CONCLUSION ON PESTICIDES PEER REVIEW

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Peer review of the pesticide risk assessment of the active substance 1-methylcyclopropene

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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 the co-rapporteur Member State Portugal for the pesticide active substance 1-methylcyclopropene are reported. The context of the peer review was that required by Commission Implementing Regulation (EU) No 844/2012. The conclusions were reached on the basis of the evaluation of the representative uses of 1-methylcyclopropene as a plant growth regulator on apples. The reliable end points, appropriate for use in regulatory risk assessment, are presented. Missing information identified as being required by the regulatory framework is listed. Concerns are identified.

Keywords: 1-methylcyclopropene, peer review, risk assessment, pesticide, plant growth regulator

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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. 1-Methylcyclopropene 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 the co-rapporteur Member State (co-RMS), Portugal, received an application from Janssen Pharmaceutica NV and AgroFresh Holding France SAS (former Rohm and Haas Europe Trading ApS) for the renewal of approval of the active substance 1-methylcyclopropene. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicants, the co-RMS (Portugal), the European Commission and the European Food Safety Authority (EFSA) about the admissibility.

The RMS provided its initial evaluation of the dossier on 1-methylcyclopropene in the renewal assessment report (RAR), which was received by EFSA on 28 April 2017. In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicants, Janssen Pharmaceutica NV and AgroFresh Holding France SAS, for comments on 26 July 2017. 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 26 September 2017.

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 1-methylcyclopropene 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.

The conclusions laid down in this report were reached on the basis of the evaluation of the representative uses of 1-methylcyclopropene as a plant growth regulator on apples following indoor post-harvest treatment, as proposed by the applicants. Full details of the representative uses can be found in Appendix A of this report.

The use of 1-methylcyclopropene according to the representative uses proposed at European Union (EU) level results in sufficient efficacy as a plant growth regulator.

A data gap was identified for more detailed assessment of the literature review for the mammalian toxicology section (including search terms and applied relevance criteria).

In the section identity, physical/chemical properties and analytical methods, data gaps were identified for additional validation data demonstrating applicability of the submitted methods or new methods for determination of 1-methylcyclopropene in dry and high oil content commodities; for analytical methods for monitoring of 1-methylcyclopropene residues in soil and water, and for a monitoring method for analysis of the active substance in body fluids and tissues.

In the section on mammalian toxicology, data gaps have been identified for further determination of metabolites after oral administration (in the expired air) and for an *in vitro* comparative metabolism study. Pending confirmation of the absorption of 1-methylcyclopropene after inhalation exposure (data gap), the systemic no observed adverse effect level (NOAEL) from inhalation studies might need to be reconsidered and taken into account for the derivation of the acceptable operator exposure level (AOEL) (issue not finalised).

In the section on residues, no data gaps or critical areas of concern for the representative use of 1-methylcyclopropene were identified.

In the area on environmental fate and behaviour, no data gaps or critical areas of concern were identified.

The risk to birds, mammals, aquatic organisms, soil-dwelling organisms and non-target plants was assessed as low. Data gaps were identified to address the risk to soil microorganisms and biological methods for sewage treatment.

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Background

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

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

In accordance with Article 1 of the Regulation, the RMS the United Kingdom and co-RMS Portugal received an application from Janssen Pharmaceutica NV and AgroFresh Holding France SAS (former Rohm and Haas Europe Trading ApS) for the renewal of approval of the active substance 1-methylcyclopropene. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicants, the co-RMS (Portugal), the European Commission and EFSA about the admissibility.

The RMS provided its initial evaluation of the dossier on 1-methylcyclopropene in the RAR, which was received by EFSA on 28 April 2017 (United Kingdom, 2017).

In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicants, Janssen Pharmaceutica NV and AgroFresh Holding France SAS, for consultation and comments on 26 July 2017. 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 26 September 2017. At the same time, the collated comments were forwarded to the RMS for compilation and evaluation in the format of a reporting table. The applicants were invited to respond to the comments in column 3 of the reporting table. The comments and the applicants' 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 applicants in accordance with Article 13(3) of the Regulation were considered in a telephone conference between EFSA and the RMS on 8 November 2017. On the basis of the comments received, the applicants' response to the comments and the RMS's evaluation thereof, 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.

