CONCLUSION ON PESTICIDES PEER REVIEW

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

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Abstract

The conclusions of EFSA following the peer review of the initial risk assessments carried out by the competent authorities of the rapporteur Member State, the United Kingdom, and co-rapporteur Member State, Slovakia, for the pesticide active substance methoxyfenozide and the assessment of applications for maximum residue levels (MRLs) are reported. The context of the peer review was that required by Commission Implementing Regulation (EU) No 844/2012. The conclusions were reached on the basis of the evaluation of the representative use of methoxyfenozide as an insecticide on table and wine grapes, maize and sweet corn, fruiting vegetables (tomato, pepper, aubergine) and leaf vegetables (lettuce and other salad plants, spinach and similar, herbs). MRLs were assessed in grape leaves and sweet corn. The reliable end points, appropriate for use in regulatory risk assessment and the proposed MRLs, are presented. Missing information identified as being required by the regulatory framework is listed. Concerns are identified.

Keywords: methoxyfenozide, peer review, risk assessment, pesticide, insecticide

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Summary

Commission Implementing Regulation (EU) No 844/2012 (hereinafter referred to as 'the Regulation') lays down the procedure for the renewal of the approval of active substances submitted under Article 14 of Regulation (EC) No 1107/2009. The list of those substances is established in Commission Implementing Regulation (EU) No 686/2012. Methoxyfenozide is one of the active substances listed in Regulation (EU) No 686/2012.

In accordance with Article 1 of the Regulation, the rapporteur Member State (RMS), the United Kingdom, and co-rapporteur Member State (co-RMS), Slovakia, received an application from Dow AgroSciences Ibérica, S.A., for the renewal of approval of the active substance methoxyfenozide. In addition, Dow AgroSciences Ibérica, S.A. submitted applications for maximum residue levels (MRLs), as referred to in Article 7 of Regulation (EC) No 396/2005. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicant, the co-RMS (Slovakia), the European Commission and the European Food Safety Authority (EFSA) about the admissibility.

The RMS provided its initial evaluation of the dossier on methoxyfenozide in the renewal assessment report (RAR), which was received by EFSA on 4 August 2016. The RAR included a proposal to set MRLs, submitted under Article 7 of Regulation (EC) No 396/2005. In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicant, Dow AgroSciences Ibérica, S.A., for comments on 20 September 2016. EFSA also provided comments. In addition, EFSA conducted a public consultation on the RAR. EFSA collated and forwarded all comments received to the European Commission on 23 November 2016.

Following consideration of the comments received on the RAR, it was concluded that additional information should be requested from the applicants and that EFSA should conduct an expert consultation in the areas of mammalian toxicology, residues, environmental fate and behaviour and ecotoxicology.

In accordance with Article 13(1) of the Regulation, EFSA should adopt a conclusion on whether methoxyfenozide can be expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009 of the European Parliament and of the Council and give a reasoned opinion concerning MRL applications as referred to in Article 10(1) of Regulation (EC) No 396/2005.

The conclusions laid down in this report were reached on the basis of the evaluation of the representative use of methoxyfenozide as an insecticide on table and wine grapes, maize and sweet corn, fruiting vegetables (tomato, pepper, aubergine) and leaf vegetables (lettuce and other salad plants, spinach and similar, herbs). MRLs were assessed in grape leaves and sweet corn. Full details of the representative uses and the proposed MRLs can be found in Appendix A of this report.

The use of methoxyfenozide according to the representative uses proposed at the European Union (EU) level results in a sufficient insecticidal efficacy against the target organisms.

A data gap was identified for evaluation of a relevant literature study concerning effects on Lepidoptera.

In the area of identity, physical/chemical properties and analytical methods, data gaps were identified for analytical methods used in support of toxicological studies for generation of pre-approval data for risk assessment and for verification of the efficiency of the extraction procedure used in the analytical methods for the determination of residues in food and feed of plant and food of animal origin.

In the area of mammalian toxicology and non-dietary exposure, issues that could not be finalised included the endocrine potential of methoxyfenozide (regarding the scientific risk assessment) and the lack of an *in vitro* comparative metabolism study. A data gap was identified to assess the relevance of some impurities.

In the residue section, the consumer dietary risk assessment is regarded as not finalised for the products of plant and animal origin based on the identified data gaps for rotational crops field trials analysing for methoxyfenozide and relevant compounds and covering the maximum predicted concentration of methoxyfenozide in soil, the outstanding data to address the potential uptake from soil and the fate of M08 compound in rotational crops and for additional residue trials compliant with the representative uses on table and wine grapes, tomato and sweet peppers/bell peppers. A full residue data set compliant with the southern Europe (SEU) good agricultural practice (GAP) (representative use) on sweet corn is requested (data gap) while the northern Europe (NEU) GAP is covered by the residue trials on sweet corn submitted in the framework of the MRL application. The livestock exposure assessment cannot be finalised considering the outstanding data to finalise the livestock dietary burden calculation and to conclude on the validity of the ruminants feeding study. Finally, the data requirement for the determination of residues in pollen and bee products for human consumption resulting from methoxyfenozide residues taken up by honeybees from crops at blossom could not be addressed.

As for the MRL applications, MRLs were proposed on grape leaves and similar species and sweet corn. In the consumer risk assessment covering those uses, the toxicological reference values have not been exceeded.

The potential for groundwater exposure from the representative field uses by methoxyfenozide and metabolite RH-131154 (M08) was above the parametric drinking water limit of 0.1 μg/L in the majority (methoxyfenozide) or all (RH-131154 (M08)) the geoclimatic situations that are represented by FOCUS groundwater scenarios. A data gap has been identified to provide further data to exclude the formation of other potentially harmful products that may result of treatment of drinking water.

In the area of ecotoxicology, further information is needed to address the risk of methoxyfenozide to aquatic organisms and sediment dwellers (issue that could not be finalised). In addition, data to address the risk to sediment dwellers for the pertinent sediment metabolites were missing. A data gap was also identified for further information to address the risk of methoxyfenozide to predatory mites. The risk assessment for honeybees (chronic adult and larvae) and non-target arthropods could not be finalised.

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Background

Commission Implementing Regulation (EU) No 844/2012[1] (hereinafter referred to as 'the Regulation') lays down the provisions for the procedure of the renewal of the approval of active substances, submitted under Article 14 of Regulation (EC) No 1107/2009[2]. This regulates for the European Food Safety Authority (EFSA) the procedure for organising the consultation of Member States, the applicant(s) and the public on the initial evaluation provided by the rapporteur Member State (RMS) and/or co-rapporteur Member State (co-RMS) in the renewal assessment report (RAR), and the organisation of an expert consultation where appropriate.

In accordance with Article 13 of the Regulation, unless formally informed by the European Commission that a conclusion is not necessary, EFSA is required to adopt a conclusion on whether the active substance can be expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009 within 5 months from the end of the period provided for the submission of written comments, subject to an extension of up to 3 months where additional information is required to be submitted by the applicant(s) in accordance with Article 13(3).

In accordance with Article 1 of the Regulation, the RMS the United Kingdom and co-RMS Slovakia received an application from Dow AgroSciences Ibérica, S.A. for the renewal of approval of the active substance methoxyfenozide. In addition, Dow AgroSciences Ibérica, S.A., submitted applications for maximum residue levels (MRLs) as referred to in Article 7 of Regulation (EC) No 396/2005[3]. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicant, the co-RMS (Slovakia), the European Commission and EFSA about the admissibility.

The RMS provided its initial evaluation of the dossier on methoxyfenozide in the RAR, which was received by EFSA on 4 August 2016 (United Kingdom, 2016). The RAR included a proposal to set MRLs, submitted under Article 7 of Regulation (EC) No 396/2005.

