Peer review of the pesticide risk assessment of the active substance maleic hydrazide

European Food Safety Authority (EFSA)

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 Denmark and co-rapporteur Member State Belgium for the pesticide active substance maleic hydrazide 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 maleic hydrazide as a plant growth regulator on onion, shallot, garlic, potato and carrot. 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: maleic hydrazide, peer review, risk assessment, pesticide, plant growth regulator

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Correspondence: pesticides.peerreview@efsa.europa.eu
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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. Maleic hydrazide 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), Denmark, and co-rapporteur Member State (co-RMS), Belgium, received an application from EU Maleic hydrazide Task Force (EMHTF) composed of Chemtura Europe Limited, Drexel Chemical Company and Agriphar s.a. for the renewal of approval of the active substance maleic hydrazide. Recently, Chemtura Europe Limited and Agriphar s.a. became part of Arysta LifeScience Great Britain Limited.

Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicants, the co-RMS (Belgium), the European Commission and the European Food Safety Authority (EFSA) about the admissibility.

The RMS provided its initial evaluation of the dossier on maleic hydrazide in the renewal assessment report (RAR), which was received by EFSA on 30 April 2015. In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicants for comments on 30 June 2015. 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 31 August 2015.

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 and residues.

In accordance with Article 13(1) of the Regulation, EFSA should adopt a conclusion on whether maleic hydrazide 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 maleic hydrazide as a plant growth regulator on onion, shallot, garlic, potato and carrot, as proposed by the applicant. Full details of the representative uses can be found in Appendix A of this report.

Data were submitted to conclude that the uses of maleic hydrazide as a plant growth regulator according to the representative uses proposed at the EU level result in a sufficient efficacy as a sprout suppressor.

A formal data gap was identified in the residue section for the RMS to report the full assessment of the results of the scientific peer-reviewed open literature search in a revised RAR.

Data gaps were identified for a method for the determination of the relevant impurity in the technical material (TC) at the level of the accepted specification and for a method for the determination of residues in body fluids and tissues.

In the mammalian toxicology area, data gaps were identified for genotoxicity studies performed with the representative TC containing 1 ppm (or lower) of the relevant impurity hydrazine, for identification of the analytical methods used in the toxicity studies (except for the acute inhalation and dermal sensitisation studies), interspecies comparative in vitro metabolism including human material and clarification of the endocrine disrupting potential of maleic hydrazide considering in particular level 2 and 3 tests currently indicated in the Organisation for Economic Co-operation and Development (OECD) Conceptual Framework. To address the consumer risk assessment, clarification of the genotoxic potential of the metabolite 3-pyridazinone is necessary, as well as toxicological information on the metabolite relevant to consumer exposure, i.e. upon repeated-dose exposure. As the technical specification is not supported by the toxicological assessment with regard to the specified level of hydrazine and positive results were obtained in non-standard genotoxicity studies with a test material containing 0.31 ppm hydrazine, a critical area of concern was identified.

In the residue section, the consumer risk assessment could not be finalised with regard to the toxicity profile of 3-pyridazinone metabolite included in the residue definition for risk assessment for animal commodities as a data gap has been identified to address the genotoxic potential of 3-pyridazinone and its toxicity upon repeated-dose exposure (see Section 2). A data gap was also identified for the determination of the residues in pollen and bee products for human consumption resulting from residues taken up by honeybees from potatoes at blossom.

With respect to fate and behaviour in the environment, data available allow finalising the necessary exposure assessment. However, a data gap has been identified for data to address the effect of water
treatment processes on the nature of residues present in surface water, when surface water is
abstracted for drinking water needs to be provided to demonstrate that the approval criteria in Article
4 of Regulation (EC) 1107/2009 are satisfied.

In the ecotoxicology section, a data gap was identified for submitting a valid study on Lemna. Also,
the available acute study on Mysidopsis bahia should be submitted for peer-review. Data gaps were
also identified in the risk assessment to honeybees. These include data gaps for refining the chronic
risk due to exposure to contaminated pollen and nectar, and the risk due to exposure to contaminated
water (guttation, puddle water). Furthermore, data gaps were identified for assessing sub-lethal
effects (i.e. hypopharyngeal glands (HPG)) and for assessing the risk due to exposure to metabolites in
pollen and nectar. A data gap was identified for the technical specification used in the ecotoxicology
studies with regard to the maximum level of hydrazine.
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Background

Commission Implementing Regulation (EU) No 844/20121 (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 1107/20092. 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 of the end of the period provided for the submission of written comments, subject to an extension of up to 8 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 Denmark and co-RMS Belgium received an application from EU Maleic hydrazide Task Force (EMHTF) composed of Chemtura Europe Limited, Drexel Chemical Company and Agriphar s.a. for the renewal of approval of the active substance maleic hydrazide. Recently, Chemtura Europe Limited and Agriphar s.a. became part of Arysta LifeScience Great Britain Limited. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicants, the co-RMS (Belgium), the European Commission and EFSA about the admissibility.

The RMS provided its initial evaluation of the dossier on maleic hydrazide in the RAR, which was received by EFSA on 30 April 2015 (Denmark, 2015).

In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicants, for consultation and comments on 30 June 2015. 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 31 August 2015. 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’ responses 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 13 October 2015. 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 and residues.

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 2016.

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 maleic hydrazide as a plant growth regulator on onion, shallot, garlic, potato and carrot, as

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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.
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, 2016), 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 (13 October 2015);
- the evaluation table (27 April 2016);
- 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 (Denmark, 2016), 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 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

Maleic hydrazide is the common name for 6-hydroxy-2H-pyridazin-3-one or 1,2-dihydropyridazine-3, 6-dione (IUPAC) as it can exist in two tautomeric forms. There is no ISO common name for this compound.

The representative formulated product for the evaluation was 'Fazor', a water-soluble granule (SG) containing 600 g/kg maleic hydrazide (in the form of its potassium salt at a content of 804 g/kg).

The representative uses evaluated are applications by foliar spraying for sprout suppression on onion, shallot, garlic, carrots and sprout suppression and control of volunteers on potatoes. Full details of the good agricultural practice (GAP) can be found in the list of end points in Appendix A.

Data were submitted to conclude that the uses of maleic hydrazide as plant growth regulator according to the representative uses proposed at EU level result in a sufficient efficacy, following the guidance document SANCO/10054/2013-rev. 3 (European Commission, 2013).