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.

A final consultation on the conclusions arising from the peer review of the risk assessment took place with Member States via a written procedure in April–May 2018.

This conclusion report summarises the outcome of the peer review of the risk assessment of the active substance and the representative formulation, evaluated on the basis of the representative uses of 1-methylcyclopropene as a plant growth regulator on apples following indoor post-harvest

[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.

treatment, as proposed by the applicants. A list of the relevant end points for the active substance and the formulation is provided in Appendix A.

In addition, a key supporting document to this conclusion is the peer review report (EFSA, 2018), 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 (10 November 2017);
- the evaluation table (22 May 2018);
- the reports of the scientific consultation with Member State experts (where relevant);
- the comments received on the assessment of the additional information (where relevant);
- the comments received on the draft EFSA conclusion.

Given the importance of the RAR, including its revisions (United Kingdom, 2018), 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

IUPAC name of the active substance is 1-methylcyclopropene. Since the name is reasonably short, a common name (ISO) is deemed unnecessary; however, '1-MCP' is an unofficial abbreviation used. 1-Methylcyclopropene is a gas, which at high concentration is chemically unstable and begins to self-react immediately. As a result of these properties and safety concerns, the active substance is never isolated in the manufacturing process or transported. Instead, either it is produced as an alpha-cyclodextrin complex, containing 4.5% of 1-methylcyclopropene (AgroFresh), or it is generated *in situ* at a concentration of up to 2.24 mg/m^3 air, using preliminary prepared chemical components in a particular gas generation device (Janssen). It should be noted that in the latter case there is no technical material or formulated product containing the active substance.

The representative formulated product for the evaluation was 'SmartFresh™', a vapour releasing product (VP) containing 33 g/kg 1-methylcyclopropene. *In situ* gas generation product 'FYSIUM®' cannot be considered as a representative formulation.

The representative use evaluated was post-harvest treatment of pome fruit (apples) in enclosed space via a gas supply generator. Full details of the representative uses can be found in the list of end points in Appendix A.

Data were submitted to conclude that the representative uses of 1-methylcyclopropene proposed at EU level result in a sufficient efficacy as a plant growth regulator following the guidance document SANCO/2012/11251-rev. 4 (European Commission, 2014).

A data gap has been identified for more detailed assessment of the literature review (as performed in accordance with the Guidance of EFSA on the submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (EFSA, 2011), including search terms and relevance criteria in relationship with mammalian toxicology.

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).

1-Methylcyclopropene is manufactured as a stabilised technical concentrate (TK) (AgroFresh). The proposed specification is based on batch data from industrial scale production. The minimum purity of the active substance as manufactured is 980 g/kg. 1-Chloro-2-methylpropene (1-CMP) and 3-chloro-2-methylpropene (3-CMP) are considered relevant impurities with a maximum content of 0.2 g/kg. In the

TK, the content of 1-methylcyclopropene is in the range of 41–49 g/kg and the maximum content of the relevant impurities is 0.01 g/kg. The manufactured TK meets the requirements of the existing FAO specification (767/TK, January 2010).

The batches used in the (eco)toxicological assessment support the proposed renewal specification (AgroFresh) but not the original reference specification (see Section 2), as a consequence, an update of the reference specification is recommended.

As the active substance for the Janssen application is generated *in situ* and a technical material is not produced, a technical specification cannot be set. However, it should be noted that the *in situ* generation of 1-methylcyclopropene is related with the generation of heptane and methylcyclohexane which are considered toxicologically relevant (see Section 2). FAO specifications are not available for this application.

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 1-methylcyclopropene or the representative formulation. The main data regarding the identity of 1-methylcyclopropene 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. 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.