In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicant, Dow AgroSciences Ibérica, S.A., for consultation and comments on 20 September 2016. EFSA also provided comments. In addition, EFSA conducted a public consultation on the RAR. EFSA collated and forwarded all comments received to the European Commission on 23 November 2016. At the same time, the collated comments were forwarded to the RMS for compilation and evaluation in the format of a reporting table. The applicant was invited to respond to the comments in column 3 of the reporting table. The comments and the applicant's response were evaluated by the RMS in column 3.

The need for expert consultation and the necessity for additional information to be submitted by the applicant in accordance with Article 13(3) of the Regulation were considered in a telephone conference between EFSA and the RMS on 18 January 2017. On the basis of the comments received, the applicant's response to the comments and the RMS's evaluation thereof, it was concluded that additional information should be requested from the applicant and that EFSA should conduct an expert consultation in the areas of mammalian toxicology, residues, environmental fate and behaviour, and ecotoxicology.

The outcome of the telephone conference, together with EFSA's further consideration of the comments, is reflected in the conclusions set out in column 4 of the reporting table. All points that were identified as unresolved at the end of the comment evaluation phase and which required further consideration, including those issues to be considered in an expert consultation, were compiled by EFSA in the format of an evaluation table.

The conclusions arising from the consideration by EFSA, and as appropriate by the RMS, of the points identified in the evaluation table, together with the outcome of the expert consultation and the written consultation on the assessment of additional information, where these took place, were reported in the final column of the evaluation table.

[1] Commission Implementing Regulation (EU) No 844/2012 of 18 September 2012 setting out the provisions necessary for the implementation of the renewal procedure for active substances, as provided for in Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market. OJ L 252, 19.9.2012, p. 26–32.

[2] Regulation (EC) No 1107/2009 of 21 October 2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. OJ L 309, 24.11.2009, p. 1–50.

[3] Regulation (EC) No 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC. OJ L 70, 16.3.2005, p. 1–16.

A final consultation on the conclusions arising from the peer review of the risk assessment and on the proposed MRLs took place with Member States via a written procedure in July–August 2017.

This conclusion report summarises the outcome of the peer review of the risk assessment of the active substance and the representative formulation, evaluated on the basis of the representative use of methoxyfenozide as an insecticide on table and wine grapes, maize and sweet corn, fruiting vegetables (tomato, pepper, aubergine) and leaf vegetables (lettuce and other salad plants, spinach and similar, herbs). MRLs were assessed in grape leaves and sweet corn. A list of the relevant end points for the active substance and the formulation and the proposed MRLs is provided in Appendix A.

In addition, a key supporting document to this conclusion is the peer review report (EFSA, 2017), which is a compilation of the documentation developed to evaluate and address all issues raised in the peer review, from the initial commenting phase to the conclusion. The peer review report comprises the following documents, in which all views expressed during the course of the peer review, including minority views, where applicable, can be found:

- the comments received on the RAR;
- the reporting table (22 January 2017);
- the evaluation table (8 August 2017);
- the report(s) of the scientific consultation with Member State experts (where relevant);
- the comments received on the assessment of the additional information (where relevant);
- the comments received on the draft EFSA conclusion.

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

It is recommended that this conclusion report and its background documents would not be accepted to support any registration outside the European Union (EU) for which the applicant has not demonstrated that it has regulatory access to the information on which this conclusion report is based.

The active substance and the formulated product

Methoxyfenozide is the ISO common name for *N-tert*-butyl-*N*′-(3-methoxy-*o*-toluoyl)-3,5-xylohydrazide (IUPAC).

The representative formulated product for the evaluation was 'GF-837' a suspension concentrate (SC) containing 240 g/L methoxyfenozide.

The representative uses evaluated were foliar spray applications after dilution in water for the control of Lepidoptera pests in a range of crops such as table and wine grapes, maize and sweet corn, fruiting vegetables (tomato, pepper, aubergine) and leaf vegetables (lettuce and other salad plants, spinach and similar, herbs). Full details of the good agricultural practices (GAPs) can be found in the list of end points in Appendix A.

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

A scientific peer-reviewed open literature search on the active substance dealing with side effects on health, the environment and non-target species and published within the last 10 years before the date of submission of dossier, was submitted in accordance with the EFSA guidance on the submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (EFSA, 2011). However, in the ecotoxicology section, a relevant study concerning the effects of methoxyfenozide on Lepidoptera was found in the literature search but was not summarised and evaluated in the assessment report.

Conclusions of the evaluation

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

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

The proposed specification is based on batch data from industrial scale production. The minimum purity of the active substance as manufactured is 970 g/kg. There is no FAO specification available. *tert*-Butylhydrazine (RH-84078, RH-99838, TBZ) is considered a relevant impurity with a maximum content of 0.001 g/kg. The relevance of other impurities should be further assessed (see data gap in Section 2). The impurity considered now as relevant was also part of the original specification. Since there are new significant impurities too, it is proposed to update the reference specification. The RMS holds the position that the reference specification should not be changed and that the original specification set for Annex I inclusion should remain the reference specification.

The assessment of the data package revealed no issues that need to be included as critical areas of concern with respect to the identity, physical, chemical and technical properties of methoxyfenozide or the representative formulation. The main data regarding the identity of methoxyfenozide and its physical and chemical properties are given in Appendix A.

Adequate methods are available for the generation of pre-approval data required for the risk assessment. However, the information provided for the methods used in support of the toxicological studies was not sufficient (see Section 2) and a data gap was identified. Methods of analysis are available for the determination of the active substance and the relevant impurities in the technical material and in the representative formulation.

Methoxyfenozide residue can be monitored in food and feed of plant origin by a high-performance liquid chromatography with tandem mass spectrometry (HPLC–MS/MS) with limit of quantification (LOQ) of 0.01 mg/kg in each commodity group. Methoxyfenozide residue in food of animal origin can be determined by HPLC–MS/MS with LOQ of 0.01 mg/kg in all animal matrices. However, it should be noted that the efficiency of the extraction procedure used in these methods was not verified. As a consequence, a data gap was identified for verification of the efficiency of the extraction procedure used in the analytical methods for the determination of residues in food and feed of plant origin and food of animal origin. It should be noted that a validated multiresidue quick, easy, cheap, effective and safe (QuEChERS) liquid chromatography with tandem mass spectrometric (LC–MS/MS) method exists for monitoring of the methoxyfenozide residue in matrices of plant and animal origin, with a LOQ of 0.01 mg/kg for all commodities. However, the efficiency of the extraction procedure used for this method was also not addressed.

Methoxyfenozide residue in soil and drinking and surface water can be monitored by HPLC–MS/MS with LOQs of 0.01 mg/kg and 0.05 μg/L, respectively. An appropriate LC–MS/MS method exists for monitoring methoxyfenozide residue in air with a LOQ of 2.79 $\mu g/m^3$.

A LC–MS/MS method can be used for monitoring of methoxyfenozide residue in body fluids with a LOQ of 0.05 mg/L. The method for monitoring of methoxyfenozide in food of animal origin can be used for determination of methoxyfenozide in body tissues.

2. Mammalian toxicity

The toxicological profile of the active substance methoxyfenozide was discussed at the Pesticides Peer Review Experts' Meeting 159 and assessed based on the following guidance documents: SANCO/221/2000-rev. 10-final (European Commission, 2003), SANCO/10597/2003-rev. 10.1 (European Commission, 2012), Guidance on Dermal Absorption (EFSA PPR Panel, 2012) and Guidance on the Application of the CLP Criteria (ECHA, 2015).

Methoxyfenozide was discussed at the Pesticides Peer Review experts' Meeting 159.