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, 2011a). However, for the residue section, a formal data gap has been identified as the RMS did not report in a revised RAR the full assessment of the comprehensive assessment of the results of scientific peer-reviewed open literature search conducted by the applicant in accordance with the EFSA guidance.

### 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), SANCO/10597/2003-rev. 10.1 (European Commission, 2012) and SANCO/825/00-rev. 8.1 (European Commission, 2010).

The reference specification for the first approval was updated. The proposed specification is based on batch data from industrial scale production. The minimum purity of the active substance as manufactured is 979 g/kg. Hydrazine was considered a relevant impurity; however, the maximum content is still open (see Section 2). According to the FAO Specification 310/TC (June 2008),\(^3\) the

\[^3\] FAO Specification in [www.fao.org](http://www.fao.org)
technical material (TC) should contain not less than 970 g/kg maleic hydrazide and maximum 1 mg/kg hydrazine.

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 maleic hydrazide or the representative formulation. The main data regarding the identity of maleic hydrazide and its physical and chemical properties are given in Appendix A.

Methods of analysis are available for the determination of the active substance in the TC and the representative formulation; however, a data gap was identified for an analytical method for the determination of hydrazine in the TC at the level of the finally agreed specification.

The analytical methods used in the toxicity studies (except for the acute inhalation and dermal sensitisation studies) have not been identified; a data gap has been identified for this information in order to check their specificity and validation.

Residues of maleic hydrazide can be analysed in food and feed of plant origin by liquid chromatography with tandem mass spectrometry (LC-MS/MS) with the limit of quantification (LOQ) of 0.01 mg/kg in all commodity groups. A LC-MS/MS method exists for monitoring maleic hydrazide in milk, eggs, muscle, liver, kidney and fat with LOQs of 0.01 mg/kg in all matrices. Maleic hydrazide can be monitored in soil and water by LC-MS/MS with LOQs of 0.01 mg/kg and 0.1 μg/L, respectively. Residues of maleic hydrazide in air can be determined by LC-MS with a LOQ of 8 μg/m³. A data gap was identified for a method of analysis for body fluids and tissues.

2. Mammalian toxicity

The following guidance documents were followed in the production of this conclusion: SANCO/221/2000-rev. 10 (final) (European Commission, 2003), SANCO/10597/2003-rev. 10.1 (European Commission, 2012) and Guidance on dermal absorption (EFSA PPR Panel, 2012).

Maleic hydrazide was discussed at the Pesticides Peer Review Experts’ Meeting 141 in February 2016.

The technical specification is not supported by the toxicological assessment as the specified level of the known relevant impurity hydrazine (at 1 ppm) has not been sufficiently tested. Hydrazine is classified according to Regulation (EC) No 1272/2008 (CLP Regulation) 4 inter alia as toxic and Carc. 1B. Positive results were obtained in non-standard genotoxicity studies with the test material containing 0.31 ppm hydrazine, but all experts agreed that levels of hydrazine up to 0.028 ppm could be considered as a safe limit as this level produced negative results in genotoxicity testing. It is therefore considered that either the applicants are able to produce TC containing maximum 0.028 ppm hydrazine or further testing should be provided to demonstrate a lack of genotoxic concern with the current specification at 1 ppm (or lower) (data gap). As the level of hydrazine tested in the long-term toxicity/carcinogenicity studies is unknown, the technical specification is also not supported by the toxicological batches regarding carcinogenicity. This issue is identified as a critical area of concern.

In the toxicokinetics studies, maleic hydrazide was extensively and rapidly absorbed (around 90%), widely distributed and eliminated, mainly via urine. Metabolism was limited; the major metabolite found in urine was its sulphate conjugate; the metabolite 3-pyridazone was found to be a minor metabolite recovered in kidneys and liver. There was no evidence for accumulation. The justification given by the applicant to waive the data requirement for interspecies comparative in vitro metabolism study was not fully convincing that no human-specific metabolite could be produced by maleic hydrazide and thus a data gap was identified to address this end point. However, it is agreed that, although some toxicokinetic parameters were not measured in absorption, distribution, metabolism and elimination (ADME) studies (such as the concentration achieved at peak blood level (C_{max}) and area under the blood concentration/time curve (AUC)), toxicokinetics were sufficiently investigated in rat and there is no need for further animals testing.

Low acute toxicity was observed when maleic hydrazide was administered by the oral, dermal or inhalation routes; no skin or eye irritation and no potential for skin sensitisation were attributed to the active substance. No phototoxic potential was observed in an in vitro 3T3 NRU test. No information has been provided on photomutagenicity. On the basis of current knowledge, the potential for photo-mutagenicity may be considered covered by phototoxicity testing.

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4 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.
Exposure to maleic hydrazide did not produce signs of toxicity up to the highest doses tested or produced sporadic signs of general toxicity such as reduced body weight. The relevant short-term and long-term no observed adverse effect level (NOAEL) is 25 mg/kg body weight (bw) per day based on reduced body weight observed in the 1-year dog and 2-year rat studies, respectively. Maleic hydrazide is unlikely to be genotoxic and carcinogenic (provided that the level of hydrazine is sufficiently low in the technical specification – see above). No neurotoxic potential was observed in the neurotoxicity studies submitted, and the only finding of increased motor activity and ambulatory counts seen in the short-term toxicity study by inhalation in rats was attributed to general signs of toxicity. In the reproductive toxicity studies, fertility and overall reproductive performance were not impaired; there was no evidence of teratogenicity or adverse effects on the development in rats and rabbits. It was however noted that sensitive parameters for fertility, sexual development and potential hormone-mediated effects were not investigated in the two-generation reproductive toxicity study (such as oestrus cycle length and normality, sperm parameters, anogenital distance, age of vaginal opening and preputial separation) that was performed before the establishment of such data requirements in the Organisation for Economic Co-operation and Development (OECD) 416 test guideline (OECD, 2001). Therefore, the data are insufficient to rule out potential endocrine-mediated effects and, although the majority of the experts agreed that no further investigations would be needed, EFSA supports the RMS conclusion in setting a data gap for further investigations on the potential endocrine-disrupting potential of maleic hydrazide following the OECD Conceptual Framework (OECD, 2012) and the EFSA Scientific Opinion on the hazard assessment of endocrine disruptors (EFSA Scientific Committee, 2013).