Gas chromatography with flame ionisation detector (GC–FID) and gas chromatography with mass spectrometry (GC–MS) with a limit of quantification (LOQ) of 0.01 mg/kg are available for monitoring of 1-methylcyclopropene residues in high water and high acid content plant commodities. A data gap for additional validation data demonstrating applicability of the submitted methods or new methods for determination of 1-methylcyclopropene in dry and high oil content commodities was identified. An analytical method for food of animal origin is not required due to the fact that no residue definition is proposed.

Residue definitions in soil and water were concluded as 1-methylcyclopropene, as a consequence, data gaps for analytical methods for monitoring of 1-methylcyclopropene in soil and water were identified.

The GC-FID method can be used for monitoring of 1-methylcyclopropene residues in air with a LOQ of 0.03 mg/m^3.

A data gap for a monitoring method for analysis of the active substance in body fluids and tissues was identified.

2. Mammalian toxicity

The following guidance documents were followed in the production of this conclusion: SANCO/10597/2003-rev. 10.1 (European Commission, 2012) and Guidance on dermal absorption (EFSA PPR Panel, 2012).

1-Methylcyclopropene was discussed at the Pesticides Peer Review Experts' Teleconference 168 (26 February 2018). With regard to the analytical methods, a monitoring method for analysis of the active substance in body fluids and tissues is still missing (data gap, see also Section 1).

The specification submitted for the renewal (AgroFresh) is supported by the composition of the batches used in the (new and old) toxicological studies. During the first peer review, the maximum levels of 1-CMP and 3-CMP (relevant impurities, being genotoxic carcinogens) were set at < 0.5 g/kg (levels not triggering classification of the technical product), whereas a specification at the lower level of 0.2 g/kg has been set for the renewal. A benchmark dose (BMD) analysis was applied to the available cancer data, resulting in a BMD_{05} (benchmark dose, representing the dose causing a cancer incidence of 5% above that in unexposed controls) of 0.6 mg/kg body weight (bw) per day for 1-CMP and 12.8 mg/kg bw per day for 3-CMP. Assuming the highest dietary exposure at the acceptable daily intake (ADI) of 1-methylcyclopropene, the margins of exposure for 1-CMP and 3-CMP are 150,000 and 3,200,000, respectively; assuming the highest non-dietary exposure at the acceptable operator exposure level (AOEL) of 1-methylcyclopropene, the margins of exposure for 1-CMP and 3-CMP are 75,000 and 1,600,000, respectively. According to the EFSA Opinion on the applicability of the Margin of Exposure approach (EFSA Scientific Committee, 2012), it can be concluded that the presence of these two impurities at 0.2 g/kg in the technical specification is unlikely to be of safety concern. The batches used in the toxicological studies support the proposed renewal specification (AgroFresh) but not the original reference specification.

During the *in situ* generation of 1-methylcyclopropene (Janssen's application), two toxicologically relevant impurities were also identified (heptane and methylcyclohexane), with theoretical maximum acceptable levels below 10%.

For 1-methylcyclopropene, a limited toxicological data set was submitted. No chronic or carcinogenicity studies were available, and a limited number of species was tested in short-term and teratology studies. Considering the results of the available toxicity studies, the representative uses of 1-methylcyclopropene and the physical nature of the active substance (very reactive gaseous compound), the limited data set was considered acceptable.

Extensively absorbed after oral administration (> 86%), 1-methylcyclopropene is rapidly excreted in air, urine and faeces. On the basis of a re-assessment of the data, including significant uncertainty, the experts agreed that the inhalation absorption value of 10% (at the low dose) should not be relied upon and a data gap has been identified. Additionally, further determination of the metabolite profiles in the expired air after oral administration has not been performed and an *in vitro* comparative metabolism study is still missing (data gaps).

In acute toxicity studies with the gas (by inhalation) or with the manufactured intermediate powder (4.5% 1-methylcyclopropene complexed with alpha-cyclodextrin in Manufacturing Use Product High Active Ingredient Powder (MUP-HAIP)), limited toxic effects were observed and it can be concluded that no classification for acute oral/dermal/inhalation routes, skin or eye irritation or skin sensitisation is required for 1-methylcyclopropene up to maximum mass content of ~5% under the CLP Regulation[3].