To assess the toxicological profile of **active substance** methoxyfenozide, the applicant submitted a set of valid toxicity studies. The toxicity studies were representative of the proposed technical specification for the active substance and associated impurities (see Section 1). *tert*-Butylhydrazine is a relevant impurity, whereas impurity RH-116267 was deemed relevant by the applicant and the RMS; however, it was not clear the basis of its relevance. A data gap is identified to confirm the relevance of this impurity and address appropriately the relevance of other impurities.

Very limited information on the methods used in support of the toxicological studies (only information was submitted for two mechanistic studies) was available and therefore a data gap was identified (see Section 1).

In the toxicokinetics studies, oral absorption was estimated to be about 60% (biliary excretion taken into account). There was no evidence for accumulation. Excretion of methoxyfenozide was predominantly through the faecal route and to lesser extent in urine. The metabolism of methoxyfenozide involves demethylation, oxidation and/or conjugation. It is unknown whether unique human metabolite might be

formed since an *in vitro* comparative metabolism study was not submitted leading to a data gap and issue that could not be finalised.

In the acute toxicity studies, methoxyfenozide has low acute toxicity when administered orally, dermally or by inhalation to rats. It is not a skin or eye irritant or a skin sensitiser. A phototoxicity study is not required for methoxyfenozide.

In short-term oral toxicity studies with rats and dogs, the target organs of toxicity were the liver (increased weight and moderate hypertrophy) and the haemopoietic system (haemolytic anaemia). Non-specific critical effects as reduced body weight gain were observed in mice. The dog was the most sensitive species. The relevant short-term oral no observed adverse effect level (NOAEL) is 9.8 mg/kg body weight (bw) per day (1-year dog study). The RMS did not agree and proposed a NOAEL of 106 mg/kg bw per day (1-year dog study).

Based on available genotoxicity studies, including new genotoxicity studies supporting the new specification, the substance is unlikely to be genotoxic.

In long-term toxicity and carcinogenicity studies with rats, the target organs of toxicity were the liver, thyroid and the haemopoietic system. The rat was the most sensitive species and the relevant long-term NOAEL is 10.2 mg/kg bw per day. In mice, methoxyfenozide has low toxicity and no substance-related adverse effects were observed at the top dose of 1,020 mg/kg bw per day. The acceptability of the long-term toxicity study in rats and the carcinogenic potential was discussed during the experts' meeting: the experts considered that the long-term toxicity study in rats is acceptable despite low survival. The majority of experts considered the incidence of thyroid C-cell adenoma and hepatocellular adenoma at the mid- and top-dose level treatment-related and adverse. Available historical control data sourced from a different laboratory and over a different period of time than recommended by regulation were not considered acceptable by the majority of experts. The relevant NOAEL for carcinogenicity is 10.2 mg/kg bw per day. The experts agreed that methoxyfenozide did not show carcinogenic potential in mice. The majority of experts considered that thyroid C-cell adenoma and hepatocellular adenoma in rats suggest that classification as 'Carc. Cat. 2 (H351)'[4] would be required for methoxyfenozide. The RMS did not agree with the proposal and considered thyroid C-cell adenoma and hepatocellular adenoma tumours not treatment related.

In reproductive toxicity studies, no effects on offsprings, on fertility and overall reproductive performance were observed in rats. The parental NOAEL is 153 mg/kg bw per day based on reduced body weight gain and liver toxicity. No developmental toxicity is evidenced in rats and rabbits up to the limit dose.

No potential for neurotoxicity was observed in the standard toxicity studies. The substance did not show a neurotoxic potential in acute and short-term neurotoxicity studies in rats.

Methoxyfenozide is not listed in Annex VI of the CLP Regulation (EC) No 1272/2008. Methoxyfenozide is not proposed to be classified as toxic for reproduction category 2 but as carcinogenic category 2 in accordance with the provisions of Regulation (EC) No 1272/2008, and therefore, the conditions of the interim provisions of Annex II, Point 3.6.5 of Regulation (EC) No 1107/2009 concerning human health for the consideration of endocrine disrupting properties are not met. With regard to the scientific risk assessment the majority of the experts agreed that more data (level 2 and level 3 studies according to OECD conceptual framework (OECD, 2012)) are needed in the light of the observed effects on thyroid such as changes in thyroid weight sometimes correlating with follicular cell hypertrophy and C-cell adenomas (data gap and issue that could not be finalised). The RMS did not agree.

The agreed acceptable daily intake (ADI) is 0.1 mg/kg bw per day, on the basis of the NOAEL of 10 mg/kg bw in the 2-year study in rats based on liver and thyroid toxicity and haemotoxicity at 411 mg/kg bw per day. The ADI is supported by the NOAEL of 9.8 mg/kg bw per day in the 1-year dog study. An uncertainty factor (UF) of 100 was applied. The same ADI was set during the first peer review process (European Commission, 2004).

The agreed acute reference dose (ARfD) is 0.1 mg/kg bw based on the NOAEL of 9.8 mg/kg bw per day for haemolytic anaemia observed at 106 mg/kg bw per day in the 1-year dog study. The ARfD is supported by the 2-week dog studies. The experts considered the 1-year dog study as a conservative but appropriate approach for setting the ARfD (an UF of 100 was applied). A different

[4] It should be noted that harmonised classification and labelling is formally proposed and decided in accordance with Regulation (EC) No 1272/2008.
Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. OJ L 353, 31.12.2008, p. 1–1355.

ARfD (0.2 mg/kg bw per day, based on 2-week dog study by applying an UF of 100) was set during the first peer review process (European Commission, 2004) but it was considered no longer appropriate, since the 2-week dog studies were not considered robust enough to establish the ARfD.

The agreed systemic acceptable operator exposure level (AOEL) and acute acceptable operator exposure level (AAOEL) are 0.06 mg/kg bw (per day) on the basis of the relevant short-term NOAEL of 9.8 mg/kg bw per day in the 1-year study in dogs based on haemolytic anaemia at 106 mg/kg bw per day. The AOEL is supported by the 2-week dog studies. Correction factor of 60% for oral absorption is needed to derive the AOEL and AAOEL. The experts considered the 1-year dog study as a conservative but appropriate approach for setting the AAOEL since the 2-week dog studies were not robust enough to establish the AAOEL. An UF of 100 was applied. A different AOEL was set during the first peer review process (European Commission, 2004).

The RMS estimated **non-dietary exposure** considering dermal absorption values of methoxyfenozide in a formulation considered similar to 'GF-837' of 0.5% for the concentrate and of 8% and 4% for the dilution I and II, respectively, as input values.

Considering outdoor representative use in **grapes, maize, sweetcorn** and **vegetables**, the operator (tractor-mounted application and hand-held application; without the use of personal protective equipment (PPE)), worker (without PPE), bystander and resident exposure were below the AOEL.

Considering indoor representative use in **fruiting vegetables**, the operator and worker exposure was below the AOEL without the use of PPE. In case bystander and resident exposure occur (pending on the type of indoor structure), it is considered that the exposure will be covered by the outdoor scenarios.

Metabolite RH-117236 (**M14**) (desmethylated parent) is of low acute toxicity to rats and unlikely to be genotoxic. M14 was a predominant metabolite in faeces and the glucuronide of M14 (i.e. M16) was a major metabolite in bile (male and female rat). EFSA considered M14 and its conjugates (M15 and M40) covered by the parent and they should be considered at least as toxic as the parent.

Metabolite RH-141511 (**M24**) (hydroxy methyl derivative of parent) was a predominant metabolite in faeces and the glucuronide of M24 (i.e. M26) was a major metabolite in bile (only in female). No toxicity studies are available on these metabolites. However, considering the metabolic pathway in the rat, their amount in bile together with structural chemical similarities with parent and metabolite M14 EFSA considered M24 and its conjugates (M26) covered by the parent and they should be considered at least as toxic as parent.