Maleic hydrazide is not classified or proposed to be classified as carcinogenic category 2 or as toxic for reproduction category 2 in accordance with the provisions of Regulation (EC) No 1272/2008 (CLP Regulation) 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.

Toxicological information (acute oral toxicity and Ames test) have been submitted on the metabolite 3-pyridazinone and reported in the list of end points (Appendix A). This information is insufficient to conclude on the toxicological profile of the metabolite and a data gap has been identified to complete the genotoxicity profile of the metabolite and address its toxicity profile relevant to consumer exposure (i.e. upon repeated-dose exposure). Regarding the groundwater metabolite maleic acid, it is not considered a relevant impurity as it occurs naturally in corn, cacao, ginseng, sour cherries and alcoholic beverages such as beer and wine.

The acceptable daily intake (ADI) of maleic hydrazide is 0.25 mg/kg bw per day based on reduced bw observed in the 2-year study in rats with a NOAEL of 25 mg/kg bw per day and using the standard uncertainty factor of 100. No acute reference dose (ARfD) is needed. The acceptable operator exposure level (AOEL) is 0.25 mg/kg bw per day based on reduced bw observed in the 1-year dog study with a NOAEL of 25 mg/kg bw per day, supported by the 28-day study by inhalation in rat, applying the standard uncertainty factor or 100; as the substance is almost completely absorbed upon oral administration (around 90%), no correction factor is needed regarding systemic bioavailability. By analogy with the ARfD reasoning, there would be no need to set an acute AOEL (AAOEL) for this compound. These reference values confirm the ones previously established during the first peer review of maleic hydrazide (European Commission, 2002c); they apply to a technical specification containing maximum levels of 0.028 ppm hydrazine (not to the currently specified level of 1 ppm).

The RMS estimated non-dietary exposure (i.e. operator, worker, bystander and resident) for the representative formulation ‘Fazor’ considering dermal absorption values of 0.6% for the concentrate and 3% for the 1:150 field spray dilution. Personal protective equipment (PPE) such as gloves during mixing and loading operations, and gloves and impermeable coveralls during application, has to be used by operators applying the product with handheld equipment according to the UK POEM model to ensure that the AOEL is not exceeded. Estimated worker and operator exposure using tractor mounted equipment do not exceed the AOEL, even when no PPE is used (according to the EUROPOEM II and German model, respectively). Estimated bystander and resident’s exposure do not exceed the AOEL.

3. Residues

The assessment in the residue section is based on the guidance documents listed in the document 1607/VI/97-rev. 2 (European Commission, 1999), the EC guideline document on MRL setting (European Commission, 2015), the Joint Meeting on Pesticide Residues (JMPR) recommendations on
livestock burden calculations (JMPR, 2004, 2007) and the OECD publication on MRL calculations (OECD, 2011).

A formal data gap was identified in the residue section for the RMS to report the full assessment of the results of the scientific peer-reviewed open literature search in a revised RAR.

Metabolism of maleic hydrazide in primary crops was investigated upon foliar application on root crops (onion, potato), using $^{14}$C maleic hydrazide. Although characterisation and identification of the total radioactive residues (TRR) was very poor for the onion crop, a sufficient level of metabolite identification was performed in potato. A significant translocation of maleic hydrazide residues from treated potato vines to tubers was observed with maleic hydrazide being the main component of the terminal residues in potato tubers (up to 84% TRR) at 7 days after treatment. The proportion of the glucose conjugate of maleic hydrazide increases with the time interval between application and harvest accounting for up to 13% TRR, 3 months after the treatment.

As maleic hydrazide showed a low persistence in soil ($DT_{50} < 4$ days) and degraded to minor metabolites, CO$_2$ and unextractable residues, confined rotational crop metabolism studies were not triggered.

The plant residue definition for monitoring and risk assessment was defined as maleic hydrazide (restricted to foliar treatment on root crops only). The potential inclusion of its glucoside conjugate in the residue definition for risk assessment was also envisaged in view of the significant level of this compound recovered in potato tuber at harvest. However, considering the representative uses intended with short pre-harvest intervals (PHIs) of 14 and 21 days, it can reasonably be assumed that the metabolism of maleic hydrazide will be less extensive and the glucoside conjugates of maleic hydrazide are expected at lower levels when the active maleic hydrazide is applied in accordance with the representative uses. Furthermore, from the residue trials where the residue levels of maleic hydrazide alone and the total maleic hydrazide and its glucoside conjugates were respectively measured (onions) or where samples were analysed separately for maleic hydrazide and the glucoside conjugates of maleic hydrazide, respectively (shallots, garlic, carrots), the contribution of maleic hydrazide glucose conjugates to the total residues was found to be insignificant for all the crops under consideration.

Under standard hydrolytic conditions, residues of maleic hydrazide were found to be stable and the residue definitions set for the primary crops also apply to the processed commodities.

A sufficient number of residue field trials conducted according to the NEU and SEU cGAPs are available respectively on shallots, garlic, potatoes and carrots. For onions, sufficient residue trials were submitted for the determination of the total residues of maleic hydrazide and its glucoside conjugates while only a few number of residue trials analysed maleic hydrazide only. However, as residue levels respectively of maleic hydrazide and total residues including its conjugates were not significantly different, EFSA is of the opinion that additional residue trials on onions and analysing maleic hydrazide alone are not requested. The results obtained in these residue trials are supported by validated analytical methods and acceptable storage stability data. Processing studies on carrots and potatoes were submitted and processing factors were derived for several processed matrices.