In short-term oral toxicity studies (with MUP-HAIP), rats and dogs showed similar adverse effects, while the dogs were more sensitive with a no observed adverse effect level (NOAEL) of 4.1 mg/kg bw per day, based on haematology and clinical chemistry changes, together with histopathological effects in the liver, testes and epididymides (90-day oral study). In the 90-day rat study by inhalation (with 1-methylcyclopropene gas), the no-observed-adverse-effect concentration (NOAEC) is 23.5 ppm (equivalent to an average systemic NOAEL of 6.5 mg/kg bw per day, and assuming 100% inhalation absorption) based on histopathological effects in the kidney (hyaline droplets) and spleen (haemosiderosis) in males. It is noted that this systemic NOAEL after inhalation exposure might need to be reconsidered pending on confirmation of the absorption of 1-methylcyclopropene during inhalation exposure (issue not finalised).

In a duplicate standard battery of genotoxicity tests, negative results were obtained and 1-methylcyclopropene was concluded as unlikely to be genotoxic.

No reproductive or developmental toxicity was observed in the available studies. For the multigeneration rat dietary study (with MUP-HAIP), the parental and offspring NOAEL is 3.8 mg/kg bw per day based on effects on body weight (gain) and food consumption, whereas for the developmental rat inhalation study (with 1-methylcyclopropene gas), the maternal NOAEL is 56 mg/kg bw per day based on spleen effects (darkened and enlarged), while the developmental NOAEL is 543 mg/kg bw per day (top dose). 1-Methylcyclopropene is not classified or proposed to be classified as toxic for reproduction category 2 or carcinogenic category 2, in accordance with the provisions of Regulation (EC) No 1272/2008, 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. On the basis of the available data and current knowledge (OECD Conceptual Framework, as analysed in the EFSA Scientific Opinion on the hazard assessment of endocrine disruptors, EFSA Scientific Committee, 2013), it is concluded that 1-methylcyclopropene is unlikely to have endocrine disrupting properties.

During the first peer review, the ADI was 0.0009 mg/kg bw per day based on the 90-day rat inhalation study (uncertainty factor (UF) 10,000), the acute reference dose (ARfD) was 0.07 mg/kg bw based on the 3-week rat inhalation study (UF 100), and the AOEL was 0.009 mg/kg bw per day based on the 90-day rat inhalation study (UF 1,000). For the renewal peer review, the **ADI** is 0.02 mg/kg bw per day based on the rat two-generation study and the dog 90-day study, applying an UF of 100, with an additional factor of 2 for subchronic to chronic/lifetime extrapolation. The **ARfD** is 0.12 mg/kg bw based on effects observed during the first week of administration in the 90-day dog study, with the application of an uncertainty factor of 100. The **AOEL** is 0.04 mg/kg bw per day based on the rat 2-generation study and the dog 90-day study, applying an UF of 100 (and without correction for oral absorption). It is noted that, pending on the inhalation absorption of 1-methylcyclopropene, the

[3] 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.

systemic NOAEL after inhalation exposure might need to be lowered and could be considered more relevant for the derivation of the AOEL value. The **acute AOEL (AAOEL)** is 0.12 mg/kg bw on the same basis as the ARfD.

With regard to the non-dietary exposure estimates, the operators are unlikely to be exposed to 1-methylcyclopropene since they will not be in the storeroom during the treatment process. An accidental exposure of 5 min would result in a level of 3% of the AAOEL, and the exposure should be more than 2 h to reach a level of 100% of the AOEL. For the workers, in the absence of detectable levels of 1-methylcyclopropene after 15 min of venting, the worst-case exposure level (half LOQ) would be 6% of the AOEL. For the contact with treated apples, the worker would need to handle 4,800 kg per day to reach 100% of the AOEL. For the bystander and residential exposure (adult and child), the measured exposure at venting and the maximum predicted environmental concentration are also below the AOEL and AAOEL values.