Metabolite RH-131154 (**M08**) is unlikely to be genotoxic. M08 is predicted to occur in groundwater above 0.1 μg/L (see Section 4) and is considered a relevant groundwater metabolite since it cannot be excluded that it shares the carcinogenic potential of the parent leading to a critical area of concern.

3. Residues

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

3.1. Representative use residues

Methoxyfenozide was discussed at the Pesticides Peer Review experts' Meeting 161.

Metabolism of methoxyfenozide was investigated after foliar applications in the fruit (apples, grapes), pulses and oilseeds (cotton), and in cereals and grass (rice) crop groups using methoxyfenozide ^{14}C-labelled on the phenyl ring, dimethylphenyl ring and *tert*-butyl moiety, respectively. In all plant parts, methoxyfenozide was the main compound of the total radioactive residues (TRR) 14–62 days after last application and accounting for 91% TRR in apples, 80% TRR in grapes, 46–67% TRR in cotton seed, and up to 68% and 58% TRR in rice straw and grain, respectively. The other identified metabolites occurred at a level < 10% TRR.

A confined rotational crop metabolism study was conducted with a bare soil application of ^{14}C methoxyfenozide at a dose rate of 2.25 kg a.s./ha (5N rate). Mustard, radish and wheat were planted at different plant-back intervals (PBIs) (30, 90 and 365 days). Methoxyfenozide was found to be extensively degraded in all crop parts and was observed mainly in mustard leaves (up to 21% TRR) and radish leaves (up to 24% TRR) and root (up to 42% TRR) at all PBIs while it was never detected or at negligible levels in wheat forage, straw and grain. M15 was found to be a major compound of the total residues (up to 33% TRR in mustard leaves, 15% TRR in radish leaves/roots and up to 35% TRR and

20% TRR in wheat forage and straw, respectively). M40 was also identified at significant levels in wheat forage only (up to 48% TRR) whilst M14 accounted for up to 45% TRR and 24% TRR in wheat straw and grain, respectively. It is noted that M15 and M40 metabolites are glycoside conjugates of M14 compound. Rotational crop field trials conducted in North America with lettuce as a cover crop (5x 0.45 kg as/ha, PBI: 7 days) confirmed the metabolic pattern depicted in the confined metabolism study with significant magnitude of M14 and M15 residues in wheat forage and straw and in rice grain compared to the parent compound. EU field trials conducted with a bare soil application (2x 144 g a.s./ha) showed methoxyfenozide residue levels of 0.017 and 0.019 mg/kg in lettuce and radish leaves, respectively. However the validity of these field trials was discussed in regard to the missing storage stability data for M14, M15 and methoxyfenozide residues and validation of the analytical method to release the conjugates of M14. Considering also the high soil persistence of methoxyfenozide (DT_{50} = > 1000 days), a data gap was identified for additional European rotational crops field trials analysing for methoxyfenozide, M14, M15 and M40 and covering the maximum predicted concentration of methoxyfenozide in soil following successive years of application. Having regard to the moderate to very high persistence in soil of metabolite M08 with DT_{50} values ranging between 30.8 and 73.1 days and uncertain higher values and therefore a DT_{90} > 100 days (i.e. 243 days or higher) for M08, confined rotational crops metabolism studies addressing the potential uptake from soil and the fate of M08 in leafy crops, small grains crops and root crops are also required (data gap).

The residue definition for monitoring and risk assessment is proposed as methoxyfenozide only for primary crops. Considering the metabolic profile of methoxyfenozide in rotational crops and the outstanding data to address the fate of M08 compound in those crops, the residue definition for risk assessment in rotational crops was provisionally set as methoxyfenozide and M14 (including its conjugates M15 and M40) expressed as methoxyfenozide.

Methoxyfenozide labelled on the methoxyphenyl ring was stable under standard hydrolysis conditions representative of pasteurisation, baking/brewing/boiling and sterilisation. Processing studies on apples, table and wine grapes, oranges and tomatoes were provided and processing factors were derived for the relevant processed commodities. Sufficient processing studies are requested on peppers and spinaches (data gap).

Sufficient residue trials were submitted to derive a MRL proposal of 0.2 mg/kg for tomatoes and aubergines (indoor), 0.4 mg/kg for sweet peppers/bell peppers (indoor), 0.01* mg/kg (*Indicates lower limit of analytical determination) for maize grain and 4 mg/kg for lettuces, salad plants (except escaroles/broad-leaved endives), herbs and edible flowers and spinaches and similar leaves. A full residue data set compliant with the southern Europe (SEU) GAP (representative use) on sweet corn is requested (data gap) while the northern Europe (NEU) GAP is covered by the residue trials on sweet corn submitted in the framework of the MRL application. Additional residue trials on table and wine grapes (NEU/SEU), on tomatoes (SEU) and on sweet peppers/bell peppers (SEU) are required (data gap). The submitted residue data are supported by storage stability studies where methoxyfenozide residues were shown to be stable in each of the different commodity categories for at least 12 months.

Metabolism in livestock (laying hens and lactating goats) was investigated using methoxyfenozide ^{14}C-labelled on the phenyl ring, dimethylphenyl ring and *tert*-butyl moiety. Methoxyfenozide was found to be a major compound of the total residues in poultry and ruminant fat (40–81% TRR), muscle (10–25% TRR) and in milk (up to 35% TRR). M16 compound, the glucuronide conjugated form of M14 was identified at significant proportions in liver (up to 29% TRR), kidney (up to 42% TRR), eggs (30% TRR) and in muscle (31% TRR). M24 and its glucuronide conjugate M26 occurred at significant proportions in poultry and ruminants' kidney (up to 33% TRR) and in milk and eggs (up to 20 and 32% TRR, respectively). The residue definition for enforcement is set as methoxyfenozide only. For risk assessment, the residue definition is provisionally set as methoxyfenozide, M24 (free and conjugated M26) and M16, expressed as methoxyfenozide. The meeting also agreed that the potential transfer of M14, M15 and M40 compounds from the rotational crops feed items in animal matrices is sufficiently addressed considering the metabolic pattern of methoxyfenozide in animals and additional metabolism studies conducted with these compounds are not requested.

A ruminant feeding study was conducted with methoxyfenozide and analysed for the parent compound in all matrices and for M16 in liver and kidney. The experts discussed the validity of this study since degradation of M16 residues (> 30%) was observed within 2 weeks under frozen storage conditions in bovine liver while the liver/kidney residue samples from the feeding study were stored for up to 230 days. The experts were unable to conclude on the analytical performance of the method used both in the storage stability study and feeding study and whether M16 residues are actually unstable in bovine liver. A data gap was identified to provide further information on the validation data

of this analytical method for the determination of M16 residues in animal matrices and to conclude on the validity of the feeding study. The livestock exposure assessment cannot be concluded yet and will be finalised considering the potential exposure to methoxyfenozide, M14 and its conjugates (M15 and M40) residues from the rotational crops feed items (data gap). In case the revised dietary burden intake calculations trigger a feeding study in poultry and a new valid feeding study in ruminants, further investigation of the magnitude of M24 (free and conjugated M26) residues may be needed.

A fish metabolism study was not provided and is not requested as methoxyfenozide residues in maize grain are below the LOQ of the method (0.01 mg/kg).

Since maize shows attractiveness to bees for pollen collection (EFSA, 2013) and treatment can take place at flowering, residues of methoxyfenozide in pollen and bee products cannot be excluded and further information is requested (data gap).