Several metabolism studies on poultry and ruminants were submitted where animals were dosed over 3.5-6 days for poultry and 3.5 days for ruminants with $^{14}$C maleic hydrazide at 15.3 mg/kg bw per day dose rate. In one set of old studies, conjugated radioactive residues were recovered in all matrices and were tentatively identified as conjugates of maleic hydrazide. In the second set of more recent studies, 3-pyridazinone metabolite was found to be the predominant compound of the total residues in poultry matrices with TRRs ranging between 34% TRR in egg yolk and 84% TRR in muscle. Maleic hydrazide accounted for 27.5% TRR and 54.5% TRR in egg white and yolk, respectively, while it was recovered at lower levels in other matrices (<10% TRR). For ruminants, both the parent compound and 3-pyridazinone metabolite were identified in significant proportions in all matrices (up to 86% TRR in kidney and up to 53% TRR in muscle, respectively) while the major component of the residues in milk was tentatively identified as conjugates of maleic hydrazide (up to 37% TRR). The submitted livestock feeding studies were considered as acceptable although the analytical method used in these studies showed a consistent low performance in muscle, liver and kidney for the determination of 3-pyridazinone residues (recoveries of ca. 40–50%) and considering the low contribution of the animal commodities to the overall consumer dietary burden (1% of the ADI). Although the 3-pyridazinone metabolite was predominant in all livestock matrices from the metabolism data, the feeding studies demonstrated higher residue levels of maleic hydrazide residues compared to 3-pyridazinone residues in all matrices. The parent maleic hydrazide was therefore considered as the most appropriate residue marker to be monitored in livestock matrices. The residue
definition for monitoring is proposed as maleic hydrazide only. For risk assessment purposes, it is proposed to include maleic hydrazide and 3-pyridazinone for all matrices (including also their conjugates for milk, only) in the residue definition. Whether the consumer dietary risk assessment is to be conducted combined or separately is pending a finalised assessment of the toxicological profile of 3-pyridazinone metabolite as a data gap was identified for a complete genotoxicity data package and repeated-dose toxicity studies on this compound (see Section 2). Conversion factors for risk assessment of 2 for muscle, liver, milk and eggs and of 1 for kidney and fat were derived from the feeding studies considering the 3-pyridazinone residue levels corrected for the low recoveries of the method. These conversion factors can apply to conduct the consumer dietary intake calculation if the toxicity of 3-pyridazinone is covered by the toxicological reference values set for the parent compound. The available storage stability data are considered as acceptable considering the low performance of the analytical method for the determination of 3-pyridazinone residues in animal matrices. Maleic hydrazide and 3-pyridazinone residues are stable for up to 5 months in eggs and 3 months in other matrices, covering the maximum storage time period of the residue samples from the feeding studies.

The consumer risk assessment was performed using the EFSA PRIMo model. A chronic intake concern was identified using the MRL values respectively for plant and animal commodities and conversion factors for risk assessment assuming for 3-pyridazinone the same toxicity as for the parent compound (theoretical maximum daily intake (TMDI): 152% of ADI, French toddlers). The chronic intake calculation was therefore further refined using the supervised trials median residue (STMR) values and the international estimated daily intake (IEDI) accounted for 33% ADI (Dutch child). An acute intake calculation was not performed as no ARfD was allocated. The consumer exposure assessment is regarded as not finalised as a data gap has been identified to address the genotoxicity potential of 3-pyridazinone and its toxicity upon repeated-dose exposure (see Section 2).

The toxicological reference values and the residue definition for both enforcement and risk assessment have not been changed compared to those used in the review of the existing maximum residue levels (MRLs) for maleic hydrazide (EFSA, 2011b).

The data requirement for the determination of the residues in pollen and bee products for human consumption resulting from residues taken up by honeybees from crops at blossom is not relevant to carrots and bulb vegetables that are harvested before flowering. The data requirement however remains for the representative use on potato, although the application period starts at the very end of the flowering stage (BBCH 69).

4. Environmental fate and behaviour

The route and rate of degradation of [14C]-maleic hydrazide in soil under dark aerobic conditions (20°C) was investigated in four soils in a study presented for the first approval. Results in two of the soils have been considered not to be reliable according to the state-of-the-art assessment criteria because they had been treated with maleic hydrazide in previous years. In the other two soils, maleic hydrazide exhibited low persistence and degraded to minor metabolites, CO₂ (max 74.21% applied radioactivity (AR) after 60 days, end of the study) and unextractable residues (extracted with 100 mM formic acid in water:methanol mixture, max 33.25% AR after 28 days). The route and rate of degradation of [14C]-maleic hydrazide have been investigated in an additional study in four soils. In this study, maleic hydrazide exhibited very low to low persistence. One major non-characterised metabolite (max 15.5% AR after 14 days) was tentatively identified as maleic acid. In addition, minor metabolites, CO₂ (max 77.5% AR after 59 days, end of the study) and unextractable residues (extracted with 10% ammonia in methanol:water mixture, max 37.3% AR after 28 days) were identified. In an additional study, maleic hydrazide route and rate of degradation in soil were investigated in one soil. No metabolites exceeding 5% AR were identified in this study. Only the formation of un-extracted residues (extraction method not reported, max 24.5% AR after 90 days, end of the study) and CO₂ (max 71.6% AR after 90 days, end of the study) is reported. Degradation of maleic acid in soil under aerobic conditions was investigated in three soils. In these experiments, maleic acid exhibited very low persistence in soil. Succinic acid has also been observed as a major metabolite in the aerobic phase of the anaerobic study. However, levels attained are within the natural occurring amounts generally found in natural soils. Both metabolites maleic acid and succinic acid are considered not relevant metabolites according to the rules given in the guidance document on assessment of the relevance of metabolites in groundwater (European Commission, 2003).

Degradation of maleic hydrazide in soil under anaerobic conditions was investigated in a reliable study provided in the renewal dossier. Degradation during the anaerobic phase of the study was
negligible. Therefore, a half-life of 1,000 days is proposed by the RMS to be used for exposure assessment in situations when anaerobic conditions are expected to occur.

Photolysis of maleic hydrazide in soil was investigated in a microbially active soil (pH, OC, clay %) under moist (75% maximum water-holding capacity (MWHC)) and dry conditions at 20°C. Photolysis may contribute to the degradation of maleic hydrazide in the dry soil samples but this is not apparent in the moist samples. Therefore, it was concluded that photolysis is not a relevant degradation route of maleic hydrazide under normal environmental conditions.

Whereas not triggered, field dissipation/leaching studies, in a number of sites in Europe and USA, are available (some of them were submitted already in the first authorisation dossier). Despite that some of the studies are of good quality, scattering of data prevented deriving reliable quantitative kinetic degradation end points. Nevertheless, the very low to low persistence of maleic hydrazide is qualitatively confirmed by these studies.

Predicted environmental concentration (PEC) soils were calculated for parent maleic hydrazide and the metabolites maleic acid for the representative uses based on standard calculation and worst-case assumptions.