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 maximum residue level (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).

1-Methylcyclopropene was discussed at the Pesticides Peer Review Experts' Meeting 173 (February 2018).

The metabolism of 1-methylcyclopropene in plants was not investigated. Instead, a laboratory-scale study mimicking commercial practice and applying 1.2 ppm radiolabelled 1-methylcyclopropene (equivalent to ca 0.00264 g a.s./m^3 or an 1.2 N rate) to apples was presented. Information on possible metabolites was not provided as the total radioactive residue (TRR) in apples amounted to maximal 0.0091 mg eq/kg.

Given that in this study four different varieties of apple at different time points and with every time freshly prepared treatment samples of 1-methylcyclopropene were used, it is found sufficient to fulfil the data requirement for magnitude of residue trials for post-harvest treatment.

The residue definition for enforcement and risk assessment is set as 1-methylcyclopropene and the MRL for apples remains unchanged as 0.01 mg/kg based on the presented data from the laboratory scale study with apples.

The estimated livestock dietary burden resulting is below 0.004 mg/kg bw per day, hence no animal studies are required based on the representative use on apples.

It is noted that in the framework of the peer review the toxicological reference values were increased (see Section 2). Long- and short-term intake concerns from the representative use of 1-methylcyclopropene on apples were not identified for consumers since the highest chronic and highest acute intakes accounted for 0.6% of the ADI (DE child) and 0.8% of the ARfD (DE child). The assessment of the risk related to the genotoxic impurities 1-CMP and 3-CMP is discussed in Section 2. It is concluded that that the presence of these two impurities at 0.2 g/kg in the technical specification results in margins of exposure of 150,000 and 3,200,000 for 1-CMP and 3-CMP respectively, which are unlikely to be of safety concern for consumers.

In the context of the review of the existing MRLs for 1-methylcyclopropene (EFSA, 2014), new radiolabelled studies complying with the therein mentioned critical Good Agricultural Practices (GAPs) on apples and bananas were requested. These studies were not provided in the framework of the renewal procedure.

4. Environmental fate and behaviour

1-Methylcyclopropene was discussed at the Pesticides Peer Review Experts' Teleconference 166 (20 February 2018).

The majority of the data as specified in Commission Regulation (EU) No 283/2013 and required to perform the environmental exposure assessment were not available. Taking into consideration that 1-methylcyclopropene is applied in controlled atmospheric facilities and the potential reduced environmental exposure, the peer review confirmed and agreed that no additional information was needed to carry out the required environmental exposure assessments at EU level for the representative use assessed.

No data on the route and rate of degradation of 1-methylcyclopropene in soil were submitted. Where required, a conservative default aerobic soil degradation DT_{50} value of 1,000 days was used in the exposure assessment for 1-methylcyclopropene. Studies of the adsorption, desorption and mobility of 1-methylcyclopropene in soil were not available. In the absence of measured values and the uncertainty of the quantitative structure–activity relationship (QSAR) estimates, very conservative default values (i.e. K_{oc} = 0 mL/g for the groundwater exposure and the aquatic phase of the surface water exposure and K_{oc} = 1,000 mg/L for the sediment phase of the surface water exposure, and 1/n = 1.0) have been applied in the exposure assessment.

Reliable hydrolytic experimental degradation data were not available. However, the study submitted to address the biodegradability of 1-methylcyclopropene showed that the active substance is stable to hydrolysis. 1-Methylcyclopropene is considered not to be readily biodegradable. As there is no UV adsorption maximum in aqueous solution > 240 nm, aqueous photolysis would not be expected. No information on the fate and behaviour of 1-methylcyclopropene in the water/sediment system was available. Where required, conservative default DT_{50} values of 1,000 days for the water and sediment phases and for the water/sediment system were used in the aquatic exposure assessment for 1-methylcyclopropene.

1-Methylcyclopropene is highly volatile and its half-life in air is estimated to be 1.47 h and therefore long-range transport in the atmosphere is highly unlikely.