For the time being, a provisional consumer dietary risk assessment can only be conducted for parent methoxyfenozide residues in primary crops considering the outstanding data to address the magnitude of relevant metabolites and the potential uptake from soil and fate of M08 in rotational crops. Furthermore, no MRLs for animal commodities can be derived in view of the outstanding data to perform a comprehensive livestock exposure assessment. Long-term or short-term intake concerns were not identified for the consumers (4% ADI (WHO Cluster diet B) and 70% ARfD (lettuce, DE child)). The consumer risk assessment through drinking water was not conducted in regard to M08 as this metabolite is considered as relevant (see Section 2).

A specific residue definition for risk assessment for rotational crops and the residue definition for risk assessment for animal matrices have been changed compared to those used in the review of the existing MRLs for methoxyfenozide (EFSA, 2014a). Therefore, a revision of the MRLs under article 12 may be necessary. Based on the proposed ADI value of 0.1 mg/kg bw per day, a chronic intake concern has not been identified for the consumers for all the existing uses assessed during the Article 12 MRL review, (12.3% of the ADI (DE child)) when the consumer dietary intake calculation is performed with consideration of the existing CXLs. In contrast, considering the ARfD value of 0.1 mg/kg bw and the highest CXL residue levels related to these existing uses, an exceedance of the ARfD is identified for the following commodities: Chinese cabbages (668% ARfD), lettuces (484% ARfD), celeries (358% ARfD), head cabbages (326% ARfD) and tomatoes (104% ARfD).

3.2. Maximum residue levels

Sufficient residue trials were submitted to derive MRLs, respectively, in grape leaves and similar species and sweet corn.

The uses in this MRL application do not trigger a revision of the calculated livestock dietary burden.

A consumer risk assessment using revision 2 of the EFSA Pesticide Residues Intake Model (PRIMo) was conducted for the grape leaves and similar species and sweet corn uses in the MRL application and for the EU representative uses. The chronic (TMDI) and acute dietary intakes (IESTI) were below the ADI and ARfD for all considered European consumer groups (max ADI 4.2% (WHO Cluster diet B); max 70% ARfD (lettuce, DE child).

4. Environmental fate and behaviour

Methoxyfenozide was discussed at the Pesticides Peer Review Teleconference 141.

The rates of dissipation and degradation in the environmental matrices investigated were estimated using FOCUS (2006) kinetics guidance.

The route and rate of degradation of methoxyfenozide was investigated in 18 soils (14 with samples ^{14}C labelled at methoxyphenyl; ring A and 4 with samples ^{14}C labelled at methoxyphenyl; ring B) under dark aerobic conditions at 20°C. Methoxyfenozide exhibits medium to very high persistence in soil. A major metabolite, RH-131154 (M08), was identified reaching a maximum at the end of the incubation time (15.83% applied radioactivity (AR)). Kinetic analysis of the formation and the degradation of this metabolite were performed for those studies where the parent is applied to soil. RH-131154 (M08) may be considered to exhibit moderate to very high persistence in soil taking into consideration values assumed for those soils where no clear decline of the metabolite is observed. Unextractable, radioactivity increased up to 27% AR at the end of one of the experiments (ring A labelled) and volatiles trapped in the alkaline trap (assumed to be CO_2) were generally low with a maximum of 24.25% AR.

Methoxyfenozide also exhibits very high persistence in soil under anaerobic conditions. Metabolites RH-131154 (M08) and RH-117236 (M14) are formed at levels above 5% AR and would need further assessment in those situations or crops for which prolonged anaerobic conditions cannot be excluded.

Photolysis at the soil surface soil was investigated in a microbial active soil. From the results of this study, it may be concluded that photodegradation is not expected to contribute to the degradation of methoxyfenozide in soil the environment.

Field dissipation studies confirm the moderate to very high persistence of methoxyfenozide under realistic conditions. In field accumulation experiments performed at sites in Spain and Germany, the residues after annual application had not reached a plateau and were still increasing even after 6 years.

The predicted environmental concentrations in soil (PEC_{soil}) were calculated for parent methoxyfenozide and the metabolite RH-131154 (M08) for the representative use in leafy crops based on standard calculations and worst case assumptions.

Batch soil adsorption/desorption studies were performed with methoxyfenozide in 16 soils, 10 of them identical to those used in laboratory incubations intended to derive parameters for aged sorption analysis. Adsorption/desorption of metabolite RH-131154 (M08) was investigated in four soils. According to these studies, methoxyfenozide may be considered to exhibit medium to high mobility in soil and metabolite RH-131154 (M08) very high mobility.

Aqueous photolysis can be considered not to contribute to the degradation/dissipation of methoxyfenozide in the aquatic environment according to the available studies.

Fate and behaviour of methoxyfenozide was investigated in four dark water sediment systems under aerobic conditions. Methoxyfenozide partially partitioned to the sediment (max 68.25% AR after 91 days). Degradation was relatively slow in both systems (DT_{50} whole system = 159.1–273.5 days). A major metabolite was formed: RH-117236 (M14) (max. 15.75% AR after 91 days in the whole system) which was considered to exhibit very high persistence. Mineralisation was practically negligible (max. 2.9% AR as CO_2 after 120 days) and the un-extractable residue in the sediment increased up to a maximum of 26.1% AR after 120 days (end of the study).

The necessary surface water and sediment exposure assessments (PEC calculations) were carried out for methoxyfenozide and RH-131154 (M08) (from soil) and RH-117236 (M14) using the FOCUS (2001) step 1 and step 2 approach (version 2.1 of the Steps 1-2 in FOCUS calculator). For the active substance methoxyfenozide, appropriate step 3 (FOCUS, 2001)[5] simulations were available for the representative uses.

Potential for ground water contamination was assessed by calculation of 80th percentile of 20 years annual average concentrations moving below the top 1 m soil layer with FOCUS (2009) scenarios and the models PEARL v.4.4.4 and PELMO v.5.5.3[5] for the active substance methoxyfenozide and metabolite RH-131154 (M08). Tier I and Tier III calculations were considered to be performed according agreed guidance based on, respectively, laboratory derived DT_{50} and field derived DT_{50} for the parent compound. The potential for groundwater exposure from the representative field uses by methoxyfenozide and metabolite RH-131154 (M08) was indicated to be above the parametric drinking water limit of 0.1 μg/L in the majority (methoxyfenozide[6]) or all (RH-131154 (M08)) geoclimatic situations that are represented by FOCUS groundwater scenarios. The use in green houses was simulated using a modified Piacenza scenario considering different application dates. The parametric drinking water limit of 0.1 μg/L was not exceeded in these simulations. However, risk managers should be aware that the representativeness of this scenario has not been validated or established. Therefore, field use simulations are considered as surrogate of low technology greenhouses not represented by the simulations provided (EFSA, 2014b).

The applicant provided information to address the effect of water treatments processes on the potential formation of *N*-nitrosodimethyl-amine (NDMA) from nature of the residues that might be present in surface water and groundwater, when surface water or groundwater are abstracted for drinking water. The conclusion of this consideration was that neither methoxyfenozide nor any of its degradation products that trigger assessment would be expected to produce NDMA due to oxidation at the disinfection stage of usual water treatment processes. However, no experimental data was presented to exclude the formation of other nitrosamines or other potentially harmful products such chlorinated organic substances. Therefore, a data gap is identified to complete the information presented with additional data in order to exclude the formation of other potentially harmful products that may result of drinking water treatment.

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

[5] Simulations used a Q10 of 2.58 and Walker equation coefficient of 0.7.
[6] For methoxfenozide, only the Sevilla scenario was below the parametric trigger although not for the use on grape vines.