As studies presented in the dossier presented for the first peer review do not fulfil current guidelines, new batch soil adsorption/desorption studies were performed with maleic hydrazide in four soils and with metabolite maleic acid in three soils. According to these studies, maleic hydrazide may be considered to exhibit high to very high mobility in soil. With respect to maleic acid, no reliable end points could be derived due to the fast degradation in soil. However, as this metabolite is not relevant with respect to groundwater contamination, no further data are deemed necessary. The high mobility of maleic hydrazide is confirmed by the results of the aged soil column leaching study available in the dossier presented for the first peer review.

Hydrolysis of maleic hydrazide in water was investigated in buffered solutions (pH 4, 7 and 9) at 50°C. According to the results of this study, maleic hydrazide may be considered stable to aqueous hydrolysis under normal environmental conditions.

Aqueous photolysis of maleic hydrazide was investigated in two studies presented in the renewal dossier to replace the ones that were submitted for the first peer review that do not fulfil any longer current guidelines due to the deficiencies identified. From these studies it may be concluded that direct photolysis of maleic hydrazide in water is slow and not expected to significantly contribute to its environmental degradation.

Maleic hydrazide is not readily biodegradable according to the study submitted in the renewal dossier.

In the aerobic mineralisation in the surface water study, submitted in the renewal dossier, degradation of maleic hydrazide was negligible over the whole study period (90 days).

The fate and behaviour of maleic hydrazide in dark water sediment systems under aerobic conditions were investigated in three studies with a total of six systems (of which only four have been considered reliable by the RMS and peer review). Maleic hydrazide partitioned to the sediment (max 27% AR after 30–62 days) but most of the product remained in the aqueous phase. Degradation was relatively slow in two systems (DT50 whole system = 222.4–304.4 days) and moderate in the other two (DT50 whole system = 30.6–57.5 days). No major metabolites were identified in these studies.

PECsw/sed were calculated for parent and maleic acid with FOCUSgw tools up to Step 2 using agreed end points (or values that represent a worst case with respect to them) except for the non-reliable soil adsorptions end points used for maleic acid (FOCUS, 2001). Nevertheless, taking into account the conservativeness of the overall input parameters used at the FOCUS Step 2 model, it is considered that calculated PECsw/sed for maleic acid may be considered to represent a realistic worst case adequate for risk assessment.

The potential for ground water contamination was assessed by calculating the 80th percentile of 20 years’ annual average concentrations of maleic hydrazide and maleic acid at 1 m depth with FOCUSgw PEARL v4.4.4 and FOCUS PELMO v.5.5.3 models (FOCUS, 2009). The limit of 0.1 μg/L was not exceeded by maleic hydrazide and maleic acid for any of the relevant scenarios and representative uses simulated with the two FOCUS models. As soil adsorption values are not reliable, modelling results for maleic acid cannot be considered reliable. RMS indicates that when calculations are performed assuming a K_foc = 0 for maleic acid also no exceedance of 0.1 μg/L is observed. In any case, no further data or simulations are required as maleic acid is considered a non-relevant metabolite.
All kinetic parameters used as end points for triggering and modelling maleic hydrazide and its metabolite maleic acid in the different environmental parameters were derived from data on the studies using FOCUS kinetic guidance (FOCUS, 2006).

Data to address the effect of water treatment processes on the nature of residues present in surface water, when surface water is abstracted for drinking water, need to be provided to demonstrate that the approval criteria in Article 4 of Regulation (EC) 1107/2009 are satisfied. This has been identified in Section 7 as a data gap and as an assessment not finalised (see Section 9.1). Article 4(3)(b) of Regulation (EC) No 1107/2009 indicates that information on this is needed for decision-making on EU-level approval.

5. Ecotoxicology

The risk assessment was based on the following documents: SANCO/10329/2002-rev.2 final (European Commission, 2002a), SANCO/3268/2001-rev 4 (final) (European Commission, 2002b), SETAC (2001), EFSA (2009, 2013). According to Regulation (EU) No 283/2013, data should be provided regarding the acute and chronic toxicity to honeybees and data to address the development of honeybee brood and larvae. As the European Commission (2002a) does not provide a risk assessment scheme which is able to use the chronic toxicity data for adult honeybees and the honeybee brood, when performing the risk assessment according to European Commission (2002a), the risk to adult honeybees from chronic toxicity and the risk to bee brood could not be finalised due to the lack of a risk assessment scheme. Therefore, the EFSA (2013) guidance was used for risk assessment in order to reach a conclusion for the representative uses.

On the basis of available data and risk assessment, a low acute and chronic risk via dietary exposure to birds and wild mammals was concluded for all representative uses of maleic hydrazide. A low risk was also concluded from secondary poisoning and from exposure via contaminated water.

Tier 1 data were sufficient to conclude a low acute and chronic risk to fish, Daphnia magna and algae for exposure to maleic hydrazide. In the RAR, an acute end point was available for M. bahia. This end point was lower than the one for D. magna; however, the original study was not submitted and therefore not peer-reviewed (data gap). It is noted that an illustrative risk assessment with such end point and PECsw calculated with FOCUS Step 2 would result in a low risk with a high margin of safety. No valid study was available for estimating the toxicity of maleic hydrazide to Lemna gibba (data gap). However, a study on Myriophyllum aquaticum was available. Based on the available end point, a low risk was concluded.

No experimental data were available for the metabolite maleic acid. A screening risk assessment was carried out by considering maleic acid ten times more toxic than the parent. Based on this screening assessment, a low risk could be concluded for all aquatic organisms.

A low risk to honeybees due to contact exposure was concluded based on the screening step in accordance with EFSA (2013). Regarding oral exposure, a high acute risk was identified for all representative uses in the screening step. However, in the acute oral test to adult honeybees carried out with potassium salt of maleic hydrazide, the single tested concentration caused minor effects (5% mortality). In the acute oral test carried out with the representative formulation, higher concentrations of maleic hydrazide were tested, without reaching 50% mortality (17% maximum). If the end point derived from the study with the formulation is used in the risk assessment, the trigger is not breached at the screening step. Overall, a low oral acute risk is concluded for all representative uses.