The representative use of 1-methylcyclopropene is as a post-harvest plant growth regulator on apples in closed systems. Therefore, there is no direct exposure of the environmental compartments during treatment. However, upon venting, 1-methylcyclopropene could be released, primarily into air, whilst exposure to soil, surface water, groundwater and sediment is only expected to occur upon deposition from the air. Exposure may also occur from washing treated apples either industrially or domestically with exposure occurring indirectly after application of contaminated sewage sludge. As this route of exposure is not commonly considered for plant protection products, the pathways and subsequent calculations used in these conclusions followed the Guidance on Biocidal Products Regulation (TGD, 2003 and ECHA, 2015). The RMS evaluation, which was based on a number of conservative assumptions in predicted environmental concentrations (PEC), both in assigning endpoint values and in the scenarios considered, was confirmed and agreed at the Pesticides Peer Review Experts' TC 166.

The risk assessment considered exposure of soil from deposition from the air after venting the closed system (two tiers) or from application of contaminated sewage sludge after industrial or end consumer washing of treated apples (one tier only). The USEPA's Industrial Source Complex, short term (ISCST3) model (USEPA, 1995),[4] a variation of a basic Gaussian plume model, was used to estimate the deposition of 1-methylcyclopropene carried in the gaseous phase up to a distance of 10 km from the controlled atmosphere facility. The amount of 1-methylcyclopropene in the sewage sludge after processing through a sewage treatment plant was modelled using SimpleTreat 3.1 in line with the recommendations of the Biocidal Products Regulation (ECHA, 2015). Exposure from deposition and sludge application were then combined to provide final PEC_{soil} values.

It should be noted that the PEC_{soil} at Tier II were estimated based on several conservative assumptions including: conservative soil degradation of 1-methylcyclopropene, no volatilisation during transport in the sewage system, the complete loss of 1-methylcyclopropene from the apples during washing, a conservative amount of 1-methylcyclopropene on the apples, a conservative domestic consumption model, a conservative air-to-soil deposition model and the simultaneous events of sewage sludge application and venting of the storeroom.

Three main routes of exposure were considered to calculate PECs for the aquatic compartment: (A) venting to the atmosphere followed by deposition to soil and subsequent exposure via drainflow or run-off (two tiers, based on FOCUS STEPs 1-2 modelling, FOCUS, 2001); (B) venting to the atmosphere followed by deposition directly onto surface water (two tiers, with the higher tier that accounts for wet and dry deposition onto a 1 ha, 30 cm deep surface water body); (C) washing of apples (industrially or by end user) leading to exposure in the sewage treatment works and then exposure of surface water directly from effluent or indirectly after application of sewage sludge (drainflow and run-off) (one tier according to ECHA, 2015). The final PEC_{sw} and PEC_{sed} to be used in the risk assessment were derived by combining all the three routes of exposure at Tier I.

[4] Users Guide for the Industrial Source Complex (ISC3) dispersion models, US Environmental Protection Agency, Office of Air Quality Planning and Standard Emissions, Monitoring and Analysis Division, Research Triangle Park, NC. Internet WRL: http://www.epa.gov/ttn/scram/

The necessary estimation of PEC_{gw} were calculated with FOCUS PEARL 4.4.4 and FOCUS PELMO 5.5.3 with appropriate FOCUS scenarios (FOCUS, 2000) based on soil deposition after venting and from sludge application following the use of 1-methylcyclopropene in apple storage rooms. The potential for groundwater exposure from the representative uses by 1-methylcyclopropene above the parametric drinking water limit of 0.1 μg/L was concluded to be low in geoclimatic situations that are represented by all nine FOCUS groundwater scenarios.

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

Taking into consideration that, should post-venting exposure of environmental compartments occur it will be at low levels, a subsequent significant exposure from metabolite formation was considered to be unlikely.

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).

1-Methylcyclopropene was discussed at the Pesticides Peer Review Experts' Teleconference 170 (6 March 2018).

1-Methylcyclopropene is applied as a gas in apple storage facilities. Contamination of the environment can take place during and after venting (see Section 4).