5. Ecotoxicology

The risk assessment was based on the following documents: European Commission (2002a,b), SETAC (2001), EFSA (2009), EFSA PPR Panel (2013) and EFSA (2013).

It is noted that the ecotoxicity studies were performed with formulations 'RH 112, 485 2F' and 'RH-2485 240SC' these formulations are considered to be equivalent to the representative formulation 'GF-837'.

It is noted that the representative uses included greenhouse use for fruiting vegetables. Since the use in non-permanent greenhouse could not be excluded, a risk envelope approach was taken considering the fact that the application pattern is the same for both field and greenhouse uses. A low acute and long-term risk to **birds** and **mammals** was concluded for methoxyfenozide and its pertinent metabolites for all the exposure routes and for all the representative uses.

A low acute risk to **aquatic organisms** was concluded for methoxyfenozide for the uses on grapes (table/wine) while a high acute risk was concluded for various FOCUS scenarios for the uses on maize/sweet corn, on fruiting vegetables and on leafy vegetables. A high chronic risk to aquatic organisms was concluded for all representative uses and all FOCUS scenarios. It has to be noted that in the absence of an assessment of the validity criteria in line with the most recent version of the OECD TG 201, all the available studies with algae were not considered valid (data gap). However, considering the model of action of methoxyfenozide, algae are not expected to be the most sensitive aquatic organisms. The available refinements to the aquatic risk assessment were discussed the Pesticide Peer Review meeting 160. The experts agreed to use the no observed effect concentration (NOEC) derived from the available mesocosm study with an assessment factor of 3. By applying the refined endpoint in the risk assessment, a high risk was still concluded for FOCUS scenarios R3 and R4 for the uses on maize/sweet corn, scenarios D6, R3 and R4 for the use on fruiting vegetables, and scenarios D6 for the uses on leaf vegetables whilst a low risk was concluded for the uses on grape (wine/table). It is, however, noted that the available information was not considered as sufficient to address the risk to sediment dwellers via exposure through the sediment. Therefore, a data gap was identified to further address the risk to sediment dwellers for all the representative uses. Toxicity data on *Chironomus riparius* (most sensitive species) were available for the pertinent surface water and sediment metabolites M08 (acute toxicity study) and M14 (chronic toxicity study, spiked water). By using these endpoints in the risk assessment, a low risk was concluded for all the representative uses.

In the case of honey**bees,** acute toxicity data were available. A chronic toxicity study and a study assessing the effects to bee larvae under laboratory conditions were not available. Semifield and field studies (including two brood feeding tests) were available. It is noted that since EFSA (2013) was not taken note, the RMS did not use it while performing the bees risk assessment. In consideration of the above a data gap has been identified. The risk assessment for bees and in particular the available higher tier studies for methoxyfenozide were discussed the Pesticide Peer Review meeting 160. Overall, the available information was not considered as sufficient to address the risk to honeybees and, therefore, the experts agreed to identify a data gap for further information to address the toxicity of methoxyfenozide on adult bees (chronic) and brood.

The risk to **non-target arthropods** was discussed at the Pesticide Peer Review meeting 160. Due to the specific mode of action of methoxyfenozide (moulting accelerating compound) the standard risk assessment was considered not relevant in the case of methoxyfenozide; it does not cover the relevant route of exposure (oral route), life stage (moulting) and the potentially most sensitive group (Lepidoptera). A field study assessing the effects of methoxyfenozide on the arthropods community in apple orchard was available. This study was, however, considered not sufficient to address the risk to non-target arthropods; it was not possible to define whether the study was robust enough to detect potential effects since the toxic standard was not an insect growth regulator. Furthermore, the study was not suitable to cover the representative uses and did not cover the off-field area which is considered as more relevant than the in-field area for Lepidoptera. A data gap was therefore identified for further information to address the in-field and off-field risk to sensitive life stages of non-target arthropods and for further information to address the off-field risk to Lepidoptera, considering specific the mode of action of methoxyfenozide. It is noted that a relevant study concerning the effects of methoxyfenozide on Lepidoptera was found in the literature search but was not summarised and evaluated in the renewal assessment report (data gap).

A low risk was concluded for methoxyfenozide for earthworms and Collembola and for metabolite RH-131154 for all **soil macroorganisms (including earthworms)**. It is noted that a standard laboratory study on the predatory mite (*Hypoaspis aculeifer*) was not available for the active

substance. A field study investigating the effects on the soil community was available. In this study, changes in the soil community with respect to the control were not observed. It is, however, noted that the toxic standard in the study did not act with the same mode of action as the active substance; therefore, there are uncertainties as to whether this study is robust enough to detect any effect on soil mites. Therefore, the available data were no considered sufficient to address the risk to soil mites for methoxyfenozide (data gap).

A low risk to soil **microorganisms** for methoxyfenozide and its pertinent metabolites and for **non-target terrestrial plants** and **biological methods of sewage treatment** for methoxyfenozide was concluded.

Considering the available information, it is unlikely that methoxyfenozide is an endocrine disruptor for fish via the estrogenic, androgenic and steroidogenic modalities. An amphibian metamorphosis assay was available which did not provide any evidence of endocrine activity or potential endocrine related adverse effects via the thyroid modality. However, pending on the data gap in Section 2, this conclusion may need to be reconsidered. No firm conclusion could be drawn for birds.

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

Table 1: Soil

Compound (name and/or code)	Persistence	Ecotoxicology
Methoxyfenozide	Medium to very high (DT_{50} = 87.2 to > 1000 days)	Data gap
RH-131154 (M08)	Moderate to very high (DT_{50} = 30.8–1000 days)	Low risk

DT_{50}: period required for 50% dissipation.

Table 2: Groundwater

Compound (name and/or code)	Mobility in soil	> 0.1 µg/L at 1 m depth for the representative uses[a]	Pesticidal activity	Toxicological relevance
Methoxyfenozide	Medium to high (K_{Foc} = 132–365 mL/g)	FOCUS GW: Yes, majority of scenarios exceed 0.1 µg/L for all field uses (Tier III calculation)	Yes	Yes
RH-131154 (M08)	Very high (K_{Foc} = 16–27 mL/g)	FOCUS GW: Yes, all of scenarios exceed 0.1 µg/L for all field uses (Tier III calculation). Also, all scenarios exceed 0.75 µg/L (max 7.48 µg/L)	No	Yes (it cannot be excluded that it shares the carcinogenic potential of methoxyfenozide; unlikely to be genotoxic)

K_{Foc}: Freundlich organic carbon adsorption coefficient; FOCUS: Forum for the Co-ordination of Pesticide Fate Models and their Use; GW: groundwater.
(a): At least one FOCUS scenario or a relevant lysimeter.

Table 3: Surface water and sediment

Compound (name and/or code)	Ecotoxicology
Methoxyfenozide	High risk (surface water), data gap (sediment)
RH-131154 (M08)	Low risk
RH-117236 (M14)	Low risk

Table 4: Air

Compound (name and/or code)	Toxicology
Methoxyfenozide	Low acute inhalation toxicity to rats

7. Data gaps

This is a list of data gaps identified during the peer review process, including those areas in which a study may have been made available during the peer review process but not considered for procedural reasons (without prejudice to the provisions of Article 56 of Regulation (EC) No 1107/2009 concerning information on potentially harmful effects).