A tier 1 risk assessment was carried out for chronic effects on adult honeybees and on larvae due to exposure to residues in pollen and nectar. It should be noted that the treated crop scenario is not relevant to carrots and bulb vegetables intended for food production, as these would be harvested before flowering. However, it should be considered that the present assessment does not cover crops used for seed production. Due to the very low soil persistence of maleic hydrazide (< 1 day), the next crop scenario is not considered relevant. Chronic tests on adult honeybees were carried out with potassium salt of maleic hydrazide and the representative formulation. No effects were seen in the two tests up to the highest tested concentrations. However, the derived end points were not sufficient to demonstrate a low chronic risk for the treated crop scenario related to the representative use on potato (data gap). It should be noted anyway that the treated crop scenario is only marginally relevant to potato, as the intended application period starts at the very end of the flowering stage (BBCH 69). Management of flowering weeds (all representative uses) is necessary to achieve a low risk. Repeated doses test on larvae were carried out with the potassium salt of maleic hydrazide and the representative formulation. A low risk was concluded for all representative uses.
No assessment was available for sublethal effects (i.e. hypopharyngeal glands (HPG), data gap). No assessment for accumulative effects was available. However, due to the lack of effects observed in the available chronic studies, accumulative effects are not likely to occur.

No information was available regarding metabolites occurring in pollen and nectar. Therefore, a data gap was identified.

A low risk to adult (acute and chronic) and larvae honeybees was concluded on the basis of the screening assessment for exposure via residues in surface water. A high risk to adult (acute and chronic) and larvae honeybees could not be excluded for exposure via residues in guttation fluid on the basis of the screening assessment (data gap). No data were submitted for estimating maleic hydrazide concentration in puddle water (data gap).

No data were available to perform a risk assessment for bumble bees and solitary bees.

Standard laboratory data were available for six species of non-target arthropods. These data showed that the most sensitive species to maleic hydrazide were Typhlodromus pyri and Aphidius rhopalosiphi. In these test studies, mortality was above 50%. Tier 2 data (extended laboratory, aged residues) were available for both species and were sufficient to conclude a low risk for all representative uses of maleic hydrazide.

A low risk to earthworms, other soil macro-organisms, soil micro-organisms and non-target terrestrial plants was concluded for all representative uses. A low risk is also concluded for biological methods of sewage treatment.

The data gap identified in Section 2 regarding the technical specification is also relevant to the ecotoxicological studies pending the maximum level of hydrazine.

For ecotoxicological assessments, no other studies were available to address the potential endocrine activity of maleic hydrazide. Pending on the outcome of the data gap in Section 2, further ecotoxicological tests might be necessary to address the potential endocrine-disrupting properties of maleic hydrazide. A data gap has been therefore identified.

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 |
|-----------------------------|-------------|---------------|
| Maleic hydrazide            | Very low to low (DT₅₀ = 0.2–3.9 days) | Low risk to soil organisms |
| Maleic acid                 | Very low (DT₅₀ = 0.28–0.58 days) | Low risk to soil organisms |

Table 2: Groundwater

| Compound (name and/or code) | Mobility in soil | > 0.1 µg/L at 1 m depth for representative uses(a) | Pesticidal activity | Toxicological relevance | Ecotoxicology |
|-----------------------------|------------------|--------------------------------------------------|---------------------|------------------------|--------------|
| Maleic hydrazide            | High to very high (Kᵢₒᵣ = 14.4–108 mL/g) | FOCUS: no Lysimeter: not available; not required | Yes                 | Yes                    | Low risk to organisms living in surface water |
| Maleic acid                 | Not required, metabolite not relevant | Not required, metabolite not relevant | No                  | Not required, metabolite not relevant | Low risk to organisms living in surface water |

(a): At least one FOCUS scenario or relevant lysimeter.
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).

- Analytical method for the determination of hydrazine in the TC at the level of the finally agreed specification (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Sections 1 and 2).
- Analytical method for the determination of maleic hydrazide in body fluids and tissues (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 1).
- Identification of the analytical methods used in the toxicity studies (except for the acute inhalation and dermal sensitisation studies) (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 1).
- Genotoxicity studies with the representative technical specification (containing 1 ppm of the relevant impurity hydrazine), unless it can be demonstrated that levels of 0.028 ppm hydrazine can be obtained in the TC (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Sections 2 and 5).
- Interspecies comparative in vitro metabolism including human material (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- Clarification of the endocrine-disrupting potential of maleic hydrazide considering in particular level 2 and 3 tests currently indicated in the OECD Conceptual Framework (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Sections 2 and 5).
- Clarification of the genotoxic potential of 3-pyridazinone and of its toxicological profile relevant to consumer exposure (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Sections 2 and 3).
- Formal data gap for the RMS to report the full assessment of the results of the scientific peer-reviewed open literature search (relevant for all representative uses evaluated; submission date proposed by the applicant: submitted; see Section 3).
- Determination of the residues in pollen and bee products for human consumption resulting from residues taken up by honeybees from potato at blossom (relevant for the representative use on potato; submission date proposed by the applicant: unknown; see Section 3).
- The effect of water treatment processes on the nature of residues present in surface and groundwater, when surface water or groundwater are abstracted for drinking water (Article 4(3)(b) of Regulation (EC) No 1107/2009) needs to be assessed. In the first instance, a consideration of the processes of ozonation and chlorination may be considered appropriate (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 4).
- The available acute study with *M. bahia* should be submitted and peer-reviewed (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).

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### Table 3: Surface water and sediment

| Compound (name and/or code) | Ecotoxicology                        |
|-----------------------------|--------------------------------------|
| Maleic hydrazide            | Low risk to aquatic organisms        |
| Maleic acid                 | Low risk to aquatic organisms        |

### Table 4: Air

| Compound (name and/or code) | Toxicology                                      |
|-----------------------------|-------------------------------------------------|
| Maleic hydrazide            | Rat LC50 Inhalation > 3.2 mg/L air every 4 h (dust, nose-only) – no classification required |
No valid study was available for estimating the toxicity of maleic hydrazide to *L. gibba* (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).

Several data gaps were identified for honeybees by performing the risk assessment according to (EFSA, 2013): (1) further information to refine the chronic risk to adult honeybees; (2) suitable data to address the risk of sublethal effects (i.e. HPG development effects) to honeybees due to exposure to maleic hydrazide; (3) further information to refine the risk to honeybees for exposure via residues in guttation fluid and puddle water (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).

