0.02	STMR (EFSA, 2010)	0.02	STMR (EFSA, 2010)
4. By-products				
Apple pomace, wet	0.69	STMR (FAO, 2013) × PF (EFSA, 2011b) (0.16 × 4.3)		
Beet sugar dried pulp	0.20	STMR (EFSA, 2010) × PF (0.02 × 10)		
Beet sugar ensiled pulp	0.06	STMR (EFSA, 2010) × PF default (0.02 × 3[(a)])		
Beet sugar molasses	0.58	STMR (EFSA, 2010) × PF (0.02 × 29)		
Brewer's grain dried	0.07	STMR Barley (EFSA, 2017, 2018a) × PF default (0.02 × 3.3[(a)])		
Canola (Rape seed) meal	0.06	STMR (FAO, 2015) × PF default (0.03 × 2.0)		
Citrus dried pulp	0.64	STMR × PF (FAO, 2013) (0.16 × 4.0)		
Distiller's grain dried	0.07	STMR (EFSA, 2010) × PF default (0.02 × 3.3[(a)])		
Flaxseed/ linseed meal	0.40	EU MRL × PF default (0.2 × 2.0)		

Feed commodity	Median dietary burden		Maximum dietary burden	
	Input value (mg/kg)	Comment	Input value (mg/kg)	Comment
Lupin seed meal	0.02	STMR (EFSA, 2017, 2018a) × PF default (0.02 × 1.1[(a)])		
Potato process waste	2.0	MRL × PF default (0.1 × 20)		
Potato dried pulp	3.8	MRL × PF default (0.1 × 38[(a)])		
Rape meal	0.06	STMR (FAO, 2015) × PF default (0.03 × 2.0[(a)])		
Rice bran/ pollard	8.8	STMR (EFSA, 2013) × PF default (0.88 × 10[(a)])		
Soya bean meal	0.004	STMR × PF (FAO, 2015) (0.01 × 0.4)		
Soya bean meal	0.02	STMR × PF (FAO, 2015) (0.01 × 2)		
Wheat gluten meal	0.04	STMR (EFSA, 2010) × PF default (0.02 × 1.8[(a)])		
Wheat milled by-products	0.14	STMR (EFSA, 2010) × PF default (0.02 × 7[(a)])		

STMR: supervised trials median residue; HR: highest residue; PF: processing factor.
(a): In the absence of processing factors supported by data, default processing factors were included in the calculation to consider the potential concentration of residues in the processed commodities.

D.2. Consumer risk assessment

Commodity	Chronic exposure assessment		Acute exposure assessment	
	Input (mg/kg)	Comment[(a)]	Input (mg/kg)	Comment
Risk assessment residue definition for plants: difenoconazole				
Chinese cabbages/ pe-tsai	0.83	STMR	3.07	HR
Kales	0.83	STMR	3.07	HR
Other leafy brassica	0.83	STMR	3.07	HR
Citrus fruit	0.16	STMR (FAO, 2013)	Acute risk assessment was undertaken only with regard to the crops under consideration.	
Pome fruit	0.16	STMR (FAO, 2013)		
Apricots	0.17	STMR (EFSA, 2017, 2018a)		
Peaches	0.15	STMR (EFSA, 2010)		
Grapes (table and wine)	0.52	STMR (FAO, 2013)		
Strawberries	0.42	STMR (FAO, 2017)		
Blackberries, raspberries	0.04	STMR (EFSA 2012)		
Blueberries	1.0	STMR (FAO, 2017)		
Azarole/Mediteranean medlar	0.8	STMR (EFSA, 2018a)		
Olives (table and oil)	0.47	STMR (EFSA, 2010)		
Kumquats	0.16	STMR (FAO, 2013)		
Kaki/Japanese persimmons	0.8	STMR (EFSA, 2018a)		
Prickly pears/cactus fruits	0.03	STMR (FAO, 2017)		