7.1. Data gaps identified for the representative uses evaluated

- Analytical methods used in support of toxicological studies for generation of pre-approval data for risk assessment (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Sections 1 and 2).
- Efficiency of the extraction procedure used in the analytical methods for the determination of residues in food and feed of plant origin and food of animal origin (relevant for all representative uses evaluated; submission date proposed by the applicant: end 2017; see Section 1).
- The basis for the relevance of impurity RH-116267 and justification of its maximum content from a toxicological point of view (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- Further assessment of the toxicological relevance of impurities other than *tert*-butylhydrazine (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- Comparative *in vitro* metabolism study on methoxyfenozide (relevant for all representative uses evaluated; submission date proposed by the applicant: ongoing; see Section 2).
- Mechanistic data investigating whether thyroid toxicity effects in rats might be endocrine-mediated, and if so, whether it might be relevant to humans (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- Full assessment of the results of the scientific peer-reviewed open literature search by RMS (relevant for all representative uses evaluated; submission date proposed by the applicant: submitted; see Section 5).
- Rotational crops field trials analysing for methoxyfenozide, M14, M15 and M40 and covering the maximum predicted concentration of methoxyfenozide in soil following successive years of application (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).
- Confined rotational crops metabolism studies addressing the potential uptake from soil and the fate of M08 in leafy crops, small grains crops and root crops (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).
- Two SEU GAP-compliant residue trials on table grapes (relevant for the representative use evaluated on table grapes; submission date proposed by the applicant: unknown; see Section 3).
- One NEU GAP-compliant residue trial and one SEU GAP-compliant residue trial on wine grapes (relevant for the representative use evaluated on wine grapes; submission date proposed by the applicant: unknown; see Section 3).
- Four SEU GAP-compliant residue trials on tomatoes (relevant for the representative use evaluated on tomatoes; submission date proposed by the applicant: unknown; see Section 3).
- Four SEU GAP-compliant residue trials on sweet peppers/bell peppers (relevant for the representative use evaluated on peppers; submission date proposed by the applicant: unknown; see Section 3).
- A complete residue data set compliant with the SEU GAP on sweet corn (relevant for the representative SEU use evaluated on sweet corn; submission date proposed by the applicant: unknown; see Section 3).
- Processing studies on sweet peppers/bell peppers and spinaches and similar leaves (relevant for the representative use evaluated on sweet peppers/bell peppers and spinaches and similar leaves; submission date proposed by the applicant: unknown; see Section 3).
- Livestock dietary burden calculation considering the potential exposure of the animals to methoxyfenozide, M14 and its conjugates (M15 and M40) residues from the rotational crops feed items (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).

- Information on the validation data of the analytical method used in the ruminants feeding study for the determination of M16 residues in animal matrices (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).
- Determination of the residues in pollen and bee products for human consumption resulting from residues taken up by honeybees from crops at blossom with regard to methoxyfenozide residues (relevant for the representative use on maize evaluated; submission date proposed by the applicant: unknown; see Section 3).
- A data gap is identified to provide further data to exclude the formation of potentially harmful products in addition to NDMA that may result from the treatment of drinking water (relevant for all representative uses evaluated; no submission date proposed by the applicant; see Section 4).
- Further information to address the effects of methoxyfenozide to algae (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).
- Further information to address the toxicity of methoxyfenozide to sediment dwellers (spiked sediment study) (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).
- Further information to address the chronic risk to aquatic organisms for scenarios R3 and R4 for the uses on maize/sweet corn, scenarios D6, R3 and R4 for the use on fruiting vegetables, and scenarios D6 for the uses on leaf vegetables (relevant for the uses on maize/sweet corn, fruiting and leaf vegetables; submission date proposed by the applicant: unknown; see Section 5).
- Further information to address the toxicity of methoxyfenozide on adult bees (chronic) and brood (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).
- A risk assessment for honeybees for methoxyfenozide and its pertinent metabolites in line with EFSA (2013) (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).
- Further information to address the risk to sensitive life stages of non-target arthropods in-field and off-field and further information to address the off-field risk to Lepidoptera, this may include, but should not be limited to, an evaluation of the study Borchert et al. (2005) (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5)
- Further information to address the risk to predatory mites for methoxyfenozide (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5)

7.2. Data gaps identified for the maximum residue level applications

None.

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

No particular conditions are proposed for the representative uses and for the MRL applications.

9. Concerns

9.1. Issues that could not be finalised

An issue is listed as 'could not be finalised' if there is not enough information available to perform an assessment, even at the lowest tier level, for the representative uses in line with the uniform principles in accordance with Article 29(6) of Regulation (EC) No 1107/2009 and as set out in Commission Regulation (EU) No 546/2011[7] and if the issue is of such importance that it could, when finalised, become a concern (which would also be listed as a critical area of concern if it is of relevance to all representative uses).

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

An issue is also listed as 'could not be finalised' if the available information is considered insufficient to conclude on whether the active substance can be expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009.

1) The need for further tests and risk assessment to unique human metabolites could not be finalised whilst an *in vitro* comparative metabolism study was not submitted (see Section 2).
2) Methoxyfenozide does not meet the interim criteria for endocrine disruption. With regard to the scientific risk assessment, a conclusion on whether thyroid toxicity effects in rats could be endocrine-mediated could not be finalised (see Sections 2 and 5).
3) The consumer dietary risk assessment is regarded as not finalised for the products of plant and animal origin and drinking water in relation with drinking water treatment products (see Sections 3 and 4)
4) The risk assessment for honeybees (chronic adult and larvae) for methoxyfenozide could not be finalised (see Section 5)
5) The risk assessment for non-target arthropods for methoxyfenozide could not be finalised (see Section 5)
6) The risk assessment for sediment dwellers for methoxyfenozide could not be finalised (see Section 5)

9.2. Critical areas of concern

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

An issue is also listed as a critical area of concern if the assessment at a higher tier level could not be finalised due to lack of information, and if the assessment performed at a lower tier level does not permit the conclusion that, for at least one of the representative uses, it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater, or any unacceptable influence on the environment.

An issue is also listed as a critical area of concern if, in the light of current scientific and technical knowledge using guidance documents available at the time of application, the active substance is not expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009.

7) Potential ground water contamination above the parametric drinking water limit of 0.1 μg/L by methoxyfenozide and toxicological relevant metabolite RH131154 (M08) (see Sections 2 and 4).

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

Table 5: Overview of concerns

Representative use		Grapes (table/wine)	Maize/sweet corn	Fruiting vegetables (field)	Fruiting vegetables (green house)	Leafy vegetables
Operator risk	Risk identified					
	Assessment not finalised					
Worker risk	Risk identified					
	Assessment not finalised					
Resident/ bystander risk	Risk identified					
	Assessment not finalised					
Consumer risk	Risk identified					
	Assessment not finalised	X[3]	X[3]	X[3]	X[3]	X[3]

Representative use		Grapes (table/wine)	Maize/sweet corn	Fruiting vegetables (field)	Fruiting vegetables (green house)	Leafy vegetables
Risk to wild non-target terrestrial vertebrates	Risk identified					
	Assessment not finalised					
Risk to wild non-target terrestrial organisms other than vertebrates	Risk identified					
	Assessment not finalised	X[4,5]	X[4,5]	X[4,5]	X[4,5]	X[4,5]
Risk to aquatic organisms	Risk identified		2/8 FOCUS scenarios	3/4 FOCUS scenarios	3/4 FOCUS scenarios	1/7 FOCUS scenarios
	Assessment not finalised	X[6]	X[6]	X[6]	X[6]	X[6]
Groundwater exposure to active substance	Legal parametric value breached	X[8]	7/8 FOCUS scenarios[8]	4/5 FOCUS scenarios[8]	X[8]	6/7 FOCUS scenarios[8]
	Assessment not finalised					
Groundwater exposure to metabolites	Legal parametric value breached[(a)]	X[8]	X[8]	X[8]	X[8]	X[8]
	Parametric value of 10 µg/L[(b)] breached					
	Assessment not finalised					

Columns are grey if no safe use can be identified. The superscript numbers relate to the numbered points indicated in Sections 9.1 and 9.2. Where there is no superscript number, see Sections 2–6 for further information.
(a): When the consideration for classification made in the context of this evaluation under Regulation (EC) No 1107/2009 is confirmed under Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008.
(b): Value for non-relevant metabolites prescribed in SANCO/221/2000-rev. 10 final, European Commission, 2003.