The risk to **birds and mammals** was assessed for exposure via inhalation when exposed to the gas released during venting and via oral route for exposure from residues on food items post-venting and for spilt treated apples. The risk from oral and inhalation exposure was assessed as low for birds and mammals.

The acute risk to **fish**, the acute risk to **aquatic invertebrates** and the risk to **algae** and **macrophytes** was assessed as low. An aquatic long-term risk assessment is procedurally triggered for fish and aquatic invertebrates and sediment dwelling organisms as 1-methylcyclopropene is stable in water and contamination of surface water after venting cannot be excluded. However, no effects were observed in the acute study with fish and daphnia up to the highest concentration tested. Furthermore, animals are not expected to be sensitive to 1-methylcyclopropene due to the specific mode of action of blocking ethylene receptors which do not occur in animals. Therefore, the experts agreed that a low risk to aquatic organisms can be concluded without additional long-term studies. The risk of bioaccumulation was assessed as low.

The risk to **non-target arthropods** including **bees** was assessed as low.

Studies were available on acute toxicity to **earthworms** with exposure to the gas trapped in the headspace above the soil surface. There is some uncertainty with regard to concentrations in the soil of the test systems. However, a large margin of safety was observed for exposure from air in the first tier risk assessment. Sublethal (reproductive) effect studies with earthworms were considered not necessary given the lack of effects in the acute studies and that animals are not likely to be sensitive to 1-methylcyclopropene. No study with **soil macroorganisms other than earthworms** was requested, as non-target arthropods are not very sensitive to 1-methylcyclopropene and the risk was assessed as low for earthworms and non-target arthropods. Overall, the risk to soil-dwelling macroorganisms was assessed as low.

The risk to **non-target plants** was assessed as low.

No effects data were submitted for **soil microorganisms** and for effects on **sewage sludge**. Microorganisms possess ethylene receptors and hence 1-methylcyclopropene might affect soil microorganisms and biological methods for sewage treatment. Data gaps were identified to address the risk to soil nitrogen transformation and biological methods for sewage treatment.

No information was made available on possible endocrine effects on vertebrates in the ecotoxicology section. Available data in the mammalian toxicology section suggest that it does not have endocrine disrupting properties. Overall, with regard to the endocrine disruption potential, as discussed in Section 2, it is unlikely that 1-methylcyclopropene has endocrine-disrupting properties in mammals. However, no firm conclusion can be drawn regarding fish, birds and other non-target vertebrates.

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
1-methylcyclopropene	No data, not required	Data gap for soil microorganisms

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
1-methylcyclopropene	No data, not required	No	Yes	Yes

(a): FOCUS scenarios or a relevant lysimeter.

Table 3: Surface water and sediment

Compound (name and/or code)	Ecotoxicology
1-methylcyclopropene	Low risk

Table 4: Air

Compound (name and/or code)	Toxicology
1-methylcyclopropene	Low toxicity by inhalation

7. Data gaps

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

- A more detailed assessment of the literature review to demonstrate that it has been performed in accordance with the Guidance of EFSA on the submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (EFSA, 2011) with sufficient details for the peer review assessment, including search terms and relevance criteria related to mammalian toxicology section (relevant for the representative uses evaluated; submission date proposed by the applicant: unknown, relevant to Section 2).
- Additional validation data demonstrating applicability of the submitted methods or new methods for determination of 1-methylcyclopropene in dry and high oil content commodities (relevant for the representative uses evaluated; submission date proposed by the applicant: unknown; see Section 1).
- Analytical methods for monitoring of 1-methylcyclopropene in soil and water (relevant for the representative uses evaluated; submission date proposed by the applicant: unknown; see Section 1).
- A monitoring method for analysis of the active substance in body fluids and tissues (relevant for the representative uses evaluated; submission date proposed by the applicant: unknown; see Sections 1 and 2).
- Further determination of metabolite profiles in the expired air after oral administration of 1-methylcyclopropene (relevant for the representative uses evaluated; submission date proposed by the applicant (AgroFresh): unknown; see Section 2).
- Experimental data on comparative *in vitro* metabolism of 1-methylcyclopropene (relevant for the representative uses evaluated; submission date proposed by the applicants: unknown; see Section 2).
- Further assessment of the absorption of 1-methylcyclopropene when administered by inhalation (relevant for the representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- Additional information on soil microorganisms should be provided to address the risk to soil nitrogen transformation (relevant for the representative uses evaluated, submission date proposed by the applicant: unknown; see Section 5).
- Additional information should be provided to address the risk to biological methods for sewage treatment (relevant for the representative uses evaluated, submission date proposed by the applicant: unknown; see Section 5).