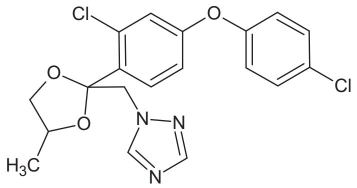
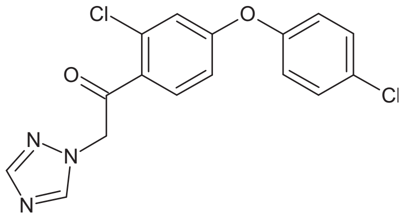
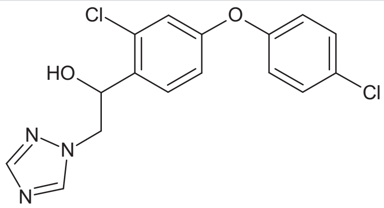
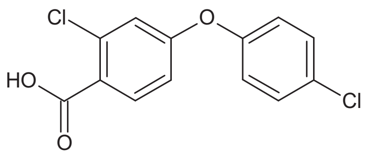
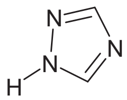
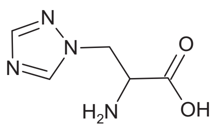
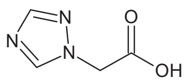
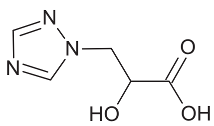
Commodity	Chronic exposure assessment		Acute exposure assessment	
	Input (mg/kg)	Comment[(a)]	Input (mg/kg)	Comment
Avocados	0.05	STMR (FAO, 2015)		
Papayas	0.01	STMR-peel (EFSA, 2013)		
Beetroots	0.08	SMTR (EFSA, 2013)		
Carrots	0.08	STMR (EFSA, 2013		
Horseradish	0.08	STMR (EFSA, 2013)		
Jerusalem artichoke	0.08	STMR (EFSA, 2013)		
Parsnips	0.08	STMR (EFSA, 2013)		
Parsley roots	0.08	STMR (EFSA, 2013)		
Radishes	0.08	STMR (EFSA, 2013)		
Salsifies	0.08	STMR (EFSA, 2013)		
Swedes, turnips	0.08	STMR (EFSA, 2010)		
Garlic	0.01	STMR (EFSA, 2013)		
Onions (bulb)	0.01	STMR (EFSA, 2013)		
Shallots	0.01	STMR (EFSA, 2013)		
Spring onions	2.8	STMR (FAO, 2013)		
Tomatoes	0.72	STMR (European Commission, 2008)		
Peppers	0.24	STMR (FAO, 2017)		
Aubergines	0.18	STMR (EFSA, 2014a)		
Okra/lady's fingers	0.18	STMR (FAO, 2017)		
Cucumbers, gherkins, courgettes	0.01	STMR (EFSA, 2012)		
Melons	0.01	STMR-peel (EFSA, 2013)		
Pumpkin, watermelon	0.01	STMR (EFSA, 2013)		
Broccoli	0.13	STMR (EFSA, 2011b)		
Other flowering brassica	0.01	STMR (EFSA, 2018a)		
Brussels sprouts	0.07	STMR (EFSA, 2018a)		
Head cabbages	0.02	STMR (EFSA, 2017, 2018a)		
Lamb's lettuces	1.45	STMR (EFSA, 2014b)		
Lettuces	0.52	STMR (EFSA, 2017, 2018a)		
Escaroles/broad-leaved endives	0.33	STMR (EFSA, 2018a,b)		
Cress and other sprouts and shoots	0.52	STMR (EFSA, 2017, 2018a)		
Land cress	0.52	STMR (EFSA, 2017, 2018a)		
Roman rocket/rucola	0.33	STMR (EFSA, 2018a)		
Red mustards	0.52	STMR (EFSA, 2017, 2018a)		
Baby leaf crops (including brassica species)	0.52	STMR (EFSA, 2017, 2018a)		
Other lettuce and other salad plants	0.52	STMR (EFSA, 2017, 2018a)		
Spinaches	0.33	STMR (EFSA, 2018a)		
Purslanes	0.33	STMR (EFSA, 2018a)		
Chards/beet leaves	0.52	STMR (EFSA, 2017, 2018a)		
Other spinach and similar	0.33	STMR (EFSA, 2018a)		