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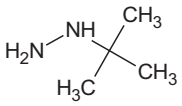
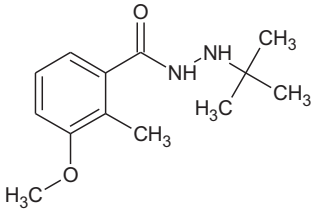
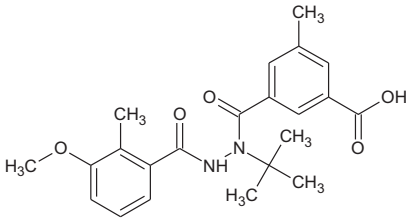
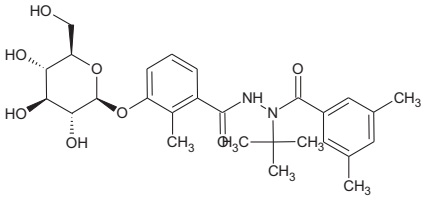
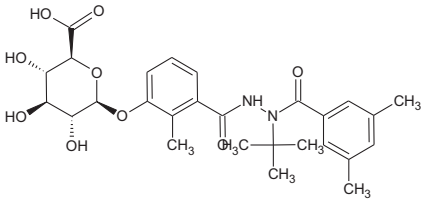
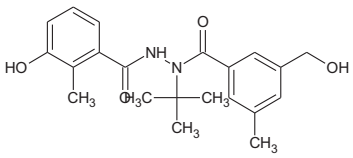
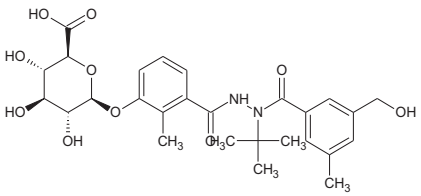
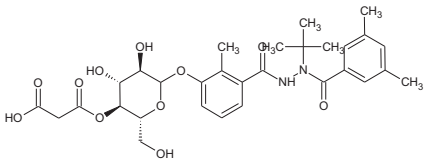
Abbreviations

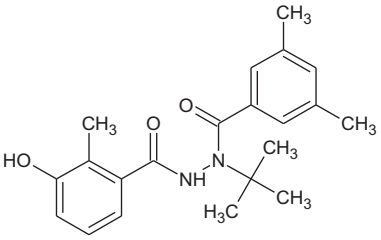
a.s.	active substance
AAOEL	acute acceptable operator exposure level
ADI	acceptable daily intake
AOEL	acceptable operator exposure level
AR	applied radioactivity
ARfD	acute reference dose
Bw	body weight
DT_{50}	period required for 50% dissipation (define method of estimation)
ECHA	European Chemicals Agency
EEC	European Economic Community
FAO	Food and Agriculture Organization of the United Nations
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
GAP	Good Agricultural Practice
HPLC–MS/MS	high-pressure liquid chromatography with tandem mass spectrometry
IESTI	international estimated short-term intake
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
JMPR	Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
K_{Foc}	Freundlich organic carbon adsorption coefficient
LC–MS/MS	liquid chromatography with tandem mass spectrometry
LOQ	limit of quantification
MRL	maximum residue level
NDMA	*N*-nitrosodimethyl-amine
NEU	northern Europe
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
OECD	Organisation for Economic Co-operation and Development
PBI	plant-back interval
PEC	predicted environmental concentration
PEC_{air}	predicted environmental concentration in air
PEC_{gw}	predicted environmental concentration in groundwater
PEC_{sed}	predicted environmental concentration in sediment
PEC_{soil}	predicted environmental concentration in soil
PEC_{sw}	predicted environmental concentration in surface water
PPE	personal protective equipment
PRIMo	(EFSA) Pesticide Residues Intake Model
QuEChERS	quick, easy, cheap, effective and safe method
RAR	renewal assessment report
RMS	rapporteur Member State
SC	suspension concentrate
SEU	southern Europe
SMILES	simplified molecular-input line-entry system
TMDI	theoretical maximum daily intake
TRR	total radioactive residue
UF	uncertainty factor
WHO	World Health Organization

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

Appendix A can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2017.4978

Appendix B – Used compound codes

Code/trivial name[a]	Chemical name/SMILES notation	Structural formula
***tert*-Butylhydrazine, RH-84078, RH-99838, TBZ**	*tert*-butylhydrazine CC(C)(C)NN	
RH-116267	*N*′-*tert*-butyl-3-methoxy-2-methylbenzohydrazide Cc1c(cccc1OC)C(=O)NNC(C)(C)C	
RH-131154 (M08)	3-{[1-*tert*-butyl-2-(3-methoxy-2-methylbenzoyl)hydrazino]carbonyl}-5-methylbenzoic acid Cc1c(cccc1OC)C(=O)NN(C(=O)c2cc(C)cc(c2)C(=O)O)C(C)(C)C	
RH-151055 (M15)	*N*′-tert-butyl-*N*′-[(3,5-dimethylphenyl)carbonyl]-3-(β-D-glucopyranosyloxy)-2-methylbenzohydrazide Cc1cc(cc(C)c1)C(=O)N(NC(=O)c3cccc(O[C@@H]2O[C@H](CO)[C@@H](O)[C@H](O)[C@H]2O)c3C)C(C)(C)C	
RH-141518 (M16)	3-({2-*tert*-butyl-2-[(3,5-dimethylphenyl)carbonyl]hydrazinyl}carbonyl)-2-methylphenyl β-D-glucopyranosiduronic acid Cc1cc(cc(C)c1)C(=O)N(NC(=O)c3cccc(O[C@@H]2O[C@@H]([C@@H](O)[C@H](O)[C@H]2O)C(=O)O)c3C)C(C)(C)C	
RH-141511 (M24)	*N*′-tert-butyl-3-hydroxy-*N*′-{[3-(hydroxymethyl)-5-methylphenyl]carbonyl}-2-methylbenzohydrazide Cc1c(cccc1O)C(=O)NN(C(=O)c2cc(C)cc(CO)c2)C(C)(C)C	
RH-141519 (M26)	3-[(2-*tert*-butyl-2-{[3-(hydroxymethyl)-5-methylphenyl]carbonyl}hydrazinyl)carbonyl]-2-methylphenyl β-D-glucopyranosiduronic acid Cc1cc(cc(CO)c1)C(=O)N(NC(=O)c3cccc(O[C@@H]2O[C@@H]([C@@H](O)[C@H](O)[C@H]2O)C(=O)O)c3C)C(C)(C)C	
RH-152072 (M40)	3-({2-*tert*-butyl-2-[(3,5-dimethylphenyl)carbonyl]hydrazinyl}carbonyl)-2-methylphenyl 4-*O*-(carboxyacetyl)-β-D-glucopyranoside Cc1cc(cc(C)c1)C(=O)N(NC(=O)c3cccc(OC2O[C@H](CO)[C@@H](OC(=O)CC(=O)O)[C@H](O)[C@H]2O)c3C)C(C)(C)C	

Code/trivial name[(a)]	Chemical name/SMILES notation	Structural formula
RH-117236 (M14)	*N*′-*tert*-butyl-*N*′-(3,5-dimethylbenzoyl)-3-hydroxy-2-methylbenzohydrazide Cc1c(cccc1O)C(=O)NN(C(=O)c2cc(C)cc(C)c2)C(C)(C)C	

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