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

No particular conditions are proposed for the representative uses evaluated.

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[5] 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).

[5] 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) Systemic NOAEL in toxicological studies where 1-methylcyclopropene was administered by inhalation could not be finalised (pending on the inhalation absorption of 1-methylcyclopropene, the systemic NOAEL after inhalation exposure might need to be lowered and could be considered more relevant for the derivation of the AOEL value) (see Section 2).

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 the higher tier level could not be finalised due to lack of information, and if the assessment performed at the 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.

No critical areas of concern have been identified.

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

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

Table 5: Overview of concerns

Representative use		Post-harvest treatment of apples in enclosed space
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	
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	
Risk to aquatic organisms	Risk identified	
	Assessment not finalised	
Groundwater exposure to active substance	Legal parametric value breached	
	Assessment not finalised	

Representative use		Post-harvest treatment of apples in enclosed space
Groundwater exposure to metabolites	Legal parametric value breached[(a)]	
	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

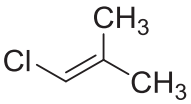
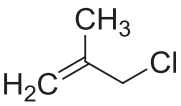
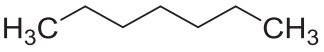
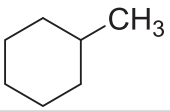
1/*n*	slope of Freundlich isotherm
a.s.	active substance
ADI	acceptable daily intake
AF	assessment factor
AAOEL	acute acceptable operator exposure level
AOEL	acceptable operator exposure level
ARfD	acute reference dose
BMD	benchmark dose
bw	body weight
CLP	classification, labelling and packaging
1-CMP	1-chloro-2-methylpropene
DAR	draft assessment report
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
FID	flame ionisation detector
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
GAP	Good Agricultural Practice
GC	gas chromatography
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
LOQ	limit of quantification

MRL	maximum residue level
MS	mass spectrometry
MUP-HAIP	Manufacturing Use Product High Active Ingredient Powder
NOAEC	no-observed-adverse-effect concentration
NOAEL	no-observed-adverse-effect level
OECD	Organisation for Economic Co-operation and Development
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
QSAR	quantitative structure–activity relationship
RAR	Renewal Assessment Report
RMS	rapporteur Member State
SMILES	simplified molecular-input line-entry system
TK	technical concentrate
TRR	total radioactive residue
VP	vapour releasing product
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.2018.5308

Appendix B – Used compound codes

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
1-CMP	1-chloro-2-methylpropene C/C(C)=C\Cl KWISWUFGPUHDRY-UHFFFAOYSA-N	
3-CMP	3-chloro-2-methylpropene C=C(C)CCl OHXAOPZTJOUYKM-UHFFFAOYSA-N	
heptane	heptane CCCCCCC IMNFDUFMRHMDMM-UHFFFAOYSA-N	
methylcyclohexane	methylcyclohexane CC1CCCCC1 UAEPNZWRGJTJPN-UHFFFAOYSA-N	

IUPAC: International Union of Pure and Applied Chemistry; SMILES: simplified molecular-input line-entry system.
(a): The metabolite name in bold is the name used in the conclusion.
(b): ACD/Name 2015 ACD/Labs 2015 Release (File version N20E41, Build 75170, 19 December 2014).
(c): ACD/ChemSketch 2015 ACD/Labs 2015 Release (File version C10H41, Build 75059, 17 December 2014).