Information to assess the risk to honeybees due to plant metabolites occurring in pollen and nectar (relevant for all 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**

PPE such as gloves during mixing and loading operations, and gloves and impermeable coveralls during application, has to be used by operators applying the product with hand-held equipment according to the UK POEM model to ensure that the AOEL is not exceeded (see Section 2).

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 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).

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 consumer risk assessment is not finalised with regard to the unknown nature of residues that might be present in drinking water, consequent to water treatment following abstraction of surface water and groundwater that might contain maleic hydrazide (see Section 4).

2) Maleic hydrazide is not classified or proposed to be classified as carcinogenic category 2 or as toxic for reproduction 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. An endocrine-disrupting potential of maleic hydrazide could not be ruled out, although no adverse effects were observed in the apical studies that could be linked to an endocrine-disrupting mode of action, sensitive parameters for fertility, sexual development and potential hormone-mediated effects were not investigated in the two-generation reproductive toxicity study (such as oestrus cycle length and normality, sperm parameters, anogenital distance, age of vaginal opening and preputial separation) (see Sections 2 and 5).

3) The consumer risk assessment could not be finalised with regard to the toxicity profile of 3-pyridazinone metabolite included in the residue definition for risk assessment for animal commodities (see Section 3).
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 a 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.

4) The technical specification is not supported by the (eco)toxicological assessment as the specified level of the known relevant impurity – hydrazine (at 1 ppm) has not been sufficiently tested. Positive results were obtained in non-standard genotoxicity studies with the test material containing 0.31 ppm hydrazine and the level of hydrazine present in the batches used in the carcinogenicity studies remaining unknown (see Sections 2 and 5).

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 below.)

All columns are in grey, as the TC specification proposed was not comparable to that of the material used in the testing that was used to derive the (eco)toxicological reference values.

Table 5: Overview of concerns

| Representative use                                      | Onion | Garlic | Shallot | Potato | Carrot |
|--------------------------------------------------------|-------|--------|---------|--------|--------|
| 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                               |       |        |         |        |        |
References

Denmark, 2015. Renewal assessment report (RAR) on the active substance maleic hydrazide prepared by the rapporteur Member State, Denmark, in the framework of Commission Implementing Regulation (EU) No 844/2012, April 2015. Available online: www.efsa.europa.eu

Denmark, 2016. Revised renewal assessment report (RAR) on maleic hydrazide, compiled by EFSA, January 2016. Available online: www.efsa.europa.eu

EFSA (European Food Safety Authority), 2009. Guidance on risk assessment for birds and mammals on request from EFSA. EFSA Journal 2009;7(12):1438, 358 pp. doi:10.2903/j.efsa.2009.1438

EFSA (European Food Safety Authority), 2011a. Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009. EFSA Journal 2011;9(2):2092, 49 pp. doi:10.2903/j.efsa.2011.2092

EFSA (European Food Safety Authority), 2011b. Review of the existing maximum residue levels (MRLs) for maleic hydrazide according to Article 12 of Regulation (EC) No 396/2005. EFSA Journal 2011;9(10):2421, 41 pp. doi:10.2903/j.efsa.2011.2421

EFSA (European Food Safety Authority), 2013. EFSA Guidance Document on the risk assessment of plant protection products on bees (Apis mellifera, Bombus spp. and solitary bees). EFSA Journal 2013;11(7):3295, 268 pp. doi:10.2903/j.efsa.2013.3295

EFSA (European Food Safety Authority), 2016. Peer review report to the conclusion regarding the peer review of the pesticide risk assessment of the active substance maleic hydrazide. Available online: www.efsa.europa.eu

EFSA PPR Panel (EFSA Panel on Plant Protection Products and their Residues), 2012. Guidance on dermal absorption. EFSA Journal 2012;10(4):2665, 30 pp. doi:10.2903/j.efsa.2012.2665

EFSA Scientific Committee, 2013. Scientific Opinion on the hazard assessment of endocrine disruptors: scientific criteria for identification of endocrine disruptors and appropriateness of existing test methods for assessing effects mediated by these substances on human health and the environment. EFSA Journal 2013;11(3):3132, 84 pp. doi:10.2903/j.efsa.2013.3132

European Commission, 1999. Guidelines for the generation of data concerning residues as provided in Annex II, Part A, section 6, and Annex III, Part A, section 8, of Directive 91/414/EEC concerning the placing of plant protection products on the market. 1607/V1/97-rev. 2, 10 June 1999.

European Commission, 2000a. Residues: guidance for generating and reporting methods of analysis in support of pre-registration data requirements for Annex II (Part A, Section 4) and Annex III (Part A, Section 5) of Directive 91/414. SANCO/3029/99-rev. 4, 11 July 2000.

European Commission, 2000b. Technical material and preparations: guidance for generating and reporting methods of analysis in support of pre- and post-registration data requirements for Annex II (Part A, Section 4) and Annex III (Part A, Section 5) of Directive 91/414. SANCO/3030/99-rev. 4, 11 July 2000.

European Commission, 2002a. Guidance document on terrestrial ecotoxicology under Council Directive 91/414/EEC. SANCO/10329/2002-rev. 2 (final), 17 October 2002.

European Commission, 2002b. Guidance document on aquatic ecotoxicology under Council Directive 91/414/EEC. SANCO/3268/2001-rev. 4 (final), 17 October 2002.

European Commission, 2002c. Review report for the active substance maleic hydrazide; finalised in the Standing Committee on the Food Chain and Animal Health at its meeting on 3 December 2002 in view of the inclusion of maleic hydrazide in Annex I of Directive 91/414/EEC. Maleic hydrazide, SANCO/10501/2002-final, 2 December 2002.

European Commission, 2003. Guidance document on assessment of the relevance of metabolites in groundwater of substances regulated under Council Directive 91/414/EEC. SANCO/221/2000-rev. 10 (final), 25 February 2003.

European Commission, 2010. Guidance document on residue analytical methods. SANCO/825/00-rev. 8.1, 16 November 2010.

European Commission, 2012. Guidance document on the assessment of the equivalence of technical materials of substances regulated under Regulation (EC) No 1107/2009. SANCO/10597/2003-rev 10.1, 13 July 2012.
European Commission, 2013. Guidance document on data requirements on efficacy for the dossier to be submitted for the approval of new active substances contained in plant protection products. SANCO/10054/2013-rev. 3, 11 July 2013.