Commodity	Chronic exposure assessment		Acute exposure assessment	
	Input (mg/kg)	Comment[(a)]	Input (mg/kg)	Comment
Witloofs/Belgian endives	1.3	STMR (EFSA, 2018a)		
Chervil, celery leaves, parsley, basil and edible flowers	4.65	STMR (EFSA, 2009)		
Chives, sage, rosemary, thyme, laurel/bay leaves, tarragon and other herbs	0.52	STMR (EFSA, 2017, 2018a		
Cardoons, celeries	1.22	STMR (EFSA, 2017, 2018a)		
Florence fennels	1.66	STMR (EFSA, 2009)		
Globe artichoke	0.51	STMR (FAO, 2017)		
Leeks	0.13	STMR (EFSA, 2017, 2018a)		
Rhubarbs	0.7	STMR (EFSA, 2018a)		
Beans	0.02	STMR (EFSA, 2017, 2018a)		
Lentils	0.02	STMR (EFSA, 2017, 2018a)		
Peas	0.03	STMR (FAO, 2017)		
Lupins/lupini beans and other pulses	0.02	STMR (EFSA, 2017, 2018a)		
Rapeseeds/canola seeds	0.03	STMR (FAO, 2015)		
Soya beans	0.01	STMR (FAO, 2015)		
Olives for oil production	0.47	STMR (Commission Regulation (EC) No 839/2008)		
Barley	0.02	STMR (EFSA, 2017, 2018a)		
Rice	1.1	STMR (FAO, 2017)		
Rye	0.02	STMR (EFSA, 2017, 2018a)		
Wheat	0.02	STMR (EFSA, 2017, 2018a)		
Liquorice, ginger, turmeric/curcuma, horseradish, root spices and other spices	0.64	STMR (carrot) × PF (8) (EFSA, 2017, 2018a)		
Sugar beet routs	0.02	STMR (EFSA, 2017, 2018a)		
Chicory roots	0.20	STMR (EFSA, 2013)		
Other plant commodities	MRL	MRLs in Regulation (EU) 2019/552		
Risk assessment residue definition for animal commodities: Difenoconazole alcohol (CGA205375) expressed as difenoconazole				
Swine meat	0.01	0.8 × STMR (0.01) muscle + 0.2 × STMR (0.03) fat		
Swine fat	0.03	STMR		
Swine liver	0.12	STMR		
Swine kidney	0.02	STMR		
Bovine, Sheep, Goat, Horse: meat	0.03	0.8 × STMR (0.02) muscle + 0.2 × STMR (0.06) fat		
Bovine, Sheep, Goat, Horse: fat	0.06	STMR		
Bovine liver	0.25	STMR		
Sheep liver	0.27	STMR		

Commodity	Chronic exposure assessment		Acute exposure assessment	
	Input (mg/kg)	Comment[(a)]	Input (mg/kg)	Comment
Goat liver	0.27	STMR		
Horse liver	0.25	STMR		
Bovine, Sheep, Goat, Horse: kidney	0.04	STMR		
Bovine, Sheep, Goat, Horse: milk	0.01	STMR		
Poultry and eggs	MRL	MRLs in Regulation (EU) 2019/552		

(a): Consumption figures in the EFSA PRIMo are expressed as meat. Since the a.s. is a fat-soluble pesticides, STMR and HR residue values were calculated considering an 80%/90% muscle and 20%/10% fat content for mammal/poultry meat, respectively (FAO, 2016).

Appendix E – Used compound codes

Code/trivial name	Chemical name/SMILES notation/ inChiKey[(a)]	Structural formula[(b)]
Difenoconazole	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 BQYJATMQXGBDHF-UHFFFAOYSA-N Clc1ccc(cc1)Oc1ccc(c(Cl)c1)C1(Cn2ncnc2)OCC(C)O1	
Difenoconazole-ketone CGA205374	1-[2-chloro-4-(4-chlorophenoxy)-phenyl]-2-[1,2,4]triazol-1-yl-ethanone HCYKJGWQCCFTNV-UHFFFAOYSA-N O=C(Cn1cncn1)c1ccc(Oc2ccc(Cl)cc2)cc1Cl	
Difenoconazole alcohol CGA205375	1-[2-chloro-4-(4-chlorophenoxy)phenyl]-2-(1*H*-1,2,4-triazol-1-yl)ethanol OC(Cn1cncn1)c1ccc(Oc2ccc(Cl)cc2)cc1Cl NBYSKMWDHCZSIP-UHFFFAOYSA-N	
Difenoconazole benzoic acid CGA189138	2-chloro-4-(4-chloro-phenoxy)-benzoic acid OC(=O)c1ccc(cc1Cl)Oc1ccc(Cl)cc1 PQYCPVXNIJXBCU-UHFFFAOYSA-N	
Triazole derivative metabolites (TDMs)		
1,2,4-triazole	1*H*-1,2,4-triazole c1ncnn1 NSPMIYGKQJPBQR-UHFFFAOYSA-N	
Triazole alanine (TA)	3-(1*H*-1,2,4-triazol-1-yl)-D,L-alanine NC(Cn1cncn1)C(=O)O XVWFTOJHOHJIMQ-UHFFFAOYSA-N	
Triazole acetic acid (TAA)	1*H*-1,2,4-triazol-1-ylacetic acid O=C(O)Cn1cncn1 RXDBSQXFIWBJSR-UHFFFAOYSA-N	
Triazole lactic acid (TLA) or Triazole hydroxy propionic acid	(2*RS*)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl) propanoic acid OC(Cn1cncn1)C(=O)O KJRGHGWETVMENC-UHFFFAOYSA-N	

IUPAC: International Union of Pure and Applied Chemistry; SMILES: simplified molecular-input line-entry system; InChiKey: International Chemical Identifier Key.
(a): ACD/Name 2019.1.3 ACD/Labs 2019 Release (File version N05E41, Build 111418, 3 September 2019).
(b): ACD/ChemSketch 2019.1.3 ACD/Labs 2019 Release (File version C05H41, Build 111302, 27 August 2019).