European Commission, 2015. Guidelines on comparability, extrapolation, group tolerances and data requirements for setting MRLs. SANCO 7525/VI/95-rev. 10.1, December 2015, p. 1–56.

FOCUS (Forum for the Co-ordination of Pesticide Fate Models and their Use), 2001. FOCUS surface water scenarios in the EU evaluation process under 91/414/EEC. Report of the FOCUS Working Group on Surface Water Scenarios. EC Document Reference SANCO/4802/2001-rev. 2, 245 pp., as updated by Generic guidance for FOCUS surface water scenarios, v. 1.1, March 2012.

FOCUS (Forum for the Co-ordination of Pesticide Fate Models and their Use), 2006. Guidance document on estimating persistence and degradation kinetics from environmental fate studies on pesticides in EU Registration Report of the FOCUS Workgroup. EC Document Reference SANCO/10058/2005-v. 2.0, 434 pp.

FOCUS (Forum for the Co-ordination of Pesticide Fate Models and their Use), 2009. Assessing potential for movement of active substances and their metabolites to groundwater in the EU. Report of the FOCUS Workgroup. EC Document Reference SANCO/13144/2010-v. 1, 604 pp., as outlined in Generic guidance for tier 1 FOCUS groundwater assessment, v. 2.0, January 2011.

JMPR (Joint Meeting on Pesticide Residues), 2004. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues, Rome, Italy, 20–29 September 2004, 383 pp.

JMPR (Joint Meeting on Pesticide Residues), 2007. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues, Geneva, Switzerland, 18–27 September 2007, 164 pp.

OECD (Organisation for Economic Co-operation and Development), 2001. Test No. 416: two-generation reproduction toxicity, OECD Guidelines for the Testing of Chemicals, Section 4, OECD Publishing, Paris. doi:http://dx.doi.org/10.1787/9789264070868-en

OECD (Organisation for Economic Co-operation and Development), 2011. OECD MRL calculator: spreadsheet for single data set and spreadsheet for multiple data set, 2 March 2011. In: Pesticide Publications/Publications on Pesticide Residues. Available online: http://www.oecd.org

OECD (Organisation for Economic Co-operation and Development), 2012. Series on Testing and Assessment: No 150: Guidance document on standardised test guidelines for evaluating chemicals for endocrine disruption. ENV/JM/MONO(2012)22, 524 pp.

SETAC (Society of Environmental Toxicology and Chemistry), 2001. Guidance document on regulatory testing and risk assessment procedures for plant protection products with non-target arthropods. ESCORT 2.

**Abbreviations**

- **3T3** standard fibroblast cell line (3-day transfer, inoculum 3 x 10⁵ cells)
- **AAOEL** acute acceptable operator exposure level
- **ADI** acceptable daily intake
- **ADME** absorption, distribution, metabolism or excretion
- **AOEL** acceptable operator exposure level
- **AR** applied radioactivity
- **ARfD** acute reference dose
- **AUC** area under the blood concentration/time curve
- **BBCH** growth stages of mono- and dicotyledonous plants
- **bw** body weight
- **CLP** classification, labelling and packaging
- **Cmax** concentration achieved at peak blood level
- **DT₅₀** period required for 50% dissipation
- **EC** European Commission
- **EEC** European Economic Community
- **EMHTF** EU Maleic hydrazide Task Force
- **EUROPOEM** European Predictive Operator Exposure Model
- **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
- **HPG** hypopharyngeal glands
- **IEDI** international estimated daily intake
- **ISO** International Organization for Standardization
- **IUPAC** International Union of Pure and Applied Chemistry
| Acronym | Description |
|---------|-------------|
| 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      | liquid chromatography |
| LC$_{50}$ | lethal concentration, median |
| LC-MS   | liquid chromatography–mass spectrometry |
| LC-MS/MS| liquid chromatography with tandem mass spectrometry |
| LOQ     | limit of quantification (determination) |
| MRL     | maximum residue level |
| MS      | mass spectrometry |
| MWHC    | maximum water-holding capacity |
| NOAEL   | no observed adverse effect level |
| NRU     | neutral red (weak cationic dye) uptake |
| OECD    | Organisation for Economic Co-operation and Development |
| PEC     | predicted environmental concentration |
| PEC$_{sed}$ | predicted environmental concentration in sediment |
| PEC$_{sw}$ | predicted environmental concentration in surface water |
| PHI     | pre-harvest interval |
| POEM    | Predictive Operator Exposure Model |
| PPE     | personal protective equipment |
| ppm     | parts per million ($10^{-6}$) |
| PRIMo   | Pesticide Residues Intake Model |
| RAR     | renewal assessment report |
| RMS     | rapporteur member state |
| SANCO   | Directorate-General for Health and Consumers |
| SG      | water-soluble granule |
| SMILES  | simplified molecular-input line-entry system |
| STMR    | supervised trials median residue |
| TC      | technical material |
| TMDI    | theoretical maximum daily intake |
| TRR     | total radioactive residue |
| 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): http://dx.doi.org/10.2903/j.efsa.2016.4492
### Appendix B – Used compound codes

| Code/trivial name⁽ᵃ⁾ | Chemical name/SMILES notation | Structural formula |
|-----------------------|-------------------------------|--------------------|
| 3-Pyridazinone        | pyridazin-3(2H)-one O=C1C=CC=NN1 | ![3-Pyridazinone](image) |
| Maleic hydrazide sulphate conjugate | 6-oxo-1,6-dihydropyridazin-3-yl hydrogen sulfate OS(=O)(=O)OC=1C=CC(=O)NN=1 | ![Maleic hydrazide sulphate conjugate](image) |
| Maleic acid           | (2Z)-but-2-enedioic acid O=C(O)/C=C\(\text{C}(=O)O) | ![Maleic acid](image) |
| Hydrazine             | Hydrazine NN                  | ![Hydrazine](image) |
| Succinic acid         | Succinic acid O=C(O)CCC(=O)O | ![Succinic acid](image) |

SMILES: simplified molecular-input line-entry system.

⁽ᵃ⁾: The compound name in bold is the name used in the conclusion.